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Oncology Pharmacists Renew Hope in Addressing Health Equity in Cancer Treatment

ALTHOUGH MUCH WORK remains in addressing the underlying causes of social determinants of health (SDOH) in the country, health care systems have made great strides by examining the diversity and equity of staffing. During July’s 2022 Advanced Topics for Oncology Pharmacy Professionals Summit in San Diego, California, keynote speaker Vibhuti Arya Amirfar, PharmD, MPH, discussed dismantling racism by moving beyond the individual and addressing systemic structures allowing racism to continue, whether the cause be environmental, social, political, or otherwise. Pharmacy Times® attended this conference, with highlights covered on page 13 of this issue. A video interview with Amirfar—a global lead for gender equity and diversity workforce development for the International Pharmaceutical Federation based in The Hague, the Netherlands—is available at pharmacytimes.com.

In the cover feature on page 10, Justin Lindhorst, MBA, examines SDOH in the context of cancer treatment. He explains how this places specialty pharmacies at a critical point in addressing SDOH that may be contributing to cancer health disparities. Lindhorst discusses 5 actionable ways to address SDOH in specialty pharmacies and the potential impact of these interventions on patient health outcomes.

As part of addressing health equity, author Dea Belazi discusses trends in oncology pharmacy that are moving the field toward virtual care and a patient-focused approach to treatment (page 18). Belazi explains how more pharmacists are shifting to high-value, patient-focused roles in response to trends remodeling the market beginning in 2022. Belazi notes that these pharmacists will have a key impact in shaping the future of the field in a strategic way.

Additionally, in this issue, Pharmacy Times Oncology Edition™ (PTOE) welcomes its new editor in chief, Lisa E. Davis, PharmD, FCCP, BCPS, BCOP, who sits on PTOE’s editorial advisory board. With a background working in the early phase clinical trial and breast cancer programs at the University of Arizona Cancer Center, Davis brings a wealth of knowledge on research and practice areas relating to medication adherence, symptom management, drug development, drug resistance, and factors influencing antineoplastic drug disposition and response. Davis examines key points affecting the oncology pharmacy field in her first Editor’s Note for PTOE.
Editor’s Note

The Enhancing Oncology Model (EOM), designed by the Centers for Medicare & Medicaid Services (CMS), was launched recently by the US Department of Health and Human Services and CMS to identify ways of improving health care providers’ ability to deliver the best possible outcomes in patient-centered care. EOM was described as a 5-year voluntary payment model implemented to improve quality of cancer care for Medicare patients and reduce costs of care.

EOM builds upon the earlier Oncology Care Model, further focusing on increasing health equity; incentivizing practices and health care providers to interact with patients between appointments; addressing patients’ cancer care experience and health outcomes; and engaging patients in discussions regarding prognosis, treatment options, symptom management, and quality-of-life screenings on social determinants of health (SDOH). For practices participating in EOM, use of electronic patient-reported outcomes (ePROs) and implementation of activities promoting health equity will be required. EOM will also require participants to identify health equity gaps within their beneficiary population and detail their evidence-based strategies for mitigating health disparities.

Oncology pharmacists will be involved in implementing EOM in their practice settings,
which will likely increase their communication with patients and opportunities to participate in—and lead—initiatives for monitoring and addressing symptoms, quality of life, and ePROs. To date, implementing ePROs in practices has been shown to enhance patient quality of life, reduce acute care visits, and improve overall survival. However, questions and challenges persist regarding implementation of ePROs into routine patient symptom and clinical care assessments.

Electronic systems have been found to help facilitate patient reporting and self-monitoring during and after cancer treatments, based on data from studies investigating multiple disease states globally. Web-based programs allow these electronic systems to be accessible on mobile devices. This can support real-time assessments and reporting that facilitate rapid patient evaluation and feedback, which can be invaluable when patients experience severe symptoms.

Additionally, ePROs allow patients to use these electronic systems in remote settings so they can quickly notify their care team of worsening symptoms or treatment complications between clinic visits. Clinical trials comparing ePRO surveys with usual care when monitoring symptoms have demonstrated significant improvements in symptom control and quality of life for patients using ePROs.

Furthermore, digital self-management support tools (DSMSTs) have been found to facilitate communication between health care providers and patients, while assisting patients with monitoring and improving their own health status. This can empower patients with cancer to feel more involved and in control of their health, potentially providing physical and mental benefits.

Digital platforms may also facilitate symptom assessment in different cultural and linguistic patient populations. Research has investigated the use of emoji-based visual analog scales by comparing these to standard pain assessment using a numeric rating scale. The results showed high levels of patient engagement in the emoji-based rating system.

As more medical emojis become available, they could be useful in annotating patient instructions and helping patients convey their symptoms to providers. However, a digital divide may exclude patients with little or no access to technology, which may affect older patients lacking the access and knowledge necessary for this type of reporting. As with other challenges related to SDOH, patients who have the greatest need for symptom monitoring and treatment support may be those with the greatest difficulty in accessing these virtual platforms to help them engage with their health care teams.

Success of ePROs depends on effective communication between patients and health care providers. The ePROs have limitations; patients who are extremely ill or too young or who have cognitive impairment may be unable to report outcome measures. Cultural or linguistic relevance of ePROs may be less important in various populations, and there are potential differences in utility between English-proficient patients and those with limited proficiency. However, oncology pharmacists have the knowledge and skills to effectively assess patients’ ability to utilize different resources, access and comprehend information, and communicate with the health care team. They can help implement new virtual systems as necessary to benefit each patient’s reporting preferences and needs.

