BY GRADE SCHOOL, most of us have a basic understanding of DNA, or deoxyribonucleic acid, the essential building block of human life. It’s what makes our eyes blue or our hair straight. DNA medicines, however, are less well known and historically have been unsuccessful in delivering what 25 years ago was touted as a revolution in therapeutics.1 Contrary to popular opinion, DNA medicines are not synonymous with “gene therapy,” but they have been challenged by the same biases and presumptions, and because of that, DNA medicines have failed to gain therapeutic ground in the treatment of human disease. Until now.

TARGETED THERAPY
How DNA Medicines Could Transform Treatment of Glioblastoma Multiforme
JEFFREY SKOHN, MD

To administer DNA medicines, the Inovio Cellectra device (above) allows a brief electrical pulse to reversibly open small pores in the cell and allow the plasmids to enter, overcoming an important limitation of similar medicines.

FIGURE 1. Cellectra DNA Medicines Delivery Device.

PRECISION MEDICINE AND OCM
Rethinking Downside Risk Protection Amid Growth in Precision Medicine
KEELEY MACMILLAN, MSPH

THE ONGOING EVOLUTION in targeted therapy has led to better outcomes—including overall survival—for patients with cancer and other rare conditions. Although only a small percentage of patients are candidates for targeted therapies, the costs of these treatments can be staggering. Self-insured employers and organizations entering into risk-based arrangements will be most impacted by these unpredictable costs, and they need to reevaluate their approach to protecting their risk to ensure that patients receive the treatment they need.

Daratumumab, for example, a targeted monoclonal antibody that helps slow or stop the progression of multiple myeloma, is used in 8% to 16% of multiple myeloma cases among participants of Medicare’s Oncology Care Model (OCM),1 an advanced alternative payment model that aims to produce higher-quality care at the same or lower cost to Medicare.2,3 Given breakthrough therapy designation for multiple myeloma in 2013,3 daratumumab was given expanded approval in 2018 for use in combination with chemotherapy for the treatment of newly diagnosed multiple myeloma in patients who are ineligible for an autologous stem cell transplant.4 Medicare spends more than $8000, on average, per administration of the drug for aligned OCM beneficiaries; for a 6-month episode of care, the cost of daratumumab is commonly more than $60,000, and at times it surpasses $100,000 per episode.1

BTK INHIBITORS
Second-Generation BTK Inhibitors Hit the Treatment Bullseye With Fewer Off-Target Effects
MAGGIE L. SHAW

ONCE KNOWN AS A PARADIGM-CHANGING class of precision oncology, or targeted, drugs,5 Bruton tyrosine kinase (BTK) inhibitors are now well established as treatment for several hematological malignancies. They are named for Lt Col Ogden C. Bruton, MD, chief of pediatrics at Walter Reed Army Medical Center in the 1950s, who in 1951 discovered the first host immunodeficiency in humans, X-linked agammaglobulinemia.6,7

CONTINUED ON SP224 »

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Biosimilars May Help Bridge the Transition From Fee-for-Service to Value-Based Care

Healthcare Providers Are Feeling the Burden of Rising Costs

Financial challenges remain the #1 concern of hospital executives according to the 2018 American College of Healthcare Executives’ annual survey. Similarly, oncology practices face significant financial strain, which has resulted in over 1600 community oncology practice closures, hospital acquisitions, and corporate mergers in the past decade.1

One way to alleviate this burden is through utilizing opportunities to recognize cost savings. For example, hospitals may be able to leverage cost savings to reallocate funds for other important projects not funded by Medicare or commercial payers. In addition, this may lead to better management of hospital budgets to optimize care and a positive budget impact on drug spend for hospital inpatients.2

The Healthcare Industry Is Feeling the Effects of the Shift to Value-Based Care

In recent years, there has been a significant transition in focus from fee-for-service to value-based care. The goal of a value-based care system is to encourage clinicians to provide quality and efficient care, as well as improved outcomes at a lower cost.3

There have been several actions in the market place to recognize this shift to value-based care. For example, the Centers for Medicare & Medicaid Services (CMS) has created value-based care programs that reward providers with incentives for lowering costs and improving the quality of care they provide to Medicare beneficiaries. An example of this type of market reform is the development of a voluntary pilot program called the Oncology Care Model (OCM), which is designed to test the effects of improved care coordination, greater access to practitioners, and appropriate clinical care on both health outcomes and the cost of care for patients receiving chemotherapy.4 Another type of market reform that was recently announced, the Patient-Centered Oncology Payment (PCOP) model, offers a way to expand on the OCM experience and represents an additional step towards innovation.5

This shift from fee-for-service to value-based care is playing a significant role in how practices and providers are viewing the cost of care.6

IN LIGHT OF THESE MARKET TRENDS

87%

of community oncologists surveyed are thinking differently about drug choices as a result of value-based care.8

In order to manage appropriate utilization and take more risk, it will be crucial to assess the expense side of the equation as well.9

As the industry shifts to value-based reimbursement models, healthcare systems will continue to realize the need for solutions that advance health initiatives and support quality care objectives in the future.10

References:
Unlocking the Potential of Biosimilars

Given the growing costs of cancer care, delivering value while maintaining efficacy and safety is a pivotal issue in today’s healthcare environment. Biosimilars may help address this issue by providing additional treatment options, at a potentially lower cost, while providing highly similar safety and efficacy to their reference biologic. They may potentially better position providers for emerging value-based care initiatives from payers and employers through availability of lower-cost treatment options resulting in reduced drug spend. In addition, biosimilars may help meet established cost targets and position for future risk-sharing for OCM practices.

Biosimilars May Prove Fundamental to the Future of Oncology Care, as We Shift to Value-Based Care as a Solution to Contain Costs

- By potentially reducing costs and helping decrease financial risk in an emerging value-based environment, biosimilars may be able to unlock resources that can be reinvested in improving patient care
- Biosimilars may potentially offer a variety of therapeutic options at a lower cost, as well as savings and efficiencies for the healthcare system
- Demonstrating the ability to lower costs for high volume, costly therapies may prove beneficial with practice discussions with payers

Introduction to Biosimilars

- A biosimilar is a biologic medicine that is highly similar to a reference biologic, with no clinically meaningful differences in terms of safety, purity, and potency
- As potential alternatives to reference biologics, biosimilars may potentially expand treatment options and lower costs to meet the growing demand for biologic therapies

Development and Approval of Biosimilars

Extensive analytical, clinical, and nonclinical studies are part of biosimilar development. The FDA approval process evaluates the totality of evidence to help ensure biosimilar quality, efficacy, and safety.

- A comparative clinical study is typically required to confirm no clinically meaningful differences between the 2 products
- Comparative human pharmacokinetic/pharmacodynamic (PK/PD) studies and clinical immunogenicity assessment are expected
- Nonclinical testing to evaluate the toxicity and safety profiles of the biosimilar is required
- Robust analytical testing, including comparative structural and functional characterization, is performed

For more information, please visit PfizerBiosimilars.com

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Where Myths Go to Die

Yes You have come upon the fabled lands where myths Go when they die.

—James Fenton
The Pitt-Rivers Museum (1983)

AS A MEDICAL STUDENT, I was struck by the number of times our teachers regaled us with the “Gordian Knot” myth as a paradigm for how we should approach understanding complex patients and seemingly indecipherable clinical data sets. As legend has it, the Gordian Knot was so complex that it was impossible to perceive where one strand began and another ended; thus, it could never be unraveled. The task was considered so great that anyone who could untie the knot was prophesied to become the ruler of a vast portion of the world as it was then known. According to one version of the legend, Alexander the Great considered the knot, and in a stroke of genius pulled out his sword and sliced the knot in half. In doing so he fulfilled the oracle’s prophesy. The lesson of this story, as espoused by my teachers, was that a simple solution frequently existed for most complex healthcare conundrums.

We now find ourselves in the midst of a golden era of cancer care in which insights gleaned from genomic data and our ability to leverage a growing armamentarium of targeted anti-cancer treatments routinely produce superior survival outcomes with an improved quality of life for many patients. Yet, these advances have come with questions and challenges about how to pay for these treatments, how to deliver them equitably to patients in need, and how to ensure that our systems of care become more patient-centered. Clinical reimbursement systems now repeatedly lag advances in cancer diagnostic and treatment technologies. The cost of some treatments (such as CAR T-cell therapies) have challenged existing payment models from both public and private payers. At the same time, our care portfolio continues to outpace our systems for delivering this care in financially sustainable ways. Rather than empower a path toward sustainable solutions, the naïve believe that a simple approach is possible. This has paralyzed us from coming to terms with the necessary complexity of what it will take to deliver precision medicine solutions to cancer patients in the future. It is time for the mythic “Gordian Knot” approach to the development of more effective and efficient cancer care delivery systems to die.

In this edition of Evidence-Based OncologyMT we look at the emergence of additional innovative anti-cancer treatments, such as the second generation of the BTK inhibitors, DNA-based therapies for glioblastoma patients, and the clinical opportunities for the detection of NRG1 gene fusion in selected patients. Beyond exploring new diagnostic and therapeutic opportunities for cancer patients, we also review the exciting potential avenues for how healthcare payment and clinical reimbursement might evolve to support sustainable delivery of innovative treatments. Mark Trusheim, MSc, of MIT discusses a long-awaited plan to improve the ability of Medicaid programs to pay for gene-based therapeutics. Keely Macmillan, MSPH, from Archway Health discusses how downside risk related to precision oncology and high-cost therapeutics can be sustainably managed in the context of oncology advanced alternative payment models.

As the practice and systems-based delivery of cancer care evolves at a breakneck pace, simple solutions are more likely to harm, than help, essential stakeholders. Effective new delivery and payment systems can only emerge, however, if healthcare leaders fully embrace the inescapable necessity of creating these systems. The writer H.L. Mencken cynically noted that, “For every complex problem there is an answer that is simple, clear and wrong.” There are many avenues in which the “Gordian Knot” approach leads to false choices and ill-conceived simple solutions. Pithy myths are a poor paradigm for navigating complex dilemmas. The path toward the broad realization of innovative, financially sustainable, equity-delivered cancer care is likely to be an arduous, painful journey. It is time to embrace that complexity and let the comforting myths die.  

Joseph Alvarnas, MD
EDITOR-IN-CHIEF
Caris Life Sciences’ technology will help Merus find patients with NRG1 fusions to participate in a clinical trial using zenocutuzumab to treat pancreatic cancer.

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TONY HAGEN

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FROM THE CHAIRMAN

Sincerely,

Mike Hennessy Sr
CHAIRMAN AND FOUNDER

Fighting the Most Difficult Cancers, and Finding Savings

THIS ERA OF PRECISION ONCOLOGY brings opportunities that were hard to imagine years ago: It makes clinical and financial sense to pursue treatments for extremely rare cancers, and we are seeing progress in hard-to-treat diseases such as pancreatic cancer. Scientists no longer talk only about a tumor type: today the discussion also involves the genetic markers that guide treatment decisions. This knowledge is gained through comprehensive testing, that includes both DNA and RNA sequencing. The president and CEO of Caris Life Sciences tells us in this issue of Evidence-Based Oncology™ that testing technology will soon drive treatment decisions based on a cancer’s pathway.

Not only can comprehensive testing steer treatment toward drugs that will work (and away from those that won’t), but as a team of Rutgers University authors found in 2018 (see SP203), using testing on the front end of a clinical trial to select the right participants can hold down research and development costs and increase the odds of success.

It’s essential then, that payers remove any remaining barriers that limit access to testing that can not only save lives but also ultimately drive down costs. Yet gaps remain, as we see in our news section: a recent study appearing in JNCCN, affiliated with the National Comprehensive Cancer Network, finds many patients still cannot get coverage for liquid biopsies. A separate study appearing in The Oncologist found that patients with non–small cell lung cancer who had access to companion diagnostics had better survival rates than those who did not.

Payer coverage for testing is also essential as both physician-scientists and the FDA rely more than ever on real-world evidence to fill information gaps. Broad-based coverage for testing will help ensure greater diversity in the data collected in claims, which will be mined by data scientists for more insights. In the time of coronavirus disease 2019, it is expected that real-world evidence will be more important than ever.

With that in mind, we bring you a timely interview with John Carpten, PhD, professor and chair of Translational Genomics at the University of Southern California Keck School of Medicine, who explained how the historic lack of diversity in clinical trials hurts everyone—and why it’s everyone’s problem to fix. And we also hear from Russell Joseph Ledet, PhD, president of The 15 White Coats, a group of aspiring Black physicians who are carrying a message of hope to the next generation.

◆

Sincerely,

Mike Hennessy Sr
CHAIRMAN AND FOUNDER
Partnership to Find Patients With NRG1 Fusions for Zenocutuzumab Trial in Pancreatic Cancer

MARY CAFFREY

A RECENT COLLABORATION BETWEEN a Netherlands-based biotech and a well-known US diagnostics company highlights the journey of cancer care today: The bispecific antibody zenocutuzumab, previously studied more broadly in solid tumors, is now being focused in the specific patients in whom it seems to work wonders. These patients have neuregulin 1 (NRG1) fusions, a rare but powerful oncogene driver that makes cancer particularly aggressively and deadly when it is present.1

Gene fusions occur when 2 previously independent genes connect, producing increased amounts of abnormal protein that trigger and fuel tumor growth. There are many types of NRG1 fusions, involving different genes, and they are a culprit in many cancers with poor survival rates, such as lung cancers among patients who never smoked and pancreatic cancer.

Zenocutuzumab targets both HER2 and HER3 and blocks the interaction of the NRG1 fusion protein with its receptor HER3; it has shown success in treating cancers fueled by NRG1 gene fusions.2 In fact, Merus, the maker of zenocutuzumab, was studying the drug’s effectiveness in breast cancer when it shifted gears to focus on patients with this rare cancer driver.

That’s where Merus’ collaborator, Caris Life Sciences, comes in: Although the strategy of matching the therapy with patients whose cancer is driven by NRG1 fusions appears to be a winner, the companies say these fusions are rare, occurring in only 0.3% to 3.0% of non–small cell lung cancer (NSCLC), 0.5% to 1.5% of pancreatic ductal cancer, and less than 1.0 % of other tumor types, based on available literature.3 Thus, it takes effort to find patients eligible for a trial.

Thus, the agreement will tap Caris’ next-generation sequencing technology to identify patients eligible for Merus’ phase 1/2 eNRGy trial and its Early Access Program.

David Spetzler, PhD, MBA, MS, president and CEO of Caris Life Sciences, said in an interview with Evidence-Based Oncology4 that when a patient receives molecular profiling, “We perform whole exome sequencing and whole transcriptome sequencing. We’re assessing every single gene in their DNA and every single gene in their RNA.” He explained that for NRG1 fusions, it is best to look at the RNA, so this is a standard part of testing.

“We’re able to identify those patients who have NRG1 fusions and assess the expression level of them as well,” he said. “So, not only can we see that the fusion event has occurred, but we can also get a sense of the magnitude of how big it is within that particular tumor type.”

The focus will be on pancreatic cancer, for which Merus received an orphan drug designation from the FDA on July 29, 2020.5 Caris will perform whole exome sequencing of DNA and whole transcriptome sequencing of RNA for certain cancer patients, and make those who potentially meet the criteria aware of the trial.

Results for Zenocutuzumab

FDAs action followed results from a proof-of-concept study presented in October 2019 at the American Association of Cancer Research/National Cancer Institute/European Platform of Cancer Research International Conference on Molecular Targets and Cancer Therapeutics. At that meeting, investigators presented results from 3 patients with NRG1 gene fusions: 2 with pancreatic cancer and 1 with NSCLC.6 The patients were not part of a clinical trial, but rather an expanded access program at Memorial Sloan Kettering.5

The patients with pancreatic cancer were a 52-year-old male who achieved a partial response and a 34-year-old male achieved who achieved stable disease; both were treated for at least 7 months. A 34-year-old male treated for NSCLC achieved partial response after being treated for at least 4.5 months. Among the 117 patients treated in the entire study, most adverse events (AEs) were grade 1 or 2, less than 5% had a grade 3 AE, and none had a grade 4 event.4

“Receiving orphan drug designation for zenocutuzumab is another important milestone for our lead program, and it validates the significant unmet need in patients with pancreatic cancer,” Bill Lundberg, MD, president, CEO, and principal financial officer of Merus, said in a statement. “We are pleased with the progress we are making in our ongoing global clinical trial and believe that zenocutuzumab has the potential to play a significant role in shifting the treatment paradigm for NRG1 fusion cancers from conventional chemotherapy to a personalized medicine approach.”5

“There’s growing evidence that we should be moving away from gene-specific associations more toward pathway-associated associations, and so the more complex signatures really can start to untangle some of the inherent complexity of these molecular systems.” —David Spetzler, PhD, MBA, MS, president and CEO, Caris Life Sciences

The Importance—and Future—of Testing

This shift in gears highlights the evolution of cancer treatment: The focus increasingly is not solely on tumor type but also on the biomarkers that the tumors or blood cancers present, and then on finding therapies that will target the genetic markers driving the cancer. In a review article on developing precision and personalized medicine strategies, authors from Rutgers University wrote in 2019 that this may make cancer treatment more complex, but it has many advantages, from sparing patients the AEs of medicines that won’t work to lowering costs.6

Using testing to define the clinical trial population is hugely beneficial, the Rutgers team wrote. “By focusing on smaller populations, clinical trial size will shrink, substantially reducing the costs. In addition, the population admitted to the trial is more likely to respond to the therapy, reducing the risk associated with failed clinical trials,” the authors wrote in Technology.6

To that end, can the Caris technology identify patients who might be good candidates for 1 treatable target of a bispecific antibody, but not the other?
Tafasitamab Combination Approved for Adults With R/R DLBCL

MARY CAFFREY

ON JULY 31, THE FDA APPROVED tafasitamab-cxix to be used in combination with lenalidomide for second-line treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), meeting the needs of patients who are not eligible for an autologous stem cell transplant.1

Tafasitamab, to be sold as Monjuvi by MorphoSys and Incyte, is a humanized Fc-modified cytolytic CD19 monoclonal antibody being studied in several B-cell malignancies. As described in the journal Blood, the treatment uses Xencor’s proprietary Xmab technology, which deploys a different technique to boost affinity for the antigen and make various receptors especially capable of binding to it.1 In 2018, authors in Annals of Oncology described how this sets off particularly effective processes that target cancer cells and regulate cell death.1

Approval was based on phase 2 results for 80 patients in the L-MIND trial, which reported an update May 2019 at the American Society of Clinical Oncology,2 with final results published in June in The Lancet.3 Results submitted to FDA showed an overall response rate of 55%, including a complete response rate of 37% and a partial response rate of 18%. Median duration of response was 21.7 months. Common adverse events (AEs) included neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, pyrexia, peripheral edema, respiratory tract infection, and decreased appetite.1

Among non-Hodgkin lymphomas, DLBCL is the most common subtype, accounting for 22% of cases in the United States and 40% worldwide, with about 18,000 US cases per year. People at higher risk if they have HIV, an autoimmune disease, or if they have had an organ transplant. More common in older people, DLBCL can be very aggressive. Although well-known treatments have been developed, there are gaps—and a notable one is when DLBCL cannot be kept in remission after chemotherapy but the patient is not eligible for an autologous stem cell transplant. Some of these patients have had chimeric antigen receptor (CAR) T-cell therapy, but this process is costly with significant AEs.3

“The FDA approval of Monjuvi in combination with lenalidomide helps address an urgent unmet medical need for patients with relapsed or refractory DLBCL in the United States,” Hervé Hoppenot, CEO of Incyte, said in a statement.4 At Incyte we are committed to advancing patient care and are proud to bring this new and much-needed targeted therapeutic option to appropriate patients and the clinical community.”

FDA had previously granted the combination fast track and breakthrough therapy designations in this indication.2

REFERENCES
Don’t Delay Cancer Care During COVID-19 Crisis

AMY MCNALLY, MD

FOR MUCH OF THE GENERAL PUBLIC, avoiding coronavirus disease 2019 (COVID-19) is the most significant health issue they are having to face. Americans are consumed with the statistics surrounding new cases and deaths, while grappling with the social and economic impacts of the virus. Collectively we wait, try to protect ourselves and our families, and hope that a persistent downward trend will mean a return to normal life.

But even though safeguarding against and caring for Americans with coronavirus is of utmost importance, other deadly health conditions have not disappeared. When the dust from the COVID-19 pandemic settles, we will almost certainly see a silent and underrepresented casualty of the crisis: Patients with cancer whose diagnosis, access to care, and treatment have been negatively affected due to the pandemic response.

Both the federal government and state officials have implemented policies and safeguards to slow transmission of the virus. Perhaps most troubling in this new environment were the state moratoriums on “elective” surgical procedures. Lack of personal protective equipment (PPE) and inadequate supplies of dependable rapid COVID testing further forced hospitals, surgical centers, and health care systems to restrict access to care and services to anything other than emergent cases in many settings. The process has been chaotic and inconsistent, with major differences even existing within the same city between hospitals only miles apart.

As a practicing surgeon and chair of The US Oncology Network’s Surgery Advisory Council who works alongside more than 190 surgeons across the country, I have witnessed firsthand the abrupt and widespread impact these actions have had on the care of our patients. For many patients with cancer, surgery is the first step in diagnosis, if not a critical component of achieving cure. Surgical procedures do not have to be emergent to play an important part in a patient’s overall well-being and care. Thousands of nonelective surgical cases were cancelled or delayed in our network of surgeons alone.

Although the restriction of certain elective procedures has been critically necessary to reduce the risk of exposure and spread of the virus, to ensure adequate supplies of protective equipment, and to maintain capacity of beds and intensive care units, it has also affected the care of those living with cancer. Rising unemployment, loss of insurance, and delays in potentially diagnostic/curative surgical therapy will have the most immediate impact. However, I anticipate a longer-term impact due to those patients who remain at home fearful of avoiding workup of their cancer symptoms, unable to access their primary care providers or who are waiting for their cancelled cancer screening tests to be rescheduled. These disruptions in care will result in further strain on our health care system in the coming months and years due to an influx of patients presenting with advanced stage cancers. This in turn will lead to higher health care costs and missed opportunities for curative therapy.

The COVID-19 pandemic has forced all of us to reexamine how we approach cancer care in this country. As advocates for our surgical patients, and the cancer community at large, we acknowledge there is an urgent need for a broader understanding and agreement on how to best serve our patients in times of limited resources and significant public health risk. The patchwork of inconsistent policies and regulations from state to state and health care system to health care system has led to widespread confusion and, I fear, devastating impacts on patient outcomes and health care costs.

In response, surgeons across The US Oncology Network, which treats nearly a million Americans across 470 locations in 25 states each year, have developed guiding principles to inform lawmakers and health care leaders as they work together to ensure timely treatment for anyone who needs a surgery as part of their cancer care. First and foremost, a patient’s need for surgery should primarily be at the discretion of the surgeon.

As my patients’ surgeon, I am most well equipped to make decisions about the course of their care. It is crucial that cancer surgery or surgery for potential cancer be identified within their own category of prioritization and not as elective surgeries for these patients. As mandates on elective surgeries are lifted, cancer surgeries must be uniformly prioritized.

To avoid further unnecessary delays in care, insurance providers must extend prior authorizations for patients with cancer who had their previously scheduled procedures cancelled, and also preauthorize all patients who had their surgeries delayed or who not yet have a confirmed surgery date. Additionally, policy makers should consider options to bridge coverage gaps to ensure seamless cancer care for patients dealing with job loss or for patients already suffering with the logistical barriers of being uninsured during this crisis.

Furthermore, patients must feel confident that they can safely seek treatment. As surgeons in The US Oncology Network, we have rapidly adapted to our new COVID-19 reality in many ways to ensure the safety of our patients, our staff, and ourselves. We are embracing telehealth, establishing clinical guidelines, reconfiguring offices, and following recommended use of PPE. However, it is not the sole responsibility of the individual surgeon to ensure that adequate protective equipment and hospital resources are available to provide safe surgeries to our patients with cancer. Hospitals and surgical centers must take the necessary measures to protect our patients’ health and safety by, at a minimum, having adequate supplies of personal protective equipment and sufficient access to rapid COVID testing.

As we weather this crisis and move forward, we must heed the lessons we have learned. There have been many. There will be more to come. We should embrace this opportunity to sit at the table so we can learn how to provide better care for our patients and to minimize the cost to our society. As a cancer surgeon, we need a seat at the table.

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Amy McNally, MD, is the chair of The US Oncology Network’s Surgery Advisory Council. She is in practice with Minnesota Oncology.

REFERENCES
Choice Is Vital to Biosimilar Savings Picture, Panelists Say

TONY HAGEN

SEVERAL TRASTUZUMAB BIOSIMILARS have been launched this year, and 6 FDA-approved adalimumab biosimilars are lined up for launch in 2023, but a cornucopia of lower-cost therapies is not looked upon by providers as favorably as might be expected. The reason? Payer policies make it difficult for providers to use the lowest-cost biosimilars available. In a webinar hosted on July 20, 2020, by The American Journal of Managed Care® and The Center for Biosimilars®, a panel of experts discussed how industry dealmaking is affecting treatment decisions and the use of resources at the provider level.

FDA-approved biosimilars are not different from reference products in any clinically meaningful way. However, for business reasons, a payer may put a particular biosimilar on formulary because of a rebate it received from the manufacturer or high-pressure sales tactics used by a rival drug producer. Often, this means that providers must use the biosimilar that the payer requires—not the lowest-cost drug. For practices that work with multiple payers, each with different biosimilar preferences, this can be “a nightmare,” panelists said.

The webinar panelists were Ali McBride, PharmD, MS, clinical coordinator of hematology/oncology for The University of Arizona Cancer Center in Tucson; Kathy Oubre, MS, chief operations officer for Pontchartrain Cancer Center, with locations in Covington and Hammond, Louisiana; and Timothy Chiu, PharmD, BCPS, the pharmacist evidence analyst and strategist for hematology/oncology at Kaiser Permanente, based in Oakland, California. Jeff Prescott, PharmD, senior vice president, Clinical Communications, of MHI Life Sciences, served as moderator.

The Difficulty of Stocking Multiple Biosimilars

Stocking multiple biosimilar brands to satisfy the preferences of multiple payers is costly, and ensuring that payer preferences are followed requires the use of controls and staff interventions that would not ordinarily be needed for treatment decisions. “There’s a lot of work by nurses, pharmacists, and finance people to transition to biosimilars,” McBride said.

Financial risk is possible, too, for a practice that uses the wrong biosimilar brand and cannot get reimbursed for it, said Oubre. Her practice has implemented a signoff procedure to ensure that the preferred drug is given to a patient. “Payers are really taking an active stand in dictating the drugs we use,” she said. Payer preferences make it difficult for a medium-size practice like Pontchartrain to provide biosimilars to patients. “It presents a lot of operational challenges.”

In his ideal scenario, McBride said, payers would not decide what biosimilars could be used. The United States would follow a European-style model in which the preferred or recommended biosimilar is the lowest-cost biosimilar available. In Denmark, for example, a biosimilar company will win a tender for a medium-size practice like Pontchartrain to provide biosimilars to patients. “It presents a lot of operational challenges.”

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MRD Should Be More Widely Used in Clinical Care of MM, Report Argues

ADVANCES IN SCIENTISTS’ UNDERSTANDING of multiple myeloma (MM) and in the ability to assess minimal residual disease (MRD) have made the metric an important method to track the efficacy of therapy in clinical trial settings. Yet, a number of questions remain about how exactly MRD can be used in day-to-day practice.

In an article in the Journal of Hematology & Oncology, corresponding author Jesús F. San-Miguel, MD, PhD, and colleagues discussed challenges to implementation of MRD in patients with MM. San-Miguel is a professor at the University of Navarra in Spain.

The authors explained that traditional methods of testing and defining success in the treatment of MM have become outdated in the new scientific paradigm. They noted that some patients in so-called complete remission (CR) are at a higher risk of progression than others, a problem that can be overcome with modern evaluations like MRD.

“Therefore, the words ‘complete’ and ‘remission’ are misleading for many patients because they may interpret that, once [they have] achieved such status, the disease has been eradicated,” the authors wrote. “Thus, it becomes evident that more sensitive techniques are needed to detect measurable (formerly called minimal) residual disease persisting below CR.”

There are some pitfalls to minimal residual disease (MRD). One is the potential for false-negative MRD results due to sampling errors. The authors also reported that although an MRD-negative result is a good prognostic sign, it bodes most well for patients when the negative result can be reproduced after 6 to 12 months.

In advocating for broader use of MRD in a clinical setting, San-Miguel and colleagues wrote that MRD meets the criteria necessary for broad use. MRD supersedes the prognostic value of CR, and MRD status appears to be reproducible in different settings and using molecular and immunophenotypic methods.

The techniques for ascertaining MRD can be broadly classified into 2 groups: those focused on finding extramedullary disease, such as positron emission tomography (PET)/CT scans, and those focused on detecting intramedullary disease, either multiparameter flow cytometry (MFC) immunophenotyping or molecular assessment of immunoglobulin gene rearrangements. Next-generation flow (NGF) cytometry and next-generation sequencing (NGS) each represent advances in techniques for detecting intramedullary disease, though the authors said these methods can lead to false-negatives.

“Thus, further improvement in the sensitivity of NGF and NGS are warranted to optimize risk stratification based on patients’ MRD status,” they wrote. “PET/CT is currently the optimal method to evaluate the disease outside the [bone marrow], and there are ongoing efforts for its standardization.”

There are, however, some pitfalls to MRD. One is the potential for false-negative MRD results due to sampling errors. The authors also reported that although an MRD-negative test result is a good prognostic sign, it bodes most well for patients when the negative result can be reproduced after 6 or 12 months.

To bring MRD testing into the clinic, the authors recommended that MRD assessment only be performed when a bone marrow aspirate is collected to confirm complete remission and only when the results of the evaluation could be useful to make specific clinical decisions.

The authors noted that a number of different methods are being considered to evaluate MRD, but they said bone marrow samples remain the ‘gold standard.’

More broadly, San-Miguel and colleagues concluded that MRD is not only important for its prognostic value, but also because it will better enable precision medicine in an era of rising drug costs.

“We have experienced great progress, and now we need to optimize the use of highly effective drugs developed including immunotherapeutics,” the authors concluded. “This should be implemented early in the course of the disease in order to overcome the poor prognosis of high-risk patients, including those with persistent MRD after optimal frontline treatment.”

REFERENCE

Analysis Locates 2 Biomarkers for Multiple Myeloma

A RECENT STUDY HAS IDENTIFIED new biomarkers that appear to correlate to the clinical characteristics and prognosis of patients with multiple myeloma (MM).

The study appeared in the journal Cancer Cell International. Corresponding author Alii He, MD, PhD, of the Second Affiliated Hospital of Xi’an Jiaotong University in China, and colleagues worked to identify key genes involved in cell adhesion in MM, as cell adhesion plays an important role in the progression of the disease. Their findings could lead to important advances in the diagnosis and treatment decisions of patients with MM.

He and colleagues first set out to find differentially expressed genes (DEGs) using the National Center for Biotechnology Information’s (NCBI’s) mRNA expression profiles from the Gene Expression Omnibus GS65477 Dataset of bone marrow plasma cells. The authors used the NCBI’s GEO2R to perform the analysis (with cutoff criteria of P < .05 and |logFC| ≥ 1). Next, they performed Gene Ontology enrichment analysis and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis to determine the biological pathways and functions associated with the DEGs identified. The authors also screened hub genes and analyzed their prognostic and diagnostic values, among other analyses.

In total, the team identified 1383 DEGs, many of which appeared to be enriched in cell adhesion. A dozen genes were identified as hub genes, and an analysis of receiver operating characteristic curves showed that 8 genes were biomarkers for the diagnosis of MM: ITGAM, ITG82, ITG85, ITG85, CDH1, IL4, ITG49, and LAMB1.

Of those, further analysis showed that ITG49 and LAMB1 had prognostic values and clinical implications in patients with MM, the authors said. He and colleagues posited theories about how the 2 genes play a role in MM.

“[Gene set enrichment analysis] and transcription factor (TF) prediction suggested that MYC may bind to ITG49 and repress its expression and HIF-1α may bind to LAMB1 to promote its expression in MM,” the authors said. “Additionally, pan-cancer analysis showed abnormal expression and clinical outcome associations of LAMB1 and ITG49 in multiple cancers.”

Specifically, abnormal expression of LAMB1 has been linked with overall survival and disease-specific survival in a number of cancers, the authors said. That may have to do with its role in cancer progression.

“LAMB1 has a high protein level in high-grade gliomas, suggesting a possible correlation with tumor progression,” they said. “That’s more. LAMB1 was identified to take part in cell attachment and have the capacity to inhibit metastasis.”
Can Artificial Intelligence Detect Early-Stage Pancreatic Cancer?

IF ARTIFICIAL INTELLIGENCE (AI) could be used to identify patients with early-stage pancreatic cancer nearly 2 years before the disease becomes apparent, clinicians could catch the disease when it is easier to treat.

A virtual presentation on July 2 at the European Society of Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer 2020 suggested that using AI to comb through electronic health records (EHRs) to look for subtle signs that individuals often present with to their doctor in the years leading up to diagnosis is a possibility, but this effort will need a larger trial, the study authors said.

Pancreatic cancer is typically diagnosed in more advanced stages, when there are few treatment options and low survival rates. Fewer than 1 in 10 patients live 5 years or more after diagnosis. Globally, 458,918 new cases were reported in 2018,1 and in the United States, pancreatic cancer affects nearly 57,000 Americans annually.2

Nonspecific symptoms, including gastrointestinal issues and back pain, may begin more frequently in years prior to diagnosis, said the study authors. Other early signs are stool changes, itchy skin, poor appetite, and weight loss. Considered separately, these symptoms are unlikely to trigger further investigations.

The preliminary study used EHRs from the UK’s Clinical Practice Research Datalink, which collects deidentified patient data from a network of general practitioner practices. The primary care data are then linked to other health records, in this case, national cancer registrations.

The data set included information about 1378 patients aged 15 to 99 years diagnosed with pancreatic cancer from 2005 to 2010. Each patient was matched by age and sex to 4 individuals who did not get pancreatic cancer. Disease, symptom, and prescription drug codes for the 24 months prior to diagnosis were used to define 58 individual symptoms.3

The investigators said in a statement they used machine learning to create logistic regression and random forest models. These models were trained on 75% of the data and tested on the remaining 25%.

Early results showed that pancreatic cancer diagnosis could be accurately predicted for 60% of the patients younger than aged 60 years, with an area under the curve of 61%, sensitivity of 76%, and a specificity of 45%.4

“Our model has estimated that around 1500 tests need to be performed to save one life from pancreatic cancer,” said study author Ananya Malhotra, PhD, a research fellow in statistics at the London School of Hygiene & Tropical Medicine.

However, that sample size is not enough to make screening a reality just yet, she said. In addition, there is no reliable screening test using blood. The carbohydrate antigen 19-9 assay may detect an antigen released by pancreatic cancer cells, but that antigen is also released via other conditions and not expressed by every patient with cancer of the pancreas.

A minority of patients (about 4% to 7%) have a germline BRCA mutation, but overall, the number of patients with a particular molecular alteration are too low to carry out a clinical trial.

Still, Malhotra said the study shows “potential to narrow down the number of people we need to screen. We should be able to reduce this quite a lot further” by matching patients with pancreatic cancer to controls.

Malhotra added: “Pairing this predictive model with a noninvasive screening test, followed by scans and biopsies, could lead to earlier diagnosis for a significant proportion of patients and a greater number of patients surviving this cancer.”

A future study will compare patients with pancreatic cancer to controls from the general population, as the controls in this study had other types of cancer.5

REFERENCES


Companion Diagnostics in NSCLC Offer Substantial Survival Benefit, but Some Patients Still Miss Out

PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) who received a companion diagnostic as part of their initial treatment had a 3-fold greater survival benefit than those who were not tested—yet some patients still don’t get tested.

That is what authors found in a study published July 6, 2020, in The Oncologist. The investigators, who reported the study was the largest real-world study of its kind, said it confirms the frustration that surrounds precision medicine in cancer care.1

“Despite level 1 evidence supporting the benefits of biomarker-driven therapeutic approaches and consensus among national and international guidelines for the routine use of [companion diagnostic] testing in NSCLC, it is not clear whether this evidence has translated to practice in real-world settings,” the authors wrote.

The results are based on an analysis of information from the Flatiron Health database using patient records from 2011 to 2018. The authors are from divisions of Roche and from Peter MacCallum Cancer Centre in Australia. Roche funded the study; it acquired Flatiron for $1.9 billion in 2018.2

What impacts who gets tested and who does not? Authors say the data show women are more likely to be tested than men, smokers are less likely to be tested than nonsmokers, and Asians as a group are likely to be tested.

The study found that as of May 31, 2018, only 14,732 patients with nonsquamous NSCLC received a companion diagnostic test out of 33,742 adult patients eligible for testing in the Flatiron Health database. However, the percentage who received testing increased significantly over time: Only 21.7% of eligible patients with nonsquamous NSCLC were tested from 2011 to 2013, and 62.2% of these patients were tested from 2014 to 2018.

Companion diagnostic (CDx) testing identifies patients most likely to benefit from biomarker-driven treatments. Much of the promise in lung cancer...
Results in JNCCN Find Payer Coverage for Liquid Biopsies Improves, Gaps Remain

THE ROLE OF CIRCULATING TUMOR DNA (ctDNA) in cancer care has advanced quickly over the past 5 years, allowing doctors to select targeted therapies or identify why treatments aren't working. To some degree, payer coverage has followed, but it has lagged in important ways, according to research published in JNCCN—the Journal of the National Comprehensive Cancer Network.1

The National Comprehensive Cancer Network (NCCN) is a group of cancer centers that develops treatment guidelines considered to be the “gold standard” for payers.

Because coverage for ctDNA-based testing panels, also known as "liquid biopsies,” can dictate access, authors from the University of California San Francisco (UCSF) and City of Hope in Duarte, California, examined how coverage had changed over time as clinical adoption increased.

Using the Canary Insights database to analyze 40,000 medical policies from both commercial and public payers, the authors found that coverage increased 38% between January 1, 2015, and July 1, 2019.

Highlights of their findings include the following:

• None of the policies provided coverage in 2016, but 38% did by mid-2019.
• The scope of policies increased from a single cancer type in 2017 to 12 types of cancer and from a single gene to 73 genes.
• The review found a trend toward use of testing across all cancer types, which the authors described as “an important shift.”
• Forty-five payers had specific policies barring coverage.

"Genomic ctDNA or liquid biopsy tests hold great potential to improve patient outcomes, although, as with any emerging test, it can be challenging to develop the most appropriate coverage policies,” said lead investigator Michael P Douglas, department of Clinical Pharmacy, UCSF Center for Translational and Policy Research on Personalized Medicine, said in a statement.2 "We think that the increased coverage, especially Medicare coverage of pan-cancer use, will expand the use of liquid biopsy in clinical practice in the future. The hope is that results in more targeted care with better treatment and diagnostic options, leading to long-term benefits.”

The investigators noted a difference between the highly specific nature of policies in private plans compared with draft and future-effective local coverage determinations with Medicare Administrative Contractors, which offer policies that will cover Medicare beneficiaries and testing across different cancer types (pan-cancer use). Among the private plans, 87% were for non-small cell lung cancer (NSCLC), 47% were for EGFR testing, and 79% were for specific brand-name tests.

The authors describe the “conundrum” in payer coverage given how these blood-based tests are used. The ctDNA test can be used at the time of diagnosis to find genomic alterations to direct targeted therapy and if the disease progresses to determine “the mechanism of therapeutic resistance.”

"The NCCN Guidelines for Non-Small Cell Lung Cancer currently state that ctDNA testing can be considered for monitoring purposes when a patient with a confirmed lung cancer diagnosis is medically unfit for invasive tissue sampling,” said David S. Ettinger, MD, of The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, who chairs the NCCN Guidelines for NSCLC panel. Ettinger was not involved with this study. »

REFERENCES

“Although coverage is expanding, it still takes too long to adapt policies, which often vary from state to state,” he said. “We recommend specific testing be conducted as part of a broad molecular profiling, at least for advanced or metastatic disease.”

Ettenger said a liquid biopsy can take less time than a diagnosis based on a tissue sample, and if positive, the liquid results are “unambiguous” and can direct clinical decision-making. If negative, there is a 30% chance the ctDNA results are not accurate, so a tissue sample should follow.

REFERENCES

OneOncology Appoints John Fox, MD, Medical Director of Managed Care

ONEONCOLOGY, A NATIONAL PARTNERSHIP of independent oncology practices, announced on July 20, 2020, the appointment of John Fox, MD, as medical director of managed care. In his role, Fox will work with OneOncology partner practices to develop, evolve, and maintain value-based contracts with commercial and public payers.

“As the transition from fee-for-service to value-based contracts continues, Dr Fox will play an integral role in supporting partner practices to develop and optimize value-based care to achieve Quadruple Aim goals,” said Jeff Patton, MD, OneOncology’s CEO.

OneOncology is a Strategic Alliance Partner of The American Journal of Managed Care®. Fox is a member of the editorial board of Evidence-Based Oncology™.

As community oncology practices transition to value-based care delivery through the implementation of alternative payment models, OneOncology supports its partner practices’ capacity for change through public policy advocacy and thought leadership, commercial health plan contract negotiation, and physician engagement and education initiatives.

OneOncology partner practices have collectively managed about 4500 episodes of care in each performance period of the Center for Medicare and Medicaid Innovation’s Oncology Care Model (OCM). OneOncology partner practices also participate in several commercial health plan value-based payment arrangements. OneOncology provides a scalable platform for generating insights, sharing best practices, and benchmarking key performance metrics among several of the most progressive practices in value-based care.

“I’m excited to join OneOncology and apply my experience to help ensure that partner practices continue to succeed transforming from volume to value,” said Fox. “OneOncology has been at the forefront of understanding the OCM and helping to shape Medicare’s next value-based oncology care model. Applying our OCM experience and aligning through all commercial value-based contracts will help drive success for patients, providers, employers, and payers.”

Fox was most recently vice president and associate chief medical officer for medical affairs at Priority Health. His initiatives included shared decision-making, advanced care planning, integrated specialty pharmacy program and value-based benefit designs, and payment reform strategies, including oncology medical home initiatives and bundled payments.

NCCN Patient Guidelines Highlight Adverse Effects of Immunotherapy, CAR T-Cell Therapy

ALTHOUGH IMMUNOTHERAPY has become an important treatment option for some cancers and is often well tolerated, it can have different adverse effects (AEs) than traditional approaches, such as chemotherapy. The National Comprehensive Cancer Network (NCCN) recently released a new set of guidelines to help patients and caregivers understand the unique and severe AEs of immune checkpoint inhibitors (ICIs), a common type of immunotherapy.1

The patient guidelines provide information on the evidence-based, expert-consensus clinical practice guidelines used by health care providers—but in consumer-friendly language so patients and caregivers can better understand treatment options.

“Immune checkpoint inhibitors have revolutionized our approach to the treatment of cancer,” John A. Thompson, MD, professor of medicine at the University of Washington and chair of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities panel, said in a statement. “ICIs are now approved by the FDA for treating more than a dozen forms of cancer, and the list is growing every year. However, by virtue of stimulating the patient’s immune white blood cells, ICI therapy sometimes causes serious [adverse] effects that mimic autoimmune disease, including significant rash and/or inflammation of the thyroid, liver, lungs, nervous system, glandular system, heart, or other organs.”

The guideline explains that immune-related AEs can start during or after immunotherapy, but most can be managed if identified and treated early.

NCCN also released patient guidelines on the AEs of chimeric antigen receptor (CAR) T-cell therapy. Olalekan Oluwole, MD, of Vanderbilt-Ingram Cancer Center and a member of the NCCN Guidelines for Management of Immunotherapy-Related Toxicities panel, explained that traditional chemotherapy attacks all cells and can leave patients with long-term complications, such as other forms of cancer, but CAR T-cell therapy attack cancer cells in a different and more targeted way.

“The targeting is akin to a heat-seeking missile that won’t stop until it takes out any cell with the target, leading to potential long-term or permanent remission,” Oluwole said in a statement. “CAR T is given one time, unlike chemotherapy, which is given over multiple cycles and could go on for months or years. However, patients are often surprised to learn that the single CAR T infusion includes a 28-day monitoring period during which they need to stay in close proximity to their treatment center.”

Patients are monitored for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In CRS, immune cells affected by the treatment release cytokines into the blood, which creates an intense systemic inflammatory response. In ICANS, there are a range of neurological AEs. However, both CRS and ICANS can be reversed if treated promptly, which is why patients are monitored closely following treatment.

“CRS can set in rapidly, pushing the patient’s body to very high temperatures and taking quite a toll,” said Oluwole. “However, we researchers are learning more about how to collaborate to predict toxicities and sharing knowledge on recognizing and treating them more quickly. The new NCCN Guidelines for Patients are yet another example of how we’re sharing this important information.”

REFERENCES
Selinexor Is Approved Under Accelerated Pathway to Treat DLBCL

The FDA granted accelerated approval to selinexor (Xpovio, Karyopharm Therapeutics) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The oral treatment is to be used after at least 2 lines of systemic therapy.

The approval was based on response rate as determined in the SADAL trial, a multicenter, single-arm, open-label trial in patients with DLBCL who had received 2 to 5 systemic regimens.

“For the significant number of patients with relapsed or refractory diffuse large B-cell lymphoma there is an important need for new therapies for this particular vulnerable patient population.”

—John P. Leonard, MD, Richard T. Silver Distinguished Professor of Hematology and Medical Oncology, Weill Cornell Medicine

The most common adverse events (AEs) were fatigue (63%), nausea (57%), decreased appetite (37%), and diarrhea (37%). Most AEs were grade 1 and 2. The most common treatment-related AEs were cytopenia and gastrointestinal and constitutional symptoms.

“For the significant number of patients with relapsed or refractory DLBCL, there is an important need for new therapies for this particularly vulnerable patient population. Unfortunately, despite often multiple types of chemotherapies and targeted drug combination therapy, many patients have disease that continues to progress,” said John P. Leonard, MD, the Richard T. Silver Distinguished Professor of Hematology and Medical Oncology at Weill Cornell Medicine and an oncologist at NewYork-Presbyterian/Weill Cornell Medical Center, and a paid consultant to Karyopharm.

Because the approval was based on response rate under the FDA accelerated approval program, continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Selinexor will become commercially available immediately, according to Karyopharm, which plans to submit a marketing authorization application to the European Medicines Agency in 2021 for the therapy to treat relapsed or refractory DLBCL.

Selinexor is already approved in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma in adults who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody.

The most common adverse events (AEs) were fatigue (63%), nausea (57%), decreased appetite (37%), and diarrhea (37%). Most AEs were grade 1 and 2. The most common treatment-related AEs were cytopenia and gastrointestinal and constitutional symptoms.

“The accelerated approval of oral Xpovio in patients with relapsed or refractory DLBCL is a significant milestone for the patients and families who currently have limited treatment options available for their disease,” Sharon Shacham, PhD, MBA, founder, president, and chief scientific officer of Karyopharm Therapeutics Inc., said in a statement. “This approval marks the first for an oral agent for patients with previously treated DLBCL and the first approval of any single drug for this highly aggressive type of lymphoma.”

The phase 2b study evaluated 134 patients who were given 60 mg of selinexor orally twice weekly for a 4-week cycle. The study had an overall response rate (ORR) of 29%, including 18 (13%) complete responses and 21 (16%) partial responses. Of the 39 patients who achieved a partial or complete response, 38% had a response duration of at least 6 months and 15% had a response duration of at least 12 months. ORR and response duration were assessed by an independent review committee.

The approval was based on the disease control rate, which was 69% (95% CI 59, 78), the complete remission rate of 60 adults with refractory or relapsed MCL who were followed for at least 6 months after their first objective disease response. The complete remission rate after treatment was 62%, and the objective response rate was 87%.

That trial’s lead investigator, Michael Wang, MD, professor in the Department of Lymphoma and Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Center, said that advances in MCL have nonetheless left treatment gaps for some patients after initial therapy.

“Many patients have high-risk disease and are more likely to keep progressing, even after subsequent treatments,” Wang said in a statement. “The availability of Tecartus as the first-ever cell therapy for patients with relapsed/refractory MCL provides an important option with a response rate of nearly 90% and early clinical evidence suggesting durable remissions in later lines of therapy.”

This is the second CAR-T cell therapy approval for Kite Pharma. The company previously received approval for axicabtagene ciloleucel (Yescarta). Both therapies are subject to a Risk Evaluation and Mitigation Strategy due to the possibility of cytokine release syndrome and neurologic toxicities.

MCL is a form of non-Hodgkin lymphoma occurring in cells from the “mantle” zone of the lymph node. It is an aggressive cancer that mostly affects men 60 years and over.

FDA gave brexucabtagene autoleucel priority review and breakthrough therapy designations, and the treatment was handled through the accelerated approval pathway. It also received orphan drug status, with granted financial incentives to encourage drug development.

REFERENCES
PATIENT EXPERIENCE

Overcoming Racial Biases in Patient Care

JEFF BENDIX, MA

JAMES ELLZY, MD, FAAFP, is a board-certified family physician, an assistant professor at the Uniformed Services University of the Health Sciences and served for 22 years in the US Navy, where he attained the rank of captain.

In spite of his sterling credentials, Ellzy, who is also a board member of the American Academy of Family Physicians (AAFP), said he frequently encounters double-takes the first time he meets with patients at his clinical practice at the Fort Belvoir Family Medicine Residency in Virginia. In part, he said, the response is due to looking younger than his 49 years. But mostly it’s because he is Black, while many of his patients are White.

“It’s not that these patients are overtly racist or necessarily aware of holding any biases against Blacks. Still, he added, “I notice the look on their face when I first meet them that says, ‘this isn’t who I was expecting to see.’”

The “this isn’t who I was expecting to see” reaction is an example of what psychologists and others who study human behavior call “implicit bias”: the unconscious, usually negative assumptions humans make about others they perceive as being in some way different from themselves.

While implicit (or “unintended”) bias affects nearly everyone, its consequences are especially significant in medicine. Because the majority of physicians are white and male, the unconscious assumptions they may hold about patients who are neither white nor male can lead to inappropriate treatment decisions, and on a larger scale, worsen disparities in health outcomes.

The good news is that as understanding of implicit bias grows, so do techniques for combatting it. Increasing numbers of health care institutions, physician organizations, and medical schools are developing training programs to help doctors recognize unintended bias and prevent it from affecting their medical decision-making.

JAMES ELLZY, MD, FAAFP
assistant professor, Uniformed Services University of the Health Sciences

MICHELLE VAN RYN, PhD
assistant professor, Oregon Health and Sciences University School of Nursing

Louis Penner, PhD, professor emeritus, Department of Oncology, Wayne State University School of Medicine

Although this form of information processing is highly efficient—and indeed vital to humans’ ability to function on a day-to-day level—psychologists note that it comes with a significant drawback: some of the information it takes in produces, or reinforces, negative stereotypes about others based on attributes such as their race, gender, ethnicity, and sexual orientation.

Michelle van Ryn, PhD, MPH, a professor at the Oregon Health and Sciences University School of Nursing who has studied and written extensively about stereotypes and implicit bias, cited the example of an experiment where 2 groups of White people were given an account of the same crime, except that in 1 account the criminal had a name usually associated with Blacks. The people in the group reading that account were more likely to recall the violent aspects of the crime than was the group who assumed the criminal was White, she said, which in turn reflects the pervasive images of Blacks as violent criminals in the news and entertainment media.

“So implicit biases are basically this [learning] system applying whatever information it’s learned, even if it’s negative and inaccurate, to whole groups of people,” she explained. Moreover, unless the process is interrupted, the brain will engage in confirmation bias by focusing on events or actions confirming what we think we already know about those groups, van Ryn said.

UNEQUAL TREATMENT,UNEQUAL OUTCOMES

The impact of unintended bias, both in individual physician–patient encounters and outcome disparities, has been well-documented in research studies, most notably in an influential 2003 Institute of Medicine report on racial and ethnic disparities in health care. It found evidence that “stereotyping, biases and uncertainty on the part of health care providers can all contribute to unequal treatment.” Moreover, even White clinicians who don’t believe they are prejudiced “typically demonstrate unconscious implicit negative racial attitudes and stereotypes.”

More recently, a 2016 study in the Journal of Clinical Oncology examined interactions between Black patients and White oncologists who had been administered a test for their levels of implicit bias.

It found that oncologists who rated higher in implicit racial bias had shorter interactions with their patients, and their patients rated the interactions as “less patient-centered and supportive” than those with less implicit bias. The study also found links between a physician’s bias level and their patients’ confidence in recommended treatments and more perceived difficulty in completing them.

Louis Penner, PhD, professor emeritus in the oncology department at Wayne State University School of Medicine and lead author of the study, noted that the results highlight another harmful result of implicit bias: patients are able to recognize their physician’s attitude and, as a result, become less likely to adhere to treatment recommendations.

“One of the effects we and other researchers have demonstrated in a variety of medical contexts is that if the doctor is high in implicit bias, the patient leaves the interaction with the feeling that the doctor doesn’t really care about them, they don’t trust the doctor, and the treatment may not work,” he said.

In the case of cancer treatment, with its expense and unpleasant adverse events, the result may well be high rates of nonadherence.
or sometimes stopping treatment entirely—outcomes which can, in turn, shape doctors’ treatment decisions.

“When happens in a lot of cases is black patients are underdosed and the rationale many physicians give is, ‘the patient’s probably not going to do the treatment anyway, so why should I make him that sick?’” Penner explains.

Accepting the Reality of Implicit Bias

While many people have difficulty acknowledging that their actions are influenced by unconscious biases, the concept is particularly troubling for doctors, who have been trained to view—and treat—patients equally, and the vast majority of whom sincerely believe that they do.

“Doctors have been moulded throughout medical school and all our training to be nonjudicial when it comes to treating patients,” said James Allen, MD, a pulmonologist and medical director of University Hospital East, part of Ohio State University’s Wexner Medical Center. “It’s not only asked of us, it’s demanded of us, so many physicians would like to think they have no biases. But it’s not true. All human beings have biases.”

“Among physicians, there’s a huge stigma attached to any suggestion of racial bias,” added Penner. “And were a person to be identified that way, there could be very severe consequences in terms of their career prospects or even maintaining their license.”

Ironically, as Penner and others pointed out, the conditions under which most doctors practice today—high levels of stress, frequent distractions, and hurried visits that allow little time to get to know patients—are the ones most likely to heighten their vulnerability to unintentional biases.

“Individuals under pressure are more likely to use mental shortcuts, such as using stereotypes,” Penner said.

A doctor under time pressure from a backlog of overdue charting and whatever else they’re dealing with will have a harder time treating all patients with the same level of empathy and concern,” van Ryn said.

Learning to Minimize the Impact

So what can physicians and health care organizations do to address these biases? Because the process that produces them is “hard-wired,” eliminating them is next to impossible, experts say. Instead, the focus should be on reducing their impact on doctor-patient interactions and medical decision-making. And that process begins by just recognizing that they exist, says Preshushee Thompson, a training and development specialist at the Kirwan Institute.

“Sometimes you become aware of your biases, you can kind of bring them to your conscious mind and be able to say, ‘I know I have this bias, so I’ll keep it in mind while I’m working with this patient, or I know that some circumstances make me more susceptible to my implicit biases so I’ll try to avoid those when I’m making decisions about my patients,’ ” she said.

Conversely, according to Barnett, “If you’re not going to acknowledge those biases, then you’re going to continue to allow your brain to work on autopilot and be influenced by them.”

Equally important is finding each patient’s unique qualities or features, thereby making it easier to see them as an individual rather than part of a faceless group. Penner cites the example of a White physician’s initial encounter with a patient who’s Black.

“If that doctor views the patient simply as a Black woman, the possibility that the doctor’s implicit bias will be activated is much greater than if she’s seen as Mrs Brown, a retired school teacher and the mother of 4 children. So he’s not looking at a social category, he’s looking at an individual,” Penner said.

“No one is immune to this”

People who have conducted training in identifying and addressing implicit bias also find it helpful to emphasize its pervasiveness.

“No one is immune to this, even those of us with the most egalitarian goals of fairness and equality,” said Danielle Jones, MPH, manager of the AAFP’s Center for Diversity and Health Equity.

“When you frame it from that perspective, I think it makes people a lot less defensive and more open to having a conversation around, ‘what are my biases, and what can I do to address them’?” That was true for Ohio State’s Allen, who earlier this year participated in a university-sponsored training session on implicit bias, an event he approached with some trepidation.

“I had this fear there were these dark sides of me that I was not aware of and that the training would make me discover that I’m a bad person without realizing it,” he recalled. So he was pleasantly surprised to find that wasn’t the goal of the training, but rather to explore different forms of bias and how to overcome them.

Allen attended the training to learn how to work better with his colleagues, who hail from a wide variety of ethnic, national, and religious backgrounds. But he soon found that it also changed how he relates to patients.

“I think it has resulted in my taking more of a shared decision-making approach in caring for my patients, rather than paternalistically dictating what the patient has to do,” he said.

“Now, I’m more sensitive to personalizing care plans depending on whether the patient wants to be more aggressive or less in their treatment.”

Another useful technique for reducing the impact of unintentional bias is by undermining stereotypes. For example, in her group training sessions, Jones might present a case study about a Black patient who’s frequently late to appointments and ask participants to discuss factors that might account for the patient’s behavior, such as difficulty finding reliable transportation.

“The goal is to find additional information or context to minimize the immediate reaction of assuming that the stereotype is true,” Jones said.

Jones encourages doctors to practice mindfulness as a way of counteracting the bias that can result from not being able to spend much time with patients. The situation may lead to assumptions—or what Jones calls “mental shortcuts”—about patients.

“These mental shortcuts are where bias kind of sneaks in,” she explained. “So when we talk about mindfulness we’re trying to make doctors aware this could be happening, and get them to maybe consider alternatives in their clinical decision-making and patient interactions.” Doing so, she added, can also help physicians develop empathy for, and build relationships with, their patients.

Although not attributing it to mindfulness, Allen said that as a result of his training he now makes a point of chatting with patients about what’s going on in their lives, such as what they did on vacation or how their children are doing. Such conversations usually add no more than a minute or two to the visit, and Allen feels it is time well spent.

“It allows me to build those ties that come from showing my interest in them as unique people,” he said. “And hopefully it lets them see that I care about them as a person and not a bunch of skin and bones that happens to have a disease.”

AUTHOR INFORMATION

Jeff Bendix, MA, is the senior editor of Medical Economics.

REFERENCE


COVID-19 and Cancer: NY Patients See High Hospitalization Rates, Poor Outcomes

Read more at: https://bit.ly/30nviM
Key Steps to Reduce Racial Cancer Disparities Include Supporting Minority Scientists, Diversifying Medical Schools and Clinical Trials

Evidence-Based Oncology™ is pleased to share a set of interviews that first appeared on the MJH Life Sciences™ broadcast channel, Medical World News®. Senior Editor Christina Mattina of The American Journal of Managed Care® (AJMC®) discussed the root causes of racial inequalities in cancer care with a pair of experts: John Carpten, PhD, professor and chair of Translational Genomics at the University of Southern California Keck School of Medicine, Los Angeles, California, who outlined the necessary steps to improve cancer outcomes for minority populations and support minority scientists; and Russell Ledet, PhD, president of The 15 White Coats and a medical student at Tulane University School of Medicine in New Orleans, Louisiana, who explained the steps to breaking down barriers to medical school for those in marginalized communities.

*Interviews by Christina Mattina*

These interviews have been edited lightly for clarity.

**JOHN CARPTEN, PHD**

AJMC®: Welcome. Can you introduce yourself and tell us about your work?

**JOHN CARPTEN, PHD:** My name is John Carpten, professor and chair of the USC Department of Translational Genomics. I’m also program co-leader for the Norris Comprehensive Cancer Center, Translational and Clinical Sciences Program. My research interests primarily center around human genetics and genome science.

Throughout my career I’ve had a strong focus in the area of cancer research, including cancer genomics, cancer cell biology, precision oncology, and I’ve also spent a large portion of my career trying to understand what we tend to consider or call cancer disparities, which are cancers that disproportionately affect underrepresented minorities and the medically underserved.

**AJMC®:** What are some root causes of racial inequities in cancer care?

**CARPTEN:** Some of the root causes of inequities and cancer care, again when we look at underrepresented minorities or the medically underserved, tend to sort of center around socioeconomics and limitations in access to quality health care. A lot of this, of course, is due to systematic racism, which has sort of created this built environment, this environment that many individuals, particularly those from underrepresented communities, reside within, where there’s limited access to quality care, there’s no strong focus on actual health care itself, on being a healthy individual. When we think about access to detrimental environmental factors, you think about certain areas where you see a significant increase in signs for cigarette smoking, signs for alcohol, and so this built environment that many individuals live in contributes significantly to these inequities that we see in health care, particularly cancer care.

Of course, the financial issues, financial toxicities—when we think about something like cancer care, can be typically really expensive. And so when we think about access to the best diagnostic methods, the best treatment options, in many cases, those things are dictated by access to private insurance or access to specific types of insurance or access to significant financial resources, which we know in many cases are not in alignment with these communities and these populations. Much of this is socioeconomics, financial issues, and financial toxicities. And then I think, of course, a lot of this is brought about through overall systemic racism and social injustices in America. I think we should also consider additional issues, when we think about these sort of inequities that we see, that again are just related to the overall systematic limitation in resources [and] overall resources in general, play a huge role.... Now, I think we can also point to policy, and the lack of push toward policies that will sort of lead to improvements in these environments and in these communities, which could then perhaps turn the table and provide individuals with the type of health care that they deserve as citizens of this country.

**AJMC®:** How do racial inequities in research lead to disparities in outcomes and mortality?

**CARPTEN:** Racial inequities in cancer research also contribute to some of the differences we see in incidence and outcomes. When we think about cancer and we think about cancer disparities, I think there are a number of things that we can point to. One is the whole issue with a lack of diversity in clinical trials—that’s one place where we can start, where many of the therapies that are developed, whether they’re therapeutic modalities that are based on improving standard of care in combination with chemotherapy, or whether they’re clinical trials to test some of the latest and greatest types of cancer therapies. In many cases, we know throughout the continuum of clinical development from the model systems that are used for early testing of these agents in animal systems, the actual tumors that are growing in the mice are typically not derived from individuals of largely European descent, and then we move on to phase 1 clinical trials, which are small trials, typically, that are in most cases going to take place within cancer centers, in academic medical centers. In many cases, the patient populations there are just not diverse at all. And then of course, we move on to the phase 2 and phase 3, the larger trials—those trials that actually are going to be those definitive clinical trials that are going to lead to an FDA approval.

We know that particularly when we look in cancer, the overall number of underrepresented minorities in those trials is infinitesimal—and this is even for cancers that have known disparities and incidence and outcomes: prostate cancer, triple negative breast cancer, colorectal cancer. We see typically numbers below 5% and sometimes below 3% in terms of the sort of the minority individuals that make up the clinical trial cohorts. That’s 1 of the big problems.
And just to expand on that just a little, I think we don't necessarily have to look at it as “Oh, we want to diversify the trials just because we want more minorities.” I think we have to look at it from the standpoint that by diversifying the cohort, we learn more about the efficacy of the therapy, right, or perhaps the toxicity profile. We shouldn't have to wait until the drug is approved and then used in practice to say, “Oh, we see a difference in sort of toxicity profile or we see a difference in the effect of this drug across different populations.” That should be built into the trials and from my perspective, by diversifying trials, we help everyone.

It's not just diversifying trials just so that we can potentially help individuals from these underrepresented minority populations, but by studying a sort of broader group of patients from the standpoint of populations, communities, perhaps we gain a broader breadth and depth of the activity of that therapy when it's being used to treat patients with cancer. That whole concept of lack of diversity in clinical trials is one of the things that hampers our ability to really eliminate and deal with some of these disparities.

“We shouldn't have to wait until the drug is approved and then used in practice to say, 'Oh, we see a difference in sort of toxicity profile or we see a difference in the effect of this drug across different populations.' That should be built into the trials and from my perspective, by diversifying trials, we help everyone.”

—John Carpten, PhD
professor and chair of Translational Genomics, USC Keck School of Medicine

I think the same thing can be said for the tools and the reagents that we use in biomedical research to understand the biology of cancer. Again, going back to some of the comments I made about clinical trials, the model systems that we use, the cell lines that we use, in many cases, are cell lines that are not diverse. They weren't derived from individuals from diverse backgrounds. So, the understanding of the biology of cancer tends to be derived from a relatively homogeneous set of reagents. And so, expanding the diversity in the biological reagents that we use for cancer research, again, could broaden our understanding of cancer and get us away from this concept of generalization if we, whatever we understand here is going to generalize over here, and that may not necessarily always be the case. I think we also see this in, for instance—I have a tremendous amount of interest in cancer genomics and that may not necessarily always be the case. I think we also see this in, for instance—I have a tremendous amount of interest in cancer genomics and the genomic alterations and changes that occur in cancer. Many of the tumors, again, were derived from largely European individuals. And we know that the diversity of those biomedical research cohorts is also significantly limited, again, even when we think about tumor types that disproportionately affect African Americans, Black and brown people, Hispanic Latinos, and so on and so forth.

So, thinking about clinical trials, thinking about these research reagents, and then finally, the workforce—we know that there has been a significant limitation in the numbers of underrepresented minority faculty members at large academic medical centers, where a lot of the health care innovation occurs. And then we can continue to move back in the career path trajectory as we go back to the early stage scientists, the postdoctoral fellows, the graduate students, undergrads, and then even high school students, right, who have access to internships in STEM [science, technology, engineering, and math]-related fields. We know that there are disparities there, and so if we don't break down those barriers, we'll continue to have this relatively homogeneous, relatively nondiverse workforce, and so that also plays a huge role in the disparities. I think that we can point to a number of areas where that can impact, but when we think about things like having access to, for instance, patient navigators or having access to individuals who work in the health care system, who can help provide and communicate most effectively with patients to educate them to help them better understand their particular medical issue, can better help them better understand their diagnosis or the various treatment options. So, because we have this workforce that's relatively homogeneous, and we really need to do a better job of diversifying our workforce. All of these things, I believe, play a significant role in cancer disparities.

AJMC®: Are there any other things that need to happen to improve cancer outcomes for minority populations?

CARPTEN: Well, I think one of the main things, and without a doubt, even though my focus is biology and trying to understand the biological factors that are driving these disparities, I think it all starts with policy. It all starts with sort of resources and access to resources, right, and equal access to resources. And, so, of course, you know, we have to get out and vote, we have to lobby our members of Congress, we have to work with patients, patient advocates, right, who have relationships with those individuals who actually can create and change policy. I think that that to me is first and foremost. Going back to the whole concept of doing a better job of diversifying the workforce, I think that's another huge issue. When we look back over time, we've made some progress, but the progress definitely hasn't been substantial enough, where we can really say that we've made a significant difference. Policy is a big deal. I think one of the other things is bridging disciplines, so bringing together individuals from various disciplines and creating transdisciplinary and multidisciplinary research programs where we bring in individuals who study the environment or environmental factors, individuals who study social stressors in the built environment, and how the environment and the societal pressures can impact physiology in a negative way, such that it sort of breeds an internal host environment, that if a cancer manifests, it's in the perfect environment to thrive. And so, I think the whole concept of interdisciplinary and transdisciplinary research will probably be part of the answer. And we have to break down the barriers, break down the walls, and break down the silos, and begin to work together and come up with novel study designs that bring to bear various disciplines to address these issues.

AJMC®: What specifically can cancer research centers do to support the needs of minority scientists?

CARPTEN: One of the biggest issues in terms of cancer centers and minority scientists is that there just aren't enough of us. I think we can look at this in 2 ways. We can look at it from the standpoint of the pipeline, right, and really working harder to increase the size of that pipeline—providing the types of educational programs for underrepresented minority students to get access to innovation, to be involved in innovation, to be a part of innovation.... And I think one of the problems is when we see many of these programs, in many cases, the students are separated, right? You may have a special program for underrepresented minority students, but you don't have mainstream students involved, right, so we tend to see these siloed programs. I think we need to develop programs where the students are all working together and learning how to collaborate and how to communicate with each other, and how to come up with innovative and novel ideas on how to solve problems. So I think coming up with better ways to build a more robust and effective pipeline, so that we can feed the students into the process, but I think we also have to look at the back end of the pipeline when the students become graduate students, and then postdoctoral fellows or faculty members, that we provide the type of environment to support their career development, again at the fellowship level, as well as at the faculty level, that they have the appropriate mentoring in place, that they have the appropriate role models in place, that resources are available for them to support their careers. So, we have to work on building a more robust pipeline, but at the same time, we have to ensure that the appropriate environments are being created in those cancer centers to support retention of the faculty that we hope to recruit into these centers.
Russell Joseph Ledet, PhD

Can you introduce yourself and tell us about your work?

My name is Dr. Russell Joseph Ledet. I'm currently the president and co-founder of The 15 White Coats. We are an organization that aims to promote cultural imagery and learning spaces, because we realized that we had an opportunity to leverage that attention for good. We've used this to capture just how far we've come and the experience itself. And so, after we had this experience, and we took these photos, we got an idea... I think we should get together a couple of my Black classmates, and we both went to historically Black colleges and universities—similar labs as I, and so we both went to historically Black colleges and universities—he went to North Carolina A&T and I went to Southern University in Baton Rouge, Louisiana—and so Black history is important to us. And so when he came down to visit, and we decided to go to the Whitney Plantation, and I brought my daughter along, and it's about 45 minutes outside of New Orleans. (Whitney Plantation is in Edgard, Louisiana, in St John the Baptist Parish.)

So on our ride back, about 15 minutes down the road, my daughter sort of interrupted me and asked this question, she was like, “Dad, you know, it’s interesting that we just left a plantation, and, you know, I’m riding in the car with 2 Black doctors.” And I’m like, “Well, why is that such a big deal?” And she’s like, “Well, just think about it.” Like there was a time when we couldn’t do that. There was a time when we couldn’t be lawyers, accountants, firefighters, any of those things, right? So, she really understood the moment and also the historical context. And so, essentially, from that, I looked over and I was like, Yeah, I got an idea...I think we should just get together a couple of my Black classmates, and we should go and take a photo.

Obviously, there was more to it than just taking a photo. There was also the experience itself. And so, after we had this experience, and we took these photos, the idea behind the photos was for us to capture just how far we’ve come, and even more so our resilience with coming back from that. And so, we released those photos, those photos got a ton of attention, and because of that, we realized that we had an opportunity to leverage that attention for good. And so, because of that, we formed the company and the idea behind the company was to promote cultural imagery and learning spaces, because we realized, it’s kind of hard to be something that you’ve never seen before. That’s half the challenge. And the other part is, too, that it was a sense that we’ll get past these issues. We’ll get past these circumstances, the systemic racism, institutional racism, systemic oppression... and we’ll still get to where we want to because, everyone’s knowledgeable of the esteem doctors are held in the United States specifically. And so, I think that’s what captivates a lot of people’s attention is that they saw 15 budding, bright-minded student physicians, who also happened to be Black.

So that was really captivating for a lot of people, and because of that we formed the organization. We put the photo up in classrooms throughout the country. We sell the photos, and nobody earns any of money from the from the proceeds. We take all of that and put it toward scholarships for minorities applying to medical school, high schools, students graduating high school, medical school... [We] also use the money to buy more posters to send out to classrooms, so schools can go to our website, sign up for a poster, and we’ll mail it out to them for free.

What are your hopes for the organization?

The hope for the organization is for us to eventually be able to pay for someone’s medical school, specifically someone from the minority community, to raise enough money to offset some of the costs that come with applying to medical school. You know, if you take into account the historical economic perspective for marginalized communities, we know that those communities are well behind in terms of opportunity to gain wealth, opportunity to maintain wealth, especially with things like the Tulsa, Oklahoma, massacre [of 1921] and things of that nature, we know of all the situations in which even when marginalized communities tried to gain wealth, it was stifled. So, we have to do something to try to offset that economic barrier. People don’t even know how much it costs to apply to medical school; in general, costs between $3500 and $10,000. That’s a lot of money just to apply. If you take that into account, and then you take into account a lot of your students are already in debt from undergrad, where you can come up with that kind of money? And so we want to try to take some money that we have and alleviate some of those costs. Then the other part of it, too, is that once you get into medical school, there are a lot of costs that come with being in medical school, whether it is some of the learning platforms you need to learn the material for school, or having professional attire, living costs, all these things. And so that’s really our hope is to try to offset some of the economic burden, specifically for marginalized communities, when it comes down to the medical school process.

What’s the importance of representation in the media for young Black children and teens, especially in a field like medicine?

The importance of representation is multipronged, obviously. I think if you think about it, just from a visual perspective, the reason why a lot of people especially, you know, Black men can aspire to be great basketball players, is because we’ve had so many Black great basketball players. If we never saw them, it’d be kind of hard for us to imagine it. It’s the same thing in medicine. We need to see representation for us to see this even possible. I’ll never forget, I had this one experience. I was shadowing a child psychiatrist. And he went to go get a patient, a young African American boy, and when the young boy walked into the room, his eyes just lit up. It’s like he...saw Jesus or something. And he sat down, and I knew why he was looking at me like that. Because he probably had never seen, you know, a Black man who looks like me with the hair, beard, in a white coat or sitting in a room, almost as if to say, like, do you belong here? [Are you supposed to be here?] Is it OK for you to be here? And I finally got an opportunity to talk to him, and he just poured out his life in front of me. And so, I think that representation goes far, just from a visual perspective, but I think there’s an underlying experiential perspective. We know that representation matters in terms of how the doctor’s visit will go, and because of the cultural understanding that that is very possible in an environment where there is some sort of congruency in experiences as well as a culture. So, that’s not a secret.

And then more so I think, you know, if you take into account the history of medicine and marginalized communities, it’s not pretty. I think her name was...
Harriet Washington wrote the book, *The Medical Apartheid*, and she talked about the atrocities that have happened for a lot of medicine to progress. And now this was done on the backs of a lot of Black people, a lot of the experiments, a lot of these falsehoods that are out there that Black people experience less pain. The experimentation has been done on Black folks for eons of time have contributed to some mistrust, and so how do we try to overcome that, or at least to some degree, try to fix it? You need some people who understand the history, some people who understand the culture, but also some people who are from those communities, providing care, because they know their people, they genuinely do. And so, accessibility in the medical school will help with that, and also accessibility when it comes to positions of influence and power within medical schools, within academia, within hospital systems. It’s not just medical school; it’s got to be institutional change at a lot of different levels. Obviously, with me being in med school, my interest right now is med school, but I’m certain that will change over time, and it will expand.

**AJMC**: So what needs to happen to change to break down these barriers to medical school?

**LEDET**: Right, so I think there are a couple things that need to happen for accessibility to medical school. I think you need to get some different people selecting who goes to med school. I think you have to get some people in the room who value people from minority communities as people, and not just because they’re trying to fill a quota, but because they genuinely value their culture, their experiences, what they bring to the table, and they’re willing to institute antiracist policies that kind of go against what’s been done for a long time. And I always say this because we, as a human race, we have accomplished some very lofty feats. Some very lofty goals like sequencing the human genome, identifying PD-1, PD-L1 as therapeutic targets for cancer. We’ve done a number of things that were absolutely incredible and pushed humanity forward. I think we can achieve true diversity and inclusion, because we can’t forget about the inclusive piece, by relearning a lot of things, unlearning some things that we use the status quo for how we go about selecting people for medical school, but also learning new ways to value people as people. And I talk about this inclusive piece because, there’s no point in recruiting me if you’re not going to include me. So, if you’re going to bring me to your building, but then it’s clear that I’m not welcome, but you’re kind of doing it to check a box, I mean, am I really going to want to stay there? And even if I get through, am I really going to want to contribute afterward? Most likely not. And so, I think another big piece to changing the paradigm is changing the culture. I think it says something that a lot of faculties in general may have 1 or 2 Black people on the faculty. That’s not good, that’s just fundamentally not good. If you’re graduating a lot of Black medical students, don’t you think you should have more Black faculty? I mean, you’re producing doctors, you should be getting them back, or you should be getting some from somewhere, and so that speaks to culture. I heard Roland Martin talk about something on ABC, and 1 of the issues was it was a culture problem. And I will say that there are some cultural issues in medical school around there not being enough antiracism being taught.

“Obviously, there was more to it than just taking a photo. There was also the experience itself. And so, after we had this experience, and we took these photos, the idea behind the photos was for us to capture just how far we’ve come.”

—Russell Joseph Ledet, PhD, president and founder, The 15 White Coats

So I think that that’ll help. Definitely the economic piece, definitely getting the right people in the room to choose who should who should be in a medical school class, and lastly, the culture. The culture needs to be overhauled, not just fixed, it needs to be overhauled. We need to be teaching about medical apartheid, and the history of how obstetrics and gynecology moved forward, how pain management moved forward, how all these different fields like surgery moved forward, and the ugly history behind it. Because if you aren’t teaching doctors that or if you aren’t teaching student physicians that, then when are they going to learn it? When they get into their specialty? No, they’ll be too busy. So, you’ve got to teach it to them at the foundation of their medical school education.

**AJMC**: Right. That’s the end of my questions. Was there anything else you wanted to add?

**LEDET**: If you want to check out The 15 White coats, you can check us out on Instagram, Twitter, or Facebook at The 15 White Coats, or you can check out our website, the15whitecoats.org. And we’ll always speak truth to power. •
Rethinking Downside Risk Protection Amid Growth in Precision Medicine

KEELY MACMILLAN, MSPH

Brentuximab vedotin, another targeted therapy, was approved by the FDA in March 2018 for use in the first-line treatment of stage III and IV Hodgkin lymphoma in combination with chemotherapy.1 It is used in 0% to 7% of lymphoma episodes among OCM participants and averages more than $22,000 per administration. Among OCM participants, Medicare spends nearly $90,000 for brentuximab vedotin, on average, during a 6-month episode of care in which the drug is used, with individual episodes of care topping $170,000 for the drug.1

Gene and cell therapies boost precision medicine costs to a new level. Chimeric antigen receptor (CAR) T-cell therapy, approved by the FDA to treat certain forms of non-Hodgkin lymphoma and leukemia, is a type of immunotherapy that harnesses a patient’s own modified white blood cells to attack cancer cells.2 Proposed by CMS to have a new Medicare severity-diagnosis-related group designation beginning in fiscal year 2021, the costs of CAR T-cell therapy would account for the highest-paid hospital admission ever, at approximately $250,000 for the Medicare Part A component alone, unadjusted for area wage and other payment policy factors.3 If finalized, this payment rate would be more than 4 times as costly as coronary bypass surgery and more than 19 times as costly as a lower extremity joint replacement.

For self-insured employers, innovation in precision medicine—and the accompanying hefty price tag—calls for a reexamination of downside risk-protection strategies to ensure that catastrophic losses are protected as efficiently and cost-effectively as possible. Before simply replicating the traditional approach of purchasing specific stop-loss coverage for protection from the high cost of rare treatments, self-funded employers should evaluate the following options:

Aggregate-Only Stop-Loss Insurance

An aggregate-only (agg-only) insurance policy is designed to limit overall losses to a certain amount, with high-cost claims counting toward an agg-only attachment point. Agg-only policies generally have lower premiums than specific policies and much lower (more protective) attachment points than aggregate policies purchased in conjunction with specific policies. Notably, agg-only policies provide coverage when an employer needs it most. In fact, a Milliman report found that 7 of 10 times, self-funded employers of small, medium and large sizes had lower overall costs with an agg-only product compared with specific insurance.4 Agg-only products can provide flexibility in attachment point, premium, deductible, and coinsurance to best fit the self-funded employer’s needs. Agg-only products also provide more competitive rate increases than specific policies that are subject to leveraged trend, a rate

CMS Seeks to Fix Medicaid Best-Price Barriers in Value-Based Contracting for High-Cost Therapies in Medicaid

IN JUNE, CMS PROPOSED long-awaited reforms to allow flexibility for value-based contracting in Medicaid, which officials said would let outcomes-based pricing seen in commercial plans to flourish in public plans and, hopefully, give low-income patients greater access to life-changing therapies.

The most important proposal would tackle longstanding barriers to creative pricing instruments, including long-term financing of costly gene therapies, which experts say are needed if the Medicaid-insured population is to have equal access to the most innovative treatments.1 Comments were due July 19.

CMS received credit for a good first step, particularly in taking on the problem of “Medicaid Best Price.” But some comments called for more flexibility and clarification to ensure that innovative payment concepts can be achieved.

The National Pharmaceutical Council (NPC), in its submitted comments, said that while it agreed that value-based payments should be based on evidence, strictly tying payment to clinical performance may miss some factors that contribute to quality of life—and perhaps reduce a patient’s out-of-pocket costs. NPC asked for a reworking of the definition of a value-based payment.4

“This [proposal] will allow payers and manufacturers to tailor contracts to the chosen product, ensuring that the measures are appropriately matched with the value a therapy can provide. However, the proposed definitions link to a medicine’s actual clinical performance or a reduction in medical expenses and may not encompass the full potential value for the patient,” the NPC stated.

MEDICAID BEST PRICE. Enacted 30 years ago, this rule requires drug manufacturers to give Medicaid programs the best price among nearly all purchasers. But the rule prevents modern value-based transactions in which manufacturers are paid on a sliding scale, based on whether a costly therapy works—including instances when the drug maker isn’t paid at all.

Such contracts create incentives on all sides to develop methods, including genetic testing, to ensure that expensive therapies are given only to those patients in whom they have a high chance of success, thus allowing down overall spending in a time of unprecedented innovation.

“CMS’s rules for ensuring that Medicaid receives the lowest price available for prescription drugs have not been updated in 30 years and are blocking the opportunity for markets to create innovative payment models,” CMS Administrator Seema Verma, MPH, said in a statement.1 “By modernizing our rules, we are creating opportunities for drug manufacturers to have skin in the game through payment arrangements that challenge them to put their money where their mouth is.”

During a June press briefing, Verma explained that under a value-based pricing (VBP) model, pricing for a gene therapy for cancer could be tied to how long a patient lived, while pricing for innovative diabetes treatments could be tied to reductions in glycated hemoglobin. Other factors that may be included in value-based contracts are a drug’s level of toxicity.
often twice as high as regular medical and pharmacy inflation. Lasers do not need to be applied for known high-cost individuals because their expected costs are reflected in the age-only attachment point.

**Multiyear Products**

Stop-loss policies in which rates are locked in for multiple years ensure greater predictability for self-funded employers. The NEWDGs FoCUS consortium’s white paper discusses the benefit of a 5-year performance-based annuity to both spread payments over multiple years and mitigate risk of catastrophic cases. Published before the coronavirus disease 2019 became a global pandemic, the report also notes that multiyear products mitigate the actuarial risk of surges in patient backlog—a reality our health care system is currently facing as it returns to a “new normal.”

**Advance Funding**

A key benefit of specific stop-loss coverage is the role it plays in cash-flow management. Specific coverage can help smooth cash flows against catastrophic claims, but an employer should not purchase high-premium specific coverage for the sole purpose of cash-flow management when advance funding options can ensure that month-to-month expenses are predictable. Advance funding can take the form of coordinated reimbursement or a flat monthly payment in which the employer automatically pays up to a certain threshold every month and the insurer covers high-cost claims.

CMS recently announced a 1-year extension of the OCM program, to June 2022. Currently in its fourth year, the program is amassing important data on ways to drive higher-value care for patients undergoing cancer treatment. It is critical that these data be evaluated and leveraged to ensure that quality and value remain priorities alongside innovation in cancer treatment.

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**CONTINUED FROM PREVIOUS PAGE**

including whether the patient required hospitalization for adverse effects. Such steps can discourage plans from simply forcing patients to jump through barriers such as traditional prior authorization to gain access, CMS said in a fact sheet.1 "Basing payment on the effectiveness of a given therapy can foster innovation in the treatments that are most impactful to patients, while reducing overall health care spending and hospital visits," the fact sheet said.

CMS said the shift would boost incentives to collect and share evidence on how well therapies work. The agency seeks changes in how manufacturers calculate their average manufacturer price of a branded drug when an authorized generic is available, and how patient assistance programs would be included in the calculation of “best price.” CMS also seeks to address the interaction between patient assistance programs and pharmacy benefit manager accumulator programs. In its comments, NPC said patients must continue to have access to these assistance programs to ensure medication adherence.

Mark Trusheim, MSc, strategic director of NEWDGs, a program of the Massachusetts Institute of Technology, spoke with Evidence-Based Oncology™ on the aspects of the plan that align with the NEWDGs FoCUS project, which has convened stakeholder sessions to develop pricing models for new therapies.4

Trusheim said CMS has taken steps to create performance levels, or outcomes tranches, which pool results and avoid the phenomenon of a single outlier setting the price for an entire state Medicaid program. In low-population states especially, it’s possible for a lone patient to be prescribed a high-cost gene therapy for a given condition, and a single poor performance should not set the market.

Trusheim said that CMS has also granted exceptions so that drug manufacturer reporting requirements can extend beyond the current limit of 3 years. However, he said, while the proposal mentions “pay-over-time” arrangements, it does so within the context of manufacturers’ reporting requirement extending beyond 3 years.

The proposed rule states that many value-based pricing arrangements “or pay-over-time models may be better suited for periods longer than 12 quarters, and manufacturers entering into such agreements may need to adjust AMPs (average manufacturer prices) and best prices beyond the condition where evidence-based or outcomes-based measures are being measured beyond a period of 12 quarters or a final installment payment occurs after this time.”

However, Trusheim said the proposal does not appear to address one other problem that NEWDGs FoCUS identified: an initial payment being interpreted as total payment in a performance- or annuity-based model. In its comments, NPC agreed that this needs clarification. Trusheim identified several elements of importance for state Medicaid programs, including:

- The proposal appears to allow capped payments for therapies, which would permit subscription-based models such as the one pursued in Louisiana for direct-acting antivirals for hepatitis C virus infection. In its comments, NPC called for more explicit guidance on subscription models.
- A State Plan Amendment process must be used to negotiate VBP arrangements that involve a Supplemental Rebate Arrangement.
- States must report VBP arrangements, naming the drugs involved, the number of prescriptions, administrative costs, and total savings. “They need not report the VBP structure or how the savings were distributed among the outcomes payment levels,” Trusheim said.

Among other comments, NPC called for more explicit guidance on subscription models, for more details on what to do with contracts that cover small numbers of patients, and for flexibility for contracts that address combination regimens, which are increasingly common—especially in oncology.

NPC also called for uncoupling proposals “not directly related to the transition from volume to value” from those related to payment innovation.

**REFERENCES**

CUTS TO PAYMENTS THAT HHS imposed for certain medications administered in outpatient clinics of 340B hospitals were based on a “reasonable interpretation of the Medicare statute” and can remain, a 3-judge panel of the US Court of Appeals for the District of Columbia ruled July 31, 2020. The 2-1 decision reverses a District Court-level ruling that HHS exceeded its authority when it imposed a 28.5% rate cut for a category of outpatient drugs used by hospitals enrolled in the discount program, which was created to support safety net hospitals serving Medicaid patients.

The American Hospital Association (AHA) and 2 allies in the effort to restore 340B cuts issued a statement that suggests they will challenge the ruling. “We will continue to fight for our hospitals and their patients, and we call on CMS to reverse this harmful policy to ensure hospitals can continue to provide the services people need the most,” read the statement from AHA, America’s Essential Hospitals and the American Association of Medical Colleges. Hospital groups have the right to seek a ruling by an en banc panel.

Under the 340B program, pharmaceutical manufacturers must allow discounts for certain drugs to qualifying hospitals—which lets the hospital pay between 20% and 50% below the average sale price, but Medicare reimburses at the normal rate. When this discount was applied to certain Medicare Part B drugs given in the outpatient setting—whose prices were calculated by specific formulas—it allowed hospitals to effectively make a profit off them, or at least CMS became convinced of this, according to the July 31 opinion. Thus, in 2017, the Trump administration sought to narrow the gap between drug payments in 340B and those in Medicare Part B. Critics of the program say the 340B “discount” gets made up in the form of higher overall costs, and the pricing dynamics hurt seniors who are forced to pay a higher copayment tied to a drug’s prediscount price. For several years, providers such as the Community Oncology Alliance have argued that the programs expansion into outpatient clinics came at their expense, since nonhospital clinics could not compete on drug prices. These providers have been aided by reports from the Government Accountability Organization, including a January report that found poor oversight of the program and that some hospitals were getting discounts for which they did not qualify. “[The] court decision is another major victory for President [Donald J.] Trump’s agenda of lower drug prices and better health care for all Americans,” HHS Secretary Alex Azar said in a statement. “Since HHS took the action that the court affirmed…we have saved more than $4.8 billion in lower drug costs and reinvested these savings in the Medicare program. However, hospitals affected by the cuts have argued the lost revenue will impair their ability to provide critical services, and as they have stepped up the courts, HHS has continued to include the cuts in annual payment rules, and at least one observer wrote that it will interesting to see what happens next, given that hospital interests are waiting on an update to the Part B hospital outpatient prospective payment system (HOPPS) for 2021. “Despite the lower court decision, CMS doubled down and maintained the cuts in the 2020 HOPPS rule while the government pursues its appeal,” wrote Alan M. Kirschenbaum. In making its ruling, the DC Circuit panel relied on the same case as the District Court, but came up with a different interpretation, Kirschenbaum noted. While the lower court found that CMS had exceeded its authority, the 2 judges on the panel ruled found otherwise. Writing for the panel, Chief Judge Padmanabhan Srikanth Srinivasan said, “Was HHS obligated to continue reimbursing 340B hospitals for outpatient drugs] in amounts substantially exceeding their costs to obtain the drugs, with the resulting effects that concerned the agency on out-of-pocket copayments owed by Medicare beneficiaries? We think the agency was not compelled to continue doing so.”

REFERENCES


MARY CAFFREY
The most common neurologic events (>10%) included encephalopathy (51%), headache (35%), tremor within the first seven days after TECARTUS infusion.

Neurologic Toxicities

Medical attention should be given to signs or symptoms of CRS at any time. At the first sign of CRS, institute treatment with tocilizumab or tocilizumab as needed.

Tecartus is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS Program.

Cytokine Release Syndrome (CRS), including life-threatening reactions, occurred following treatment with TECARTUS. In ZUMA-2, 3 CRS occurred in 91% (75/82) of patients receiving TECARTUS, including ≥ Grade 3 CRS in 18% of patients. Among the patients who died after receiving TECARTUS, one had a fatal CRS event. The median time to onset of CRS was three days (range: 1 to 13 days) and the median duration of CRS was ten days (range: 1 to 50 days). Among patients with CRS, key manifestations (>10%) included fever (99%), hypotension (65%), hypoxia (37%), chills (33%), tachycardia (37%), headache (24%), fatigue (19%), nausea (13%), alanine aminotransferase increased (13%), aspartate aminotransferase increased (12%), and diarrhea (11%). Serious events associated with CRS included hypotension, fever, hypoxia, acute kidney injury, and tachycardia. Ensure that a minimum of two doses of tocilizumab are available for each patient prior to infusion of TECARTUS. Provide supportive care and/or corticosteroids as needed.

Neurologic Toxicities, including life-threatening reactions, occurred in patients receiving TECARTUS, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with TECARTUS. Provide supportive care and/or corticosteroids as needed.

Severe Infections: Serous or life-threatening infections occurred in patients after TECARTUS infusion. In ZUMA-2, infections (all grades) occurred in 56% of patients. Grade 3 or higher infections, including bacterial, viral, and fungal infections, occurred in 30% of patients. TECARTUS should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after infusion and treat appropriately. Administer prophylactic antimicrobials according to local guidelines.

Fibolea neutropenia was observed in 6% of patients after TECARTUS infusion and may be concurrent with CRS. In the event of severe neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

Prolonged Cytophenia: Patients may exhibit cytopenia for several weeks following lymphodepleting chemotherapy and TECARTUS infusion. In ZUMA-2, Grade ≥ 3 cytopenias not resolved by Day 30 following TECARTUS infusion occurred in 55% of patients and included thrombocytopenia (38%), neutropenia (37%), and anemia (17%). Monitor blood counts after infusion.

Hypogammaglobulinemia and B-cell aplasia can occur in patients receiving treatment with TECARTUS. In ZUMA-2, hypogammaglobulinemia occurred in 16% of patients. Monitor immunoglobulin levels after treatment with TECARTUS and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

Secondary Malignancies may develop. Monitor lifelong for secondary malignancies. In the event that it occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

Efficacy of Ability to Drive and Use Machines: Due to the potential for neurologic events, including altered mental status or seizures, patients are at risk for altered or decreased consciousness or coordination in the 8 weeks following TECARTUS infusion. Advise patients to refrain from driving and engaging in hazardous activities, such as operating heavy or potentially dangerous machinery, during this period.

Adverse Reactions: The most common adverse reactions (incidence ≥ 20%) were pyrexia, CRS, hypotension, encephalopathy, fatigue, tachycardia, arthralgia, infection – pathogen unspecified, chills, hypoxia, cough, tremor, musculoskeletal pain, headache, nausea, edema, motor dysfunction, constipation, diarrhea, decreased appetite, dyspepsia, rash, insomnia, pleural effusion, and aphasia. Severe adverse reactions occurred in 66% of patients. The most common serious adverse reactions (>2%) were encephalopathy, pyrexia, infection – pathogen unspecified, CRS, hypoxia, aphasia, renal insufficiency, pleural effusion, respiratory failure, bacterial infections, dyspepsia, fatigue, arthralgia, tachycardia, and viral infections.

Please see full Prescribing Information, including BOXED WARNING and Medication Guide.

2. TECARTUS™ (brexucabtagene autoleucel). Prescribing Information. Kite Pharma, Inc. 2020
3. CART cells target antigen receptor (TCR) on malignant cell surface/lymphoma, R, Enveloped or refractory.

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CRS Grade 3: Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO₂, or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminas. —Administer tocilizumab per Grade 2. If improving, discontinue tocilizumab. —Administer methylprednisolone 10 mg intravenously every 6 hours until Grade 1, then taper corticosteroids. If improving, manage as Grade 2. If not improving, manage as Grade 4. —CRS Grade 4: Life-threatening symptoms. Requirements for ventilator support or continuous renal replacement therapy (CRRT). —Administer tocilizumab per Grade 2. If improving, discontinue tocilizumab. —Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, taper corticosteroids, and manage as Grade 3. If not improving, consider alternate immunosuppressants.

(a) Lee et al 2014, (b) Refer to management of neurologic toxicity, (c) Refer to tocilizumab Prescribing Information for details.

**Neurologic Toxicity:** Monitor patients for signs and symptoms of neurologic toxicities (grading guidance below). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. Consider non-seedling anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

**Neurologic Toxicity (NT) Grading and Management Guidance**

- **NE Grade 1:** Examples include: somnolence — mild drowsiness or sleepiness; confusion — mild disorientation; encephalopathy — mild limitation of ADSLs; dysphasia — impaired ability to communicate spontaneously; seizures(s).
  - If concurrent CRS: administer tocilizumab per management guidance for Grade 1 CRS.
  - If there is no concurrent CRS, use supportive care.

- **NE Grade 2:** Examples include: somnolence — moderate limiting instrumental ADSLs; confusion — moderate disorientation; encephalopathy — limiting instrumental ADSLs; dysphasia — moderate impairment ability to communicate spontaneously; seizures(s).
  - If concurrent CRS: administer tocilizumab per management guidance for Grade 2 CRS. If not improving within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab. If still not improving, manage as Grade 3.
  - If no concurrent CRS: administer tocilizumab per Grade 2 and continue dexamethasone every 6 hours until the event is Grade 1 or less. If improving, manage as Grade 4.

- **NE Grade 3:** Examples include: somnolence — obtundation or stupor; confusion — severe disorientation; encephalopathy — limiting self-care ADSLs; dysphasia — severe receptive or expressive characteristics; impaired ability to read, write, or communicate intelligently.
  - If concurrent CRS: administer tocilizumab per management guidance for Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and then repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab and manage as Grade 2 if still not improving, manage as Grade 4.
  - If no concurrent CRS: administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If not improving, manage as Grade 4.

- **NE Grade 4:** Life-threatening consequences; urgent intervention indicated; requirement for mechanical ventilation; consider cerebral death.
  - If concurrent CRS: Administer tocilizumab per management guidance for Grade 4 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.
  - If no concurrent CRS: administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If not improving, manage as Grade 4.

**CONTRAINDICATIONS:** None.

**WARNINGs AND PRECAUTIONS**

**Cytokine Release Syndrome:** CRS, including life-threatening reactions, occurred following treatment with TECARTUS. In ZUMA-2, CRS occurred in 71% (71/126) of patients receiving TECARTUS, including ≤8% (10/126) in the control arm. The most common CRS reactions were grade 2 and consisted of pyrexia (59%), cough (37%), fatigue (36%), chills (62%), tremor (37%), hypoxia (28%), headache (36%), nausea (27%), and nausea with vomiting (25%). CRS reactions were associated with elevations in transaminases (minimal effect), leukopenia, and lymphopenia. CRS was treated with tocilizumab and dexamethasone. CRS reactions resolved following tocilizumab (Grade 2) or tocilizumab plus dexamethasone (Grade 1). CRS reactions were manageable and fatal CRS reactions were rare (1% of patients treated with TECARTUS).

**Hypersensitivity Reactions:** Further information is available at www.YescartaTecartusREMS.com or 1-844-454-KITE (5483).

**Pregnancy andBreastfeeding:** Monitor patients for signs and symptoms of CRS for four weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab, or corticosteroids as indicated.

**Neurologic Toxicities:** Neurologic events including those that were life-threatening, occurred following treatment with TECARTUS. In ZUMA-2, neurologic events occurred in 81% of patients, 37% of whom experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The most common neurologic event for neurologic toxicities was headache. The most severe neurologic events included 52 out of 66 (79%) patients with a median duration of 21 days (range: 2 to 404 days). Three patients had ongoing neurologic events at the time of death, including one patient with serious encephalopathy. The remaining unobserved neurologic events were either Grade 1 or Grade 2. Fifty-four (54%) of patients experienced CRS before the onset of neurologic events. Five (6%) patients did not experience CRS with neurologic events and eight patients (10%) developed neurologic events after the resolution of CRS. Eighty-five percent of all treated patients experienced the first CRS or neurologic event within the first seven days after TECARTUS infusion. The most common neurologic events (>1%) included encephalopathy (51%), headache (35%), tremor (38%), aphasia (23%), and delirium (16%). Serious events including encephalopathy, aphasia, and seizures occurred after TECARTUS. Methylprednisolone 500 mg intravenously per day for three days after TECARTUS was recommended for severe neurologic events.

**Special Instructions**

- **ADSLs:** activities of daily living scale.
- **NE:** Neuropsychiatric event.
- **(a)** Severity based on Common Terminology Criteria for Adverse Events.
- **CONTRAINDICATIONS:** None.

**ALL CLINICAL STUDIES**

- **Owing to the higher risk of CRS, patients with a history of severe CRS (CRS grade 3 or 4) are not eligible for treatment with TECARTUS.**
YESCARTA and TECARTUS REMS Program: Because of the risk of CRS and neurologic toxicities, TECARTUS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS Program. The required components of the YESCARTA and TECARTUS REMS Program are:

- Healthcare facilities that dispense and administer TECARTUS must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within two hours after TECARTUS infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer TECARTUS are trained in the management of CRS and neurologic toxicities.

Further information is available at www.yescartat经济技术.com or 1-844-454-451E (5438).

Hypersensitivity Reactions: Serious hypersensitivity reactions, including anaphylaxis, may occur due to dimethyl sulfone (DMSO) or residual gentamicin in TECARTUS.

Severe Infections: Severe or life-threatening infections occurred in patients after TECARTUS infusion. In ZUMA-2, infections (all grades) occurred in 56% of patients (Grade 3 or higher infections, including bacterial, viral, and fungal infections, occurred in 30% of patients). TECARTUS should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after TECARTUS infusion and treat appropriately. Administer prophylactic antimicrobial agents according to local guidelines. Febrile neutropenia was observed in 0% of patients after TECARTUS infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

Toxicity of CRS: CRS is a cytokine release syndrome. The incidence of CRS in the pivotal ZUMA-1 trial was 90% (in 23 of 26 patients treated with TECARTUS). The median duration of CRS was 13 days (range: 1 to 50 days). Among patients with CRS, 37% of whom experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The most common adverse reactions (incidence ≥ 20%) were pyrexia, CRS, chills, hypoxia, cough, tremor, musculoskeletal pain, headache, nausea, edema, motor dysfunction, ataxia, tachycardia, and viral infections. The most common (> 10%) Grade 3 or higher reactions were anemia, neutropenia, thrombocytopenia, hypotension, hypophosphatemia, encephalopathy, leukopenia, hypoxia, pyrexia, hypotension, hypertension, infection-pathogen unspecified, pneumonia, hypocalemia, and lymphopenia.

Summary of Adverse Reactions Observed in at Least 10% of Patients Treated with TECARTUS in ZUMA-2 (N=62)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade (%)</th>
<th>Grade 3 or Higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Coagulopathy</td>
<td>10</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Non-ventricular Arrhythmias</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Oral pain</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
<td>10</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>48</td>
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<tr>
<td></td>
<td>Chills</td>
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<tr>
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<td>Edema</td>
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<tr>
<td></td>
<td>Dyspnea</td>
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<tr>
<td>Immune system disorders</td>
<td>Cytokine release syndrome</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>Hypogammaglobulinemia</td>
<td>16</td>
</tr>
</tbody>
</table>

For a complete list of events that contributed to the incidence of certain adverse reactions, please see footnote below Table 3 in Section 6.1 of the Full Prescribing Information.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with TECARTUS include the following urologic disorders: dry-thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to biosafety guidelines for handling and disposal of TECARTUS to avoid potential transmission of infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab

Administer tocilizumab per Grade 2. If improving, discontinue tocilizumab.

— Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, discontinue tocilizumab.

Neurologic Toxicity (NT) Grading and Management Guidance

Patients treated with TECARTUS may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-451E (5438) to obtain instructions on patient samples to collect for testing.

Effects on Ability to Drive and Use Machines: Due to the potential for neurologic events, including altered mental state or seizures, patients receiving TECARTUS are at risk for altered or decreased consciousness or coordination for at least six weeks following TECARTUS infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

ADVERSE REACTIONS: The following clinically significant adverse reactions are described in Warnings and Precautions: Cytokine Release Syndrome, Neurologic Toxicities, Hypersensitivity Reactions, Severe Infections, Prolonged Cytopenias, Hypogammaglobulinemia.

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Patients with Relapsed/Refractory Mantle Cell Lymphoma (MCL): The safety of TECARTUS was evaluated in a Phase 2 single-arm, clinical study (ZUMA-2) in which a total of 82 patients with relapsed/refractory MCL received a single dose of CAR-positive viable T cells (> 10^6 or 0.5 × 10^6 anti-CD19 CAR T cells/kg) that was weight-based. The most common adverse reactions (incidence ≥ 20%) were pyrexia, CRS, hypotension, encephalopathy, fatigue, tachycardia, arrhythmia, infection – pathogen unspecified, chills, hypoxia, cough, tremor, mucoskeletal pain, headache, nausea, edema, motor dysfunction, constipation, diarrhea, decreased appetite, dyspepsia, rash, insomnia, pleural effusion, and anemia. Serious adverse reactions occurred in 69% of patients. The most common serious adverse reactions (>2%) were encephalopathy, pyrexia, infection – pathogen unspecified, CRS, hypoxia, apnea, respiratory insufficiency, pleural effusion, respiratory failure, bacterial infections, dyspepsia, fatigue, arthralgia, tachycardia, and viral infections.

Summary of Adverse Reactions Observed in at Least 10% of Patients Treated with TECARTUS in ZUMA-2 (N=62)
How DNA Medicines Could Transform Treatment of Glioblastoma Multiforme

JEFFREY SKOLNIK, MD

CONTINUED FROM SP224

A recent resurgence of DNA medicines is due in large part to improvements in the technology that has enabled their reintroduction into the clinic. Over the past several years, Inovio, a small biotechnology company outside of Philadelphia, has begun to master the utility of DNA medicines and to optimize their delivery for clinical use in treating and preventing human disease. Inovio is currently investigating its DNA medicines using a proprietary platform that couples optimization of DNA plasmids with efficacy-enabling delivery through the use of a smart device known as Cellectra (Figure 1, Cover) to treat and protect people from precancer, cancer, and infectious diseases. This device uses a short electrical pulse to open pores in the cell, allowing plasmids to enter. This ensures efficient delivery of the DNA medicine, overcoming limitations of earlier approaches.1

Most recently, the company has received significant media coverage for INO-4800, a DNA vaccine designed in 3 hours and brought from the bench to the clinic in 83 days to support the fight against coronavirus disease 2019.2 But the company’s history dates back several decades to the creation of its first products, followed by clinical investigation into the treatment of human papillomavirus-related diseases, such as cervical intraepithelial neoplasia (CIN). Its most advanced DNA medicine candidate, VGX-3100, is currently in a phase 3 trial for the treatment of high-grade CIN.3

The proprietary technology uses a computer algorithm to build DNA medicines that can target almost any antigen that can be presented to the human immune system through the major histocompatibility class I system. DNA medicines are built in the form of circular strands of synthetic DNA called plasmids, which can neither propagate nor integrate into the human genome. These plasmids have several specific and unique characteristics:

• First, they are designed to produce an optimal immune response when translated by the cell in which they are taken up.
• Second, they are able to be designed to any antigen that the human immune system can recognize.
• Third, they are translated as full-length proteins, which allow the cell to process and present the encoded antigen as intended by the native immune system.
• Finally, they are able to be kept, stored, transported, and dosed under a range of conditions and temperatures that support an extended shelf-life and optimal supply chain.

Taken together, these factors provide an extremely versatile platform that can target and treat a range of human diseases. This is what has enabled Inovio to investigate multiple therapeutic areas simultaneously.

The DNA medicine plasmid technology is coupled with a smart delivery device that improves plasmid uptake and, subsequently, increases immunogenicity. The Cellectra device is responsible for improving DNA plasmid uptake into cells and is among the major advances in DNA medicines over the past decade. Prior to the use of the device, DNA plasmids, upon injection into the muscle or intradermal space, were less likely to be taken up by the cell, which prohibited their subsequent translation into suitable immunogenic proteins. But with the device, Inovio has used in vivo study results to demonstrate that immunogenicity can be increased 1000-fold, secondary to the ability of Cellectra to empower cells to take up the DNA plasmids and thereby translate their contents into viable antigens for the immune system to recognize.4,5

Applicability in Treating Glioblastoma

Glioblastoma (GBM), or grade IV astrocytoma, remains in the majority of cases an incurable and devastating disease. The disease originates from the supportive glial cells of the brain, and patients present at diagnosis with diffuse disease that has locally spread throughout the cerebral cortex, even if radiographically appearing isolated. Presentation can be sudden; common signs include headaches, ataxia, changes in speech or motor movements, and seizures. Although surgery is the initial recommended therapy, not all patients can undergo optimal or complete resection, depending on where in the brain the tumor is located. Surgery is almost always followed by radiation and chemotherapy, usually with temozolomide; this standard was set 15 years ago6 and has changed very little since. At that time, temozolomide, when added to standard-of-care radiation, provided a median overall survival of 14.6 months, an advantage of 2.5 months over radiation alone. A slight but significant prolongation has been seen in patients who use the tumor-treatment field device Optune, but this improvement is about 3 months.7

Several treatments have recently made their way to the clinic in an effort to harness the power of the human immune system to treat GBM. Many of these therapies aim to create a robust response to GBM. These include protein- or peptide-based vaccines; ex vivo manipulated immune cells, including chimeric antigen receptor T cells, which have been used in certain blood cancers; and checkpoint inhibitors, which have been successful in treating multiple blood and solid tumor cancers. Unfortunately, several randomized studies of PD-1 receptor inhibitors have failed to demonstrate a clinical benefit in GBM to date.8 As such, patients with GBM continue to await a new therapy that can leverage or improve upon an immune response to GBM.

Inovio has developed INO-5401, a DNA medicine that is made up of 3 synthetic DNA plasmids encoding for human telomerase, Wilms Tumor 1 protein, and prostate-specific membrane antigen (PSMA). The company recently announced clinical data evaluating the percentage of patients alive at 12 months following their first dose of the DNA medicine candidate. INO-5401 was given...
with INO-9012, a synthetic DNA plasmid encoding for human interleukin-12, and with cemiplimab, a PD-1 inhibitor from Regeneron.13 In this 52-patient study, approximately 85% of patients were alive at 12 months, a potential improvement above historical controls (Figure 2).14 Importantly, an immune response was seen in a majority of patients tested. In addition, evidence of an antigen-specific T-cell population that was activated and primed to kill GBM cells was identified by both ELISpot and by flow cytometry. These novel therapies—INO-5401 and INO-9012 plus cemiplimab—were able to be given with both radiation and temozolomide chemotherapy. Reported adverse events were consistent with the known tolerability profile of the individual study drugs as well as with radiation, temozolomide, and the disease under investigation. Previous research had demonstrated that more patients were progression-free at 6 months than when compared with historical controls.13 Together, these promising, albeit early, clinical data provide hope that Inovio’s novel DNA medicines have the potential to extend overall survival in patients with GBM. Additional survival results of this study will be available toward the end of 2020.

Although it has taken more than a decade, DNA medicines are now ready for success not only against infectious diseases and precancerous conditions such as HPV-related cervical dysplasia, but against some of the deadliest diseases, such as GBM. With Inovio’s INO-5401 offering hope for patients with a fatal prognosis, there is the promise that technology can transform the treatment of GBM while improving quality of life and, ultimately, extending life.

AUTHOR INFORMATION
Jeffrey Skolnik, MD, vice president of clinical development at Inovio, leads Inovio’s immuno-oncology DNA medicines team and several other clinical programs. He is a key member of the leadership team overseeing global clinical assets for DNA medicines aimed to treat cancers and other diseases.

REFERENCES

**FIGURE 2.** DNA Medicine INO-5401 in Combination With INO-9012 and Cemiplimab for Newly Diagnosed GBM: Phase 1/2 12-Month Data

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N alive/N total</th>
<th>OS12 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGMT unmethylated</td>
<td>27/32</td>
<td>84.4% (67.2-94.7)</td>
</tr>
<tr>
<td>MGMT methylated</td>
<td>17/20</td>
<td>85.0% (62.1-96.8)</td>
</tr>
<tr>
<td>Combined</td>
<td>44/52</td>
<td>84.6% (71.9-93.1)</td>
</tr>
</tbody>
</table>

Majority of patients tested had a T-cell immune response to ≥1 tumor-associated antigen encoded by INO-5401.
Second-Generation BTK Inhibitors
Hit the Treatment Bullseye With Fewer Off-Target Effects

MAGGIE L. SHAW

CONTINUED FROM COVER

The BTK protein is essential to helping B cells develop and mature into functional and specialized white blood cells; these are part of the adaptive immune response in producing antibodies, or immunoglobulins.4 But mutations in the BTK gene, more than 600 of which have been identified, can lead to a sizeable reduction in the number of circulating B cells, along with reduced ability to fight infection, absence of the BTK protein, production of abnormal BTK protein, or cancer cell growth.5,6

Mutated immunoglobulins essentially malfunction in their roles as antigen receptors on the surfaces of B cells, especially in the cancer space, by not recognizing antigens as damaging or by not sending the correct signals to destroy the malignant cells. This is where BTK inhibitors come in. They help to trigger cell death by blocking the B-cell receptor signaling that leukemias and lymphomas use to grow and survive.2

The first-generation BTK inhibitor ibrutinib (Imbruvica) came to market in 2013, when it was approved by the FDA to treat adult patients with mantle cell lymphoma. A targeted treatment, it stops cancer cells from surviving and multiplying by blocking abnormal protein signaling.4 Other indications, as monotherapy or in combination, have been approved for chronic lymphocytic leukemia, Waldenström macroglobulinemia, small lymphocytic lymphoma, relapsed/refractory marginal zone lymphoma, and chronic graft-versus-host disease.9 Ibrutinib is a once-daily oral agent and can be used in the frontline and relapsed settings.10

Despite its many benefits and indications, however, ibrutinib as BTK inhibition is also associated with numerous adverse effects (AEs) on nonmalignant cells, which range from common to uncommon and from mild to severe, making ibrutinib’s toxicity profile notorious.2

Among the most severe AEs are hemorrhage; high blood pressure; heart rhythm irregularities, including ventricular arrhythmias, atrial fibrillation, and atrial flutter; second primary cancers (eg, skin, other organs); and tumor lysis syndrome.11 Some of the most common AEs, occurring in more than 30% of patients, are hematological (eg, decreased platelets, neutrophils, and hemoglobin), musculoskeletal, and respiratory in nature.

Additional possible AEs include diarrhea, constipation, vomiting, skin infections, dizziness, dehydration, petechiae, arthralgia, stomatitis, rash, and fatigue.12 Ibrutinib carries warnings for use among those with bleeding problems, liver problems, and for those who are planning surgery or recently had surgery; women who are pregnant or thinking of becoming pregnant; women who breastfeed or plan to do so; and men with female partners capable of pregnancy.

Second-generation BTK inhibitors seek to improve upon first-generation agents like ibrutinib by having less cardiotoxicity, fewer AEs that result in stopping treatment, and fewer off-target effects. For example, ibrutinib inhibits the activity of 3 major off-targets: epidermal growth factor, which can result in severe skin toxicities13; interleukin-2 inducible kinase, which impairs natural killer cells’ cytotoxic abilities;14 and the Tec family of kinases, decreasing their ability to aid in phosphorylation.15

In updated results of the ASPEN trial presented at this year’s virtual American Society of Clinical Oncology (ASCO) 2020 Annual Meeting, zanubrutinib (Brukinsa), the most recent second-generation BTK inhibitor to hit the US market, was shown to have a survival advantage over ibrutinib in patients with Waldenström macroglobulinemia who lacked the MYD88 mutation typically associated with successful treatment.16

ASPN first compared zanubrutinib with ibrutinib in patients with Waldenström macroglobulinemia who have the MYD88 mutation, and zanubrutinib was shown in December 2019 to increase the incidence of complete response (CR) or very good partial response (VGPR) by close to 46% compared with ibrutinib—28.9% vs 19.8%, respectively—in patients with relapsed or refractory disease.17

The updated results, from 5 additional months of data, widened this gap, showing a 30.4% CR plus VGPR rate for zanubrutinib compared with 18.2% for ibrutinib, as well as less occurrence of atrial fibrillation/flutter of any grade, bleeding of any grade, major hemorrhage, diarrhea, and hypertension. In addition, patients without the MYD88 mutation had an overall response rate of 80.8%, which included a 50.0% major response rate—which itself included a VGPR rate of 26.9%—and 12-month progression-free survival of 72.4%.18

Lead investigator, Constantine Tam, MBBS, MD, a clinical hematologist and professor at the Peter MacCallum Cancer Centre in Victoria, Australia, noted of zanubrutinib, “Those patients who potentially have a history of hypertension or have a history of atrial fibrillation—or have an abnormal ECG or abnormal echocardiogram—maybe they’re the ones who would be better off on (zanubrutinib) compared with ibrutinib. We think it’s how clean the targeting is.”19

Zanubrutinib is associated with less incidence of muscle spasm, peripheral edema, pneumonitis, and pneumonia. In essence, fewer overall AEs with second-generation BTK inhibitors means less of a need to reduce dosing and a greater likelihood of being able to stay on treatment longer. Tam noted that most AEs happen in the first year on treatment, before their incidence plateaus, whereas prolonged treatment with ibrutinib has a greater chance of inducing cumulative damage to the vascular system.20

Compared with first-generation BTK inhibitors, the second-generation drugs are associated with fewer concerns about primary and acquired drug resistance. For example, ibrutinib use among patients with relapsed/refractory mantle cell lymphoma has been shown to both have no effect on the disease and have a negative impact on additional therapies.21

These resistance mechanisms of action are 2-fold. They are molecular, in that they involve sustained distal B-cell receptor signaling through PI3K-AKT [protein kinase B] pathway activation, NFkB pathway activation, and cell cycle progression. They also are therapeutic, in that lines of therapy administered after BTK inhibitors do not produce prolonged responses or exceptional overall survival.21

Less Cardiotoxicity in Second Generation

Some of the strongest gains in this newer generation of BTK inhibitors, however, can be seen in the cardiovascular space, when compared with the toxicities of the first-generation inhibitors that often lead to treatment discontinuation, especially among older, sicker patients who have a history of cardiac disease. In fact, most BTK inhibitors are prescribed for older patients, because the class of drugs is used primarily to treat chronic lymphocytic
leukemia, for which the average age of onset is older than 60 years. 13

“I think it’s a lot of the toxicities are related to off-target effects, meaning the binding of the inhibitor drug to receptors or molecules that are not the ones that they’re supposed to be treating the cancer for,” said Michael Kolodziej, MD, FACP, vice president and chief innovation officer, ADVF Health, in an interview with Evidence-Based Oncology. 14

“The big ones that were identified with the first-generation inhibitors were cardiovascular, or hypertension—and atrial arrhythmias, atrial fibrillation. And they were not rare side effects.”

Kolodziej explained that the second-generation drugs have fewer off-target effects—less cardiovascular toxicity, atrial arrhythmias, and hypertension—because of their improved toxicity profile, “largely because the drugs are just better at being BTK inhibitors. It’s not any more complicated than that.”

The chief challenge of the first-generation BTK inhibitors is that the AEs cause clinicians and patients to stop treatment with them, Kolodziej noted. The cancer does not become resistant, but the toxicities become unbearable and the patients become intolerant, he emphasized.

“The thinking is that the reduced cardiovascular side effects, the reduced bleeding, are going to allow a better persistence on the second-generation drugs,” he explained.

Tolerability and Payers

Indeed, in a pooled analysis of clinical trials of the second-generation BTK inhibitor acalabrutinib (Calquence), also presented in May at ASCO, lead author Richard R. Furman, MD, of Weill Cornell Medicine in New York, found that at a median follow-up of 26.4 months, 65% of patients were still on treatment. Of the 34% of patients who stopped acalabrutinib, half (17%) did so because their disease progressed; only 9% stopped due to treatment-related AEs. 15

Tolerability, especially as patients define it, is increasingly important to payers, starting with Medicare. The Center for Medicare and Medicaid Innovation has announced that it will incorporate patient-reported outcomes (PROs) into the Oncology Care First model, the proposed successor to the Oncology Care Model. 16 Advocates for including PROs in payment models are encouraging drug developers to broaden definitions of tolerability, to include quality-of-life data in trial designs. 17

It’s a straightforward idea: When patients can tolerate treatment, it improves their chances of survival. “This is important,” Tam said during ASCO. “The longer you take the drug, the better your responses become.” 18

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