As we address SDOH and the evolving nature of the digital transformation in health care after COVID-19, ePROs and DSMSTs will frequently be used and evaluated in research and standard care settings. Oncology pharmacists should be involved in their design, implementation, and assessment, and should utilize them for monitoring patient symptoms, addressing gaps in health equity, and demonstrating their roles and value in interventions to improve health outcomes and quality of life in cancer care.
Promoting an Inclusive Health Care Setting
Vivienne Hau, MD, a clinical assistant professor with the Kaiser Permanente Bernard J. Tyson School of Medicine in Pasadena, California, speaks with The American Journal of Managed Care® on the important role physicians have in curating an inclusive health care environment for all patients.

TO WATCH: https://bit.ly/3OoVBmq

The Street Vet
Veterinarian and animal consultant for Netflix, Kwane Stewart, DVM, explains how he started providing free veterinary care to homeless animals, leading him to cofound Project Street Vet.


Deep Dive Into Upright Proton Cancer Therapy
Paul Harari, MD, professor and chairman of the Department of Human Oncology at the University of Wisconsin School of Medicine and Public Health, discusses upright proton cancer therapy, which will be offered at University of Wisconsin Health.

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Although advances in screening, treatment, and survivability provide hope for patients with cancer, data demonstrating ongoing disparities in health outcomes indicate these benefits are not experienced equally. A recent study showed that over 2 decades, the 5-year survival rate for patients younger than 50 with colorectal cancer improved for White individuals but not for those who are Black, Hispanic, or Asian American. Additionally, Black patients with multiple myeloma have more than double the mortality rate seen among White patients.¹

However, the data show that disparities in cancer care are not solely experienced by populations based on race, as members of the LGBTQ+ community face disadvantages compared with heterosexual patients in terms of screening, diagnosis, and treatment.² In rural areas of the country, the data show that LGBTQ+ individuals have a 17% higher cancer death rate.³ These and other widely documented cancer health disparities are a pervasive challenge threatening health outcomes for patients with cancer and the achievement of health equity in the United States.

Disparities occur most frequently in population groups defined by race/ethnicity/national origin, disability, sexual orientation, gender identity, geographic location, income, education, and age.⁴ As we identify and learn more about cancer and the health disparities facing populations within this field, complex interrelated social determinants of health (SDOH) are increasingly understood to be major drivers of individual and public health. Examining SDOH in the context of cancer treatment within specialty pharmacies is critical to helping address SDOH and cancer health disparities more broadly.

Social Determinants of Health Play Key Role in Patients’ Health Journey

Specialty pharmacies are well positioned to address disparities that affect outcomes.

JUSTIN LINDHORST, MBA

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SDOH and Cancer Disparities

To help clarify the growing use of this term in the field, SDOH are defined as “the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health functioning, and quality of life outcomes and risks.”

Healthy People 2030 was approved by the US Department of Health and Human Services (HHS) in June 2018 and developed based on recommendations made by the HHS Secretary’s Advisory Committee on National Health Promotion and Disease Prevention Objectives for 2030. Healthy People 2030 groups SDOH into 5 domains: economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context.

Specialty pharmacies are positioned at the treatment phase of the patient journey, with SDOH in this context including myriad issues that can affect outcomes. For example, patients from underserved communities may present with more advanced forms of cancer due to their living environment; behavioral and psychological risk factors; genetic predisposition; and lack of access to screening, prevention, and quality health care. These patients also may not trust providers due to previously experienced discrimination or bias. Communication barriers, low levels of health literacy, and financial toxicity are also challenges experienced at a higher level among populations predisposed to health disparities.

Black and Hispanic patients have been shown to experience financial toxicity twice as often as White patients, which can lead to financial coping behaviors such as skipping doses or rationing medications.

Among the underserved and communities of color, the data show that unmet socioeconomic needs negatively impact cancer therapy adherence. For example, Black and Hispanic patients have been shown to experience financial toxicity twice as often as White patients, which can lead to financial coping behaviors such as skipping doses or rationing medications. Additionally, racial and ethnic minority populations have a documented higher rate of negative adverse effects (AEs) while undergoing cancer treatment.

Addressing SDOH in Specialty Pharmacies

Achieving health equity requires action from all stakeholders in health care. The National Academy of Medicine recommends 5 actionable ways to address SDOH: awareness, adjustment, assistance, alignment, and advocacy. Specialty pharmacies can use this approach to improve, refine, and advance service and support for patients in a way that promotes positive outcomes while addressing SDOH.

Awareness

For specialty pharmacies, approaches that address awareness include ensuring leadership and staff understand SDOH and the resulting disparities, as well as the importance of culturally competent care. Awareness in specialty pharmacies also includes efforts to analyze the organization’s structural components to uproot policies or practices that could unintentionally marginalize or stigmatize patients (or employees). It may also mean taking a critical, ongoing look at programs and services, identifying how patients with cancer are triaged to
community and other support resources, identifying potential gaps, and tracking service outcomes relative to SDOH.

**Adjustment**
Approaches that address adjustment in specialty pharmacies include changes to policies and procedures, as well as the provision of support in clinical and nonclinical settings to better meet social needs that may be influencing patient health.

**Assistance**
To address assistance in specialty pharmacies, approaches can include allocation of clinical and other support resources to reduce barriers to care, provision of patient navigation services, and promoting adherence to therapy while minimizing AEs and reactions.

**Alignment**
Specialty pharmacies can take approaches that address alignment through developing and sustaining partnerships with other health care stakeholders, community partners, and local support agencies to address SDOH challenges and health disparities.

**Advocacy**
A key area for specialty pharmacies is advocacy, which can be accomplished by ensuring a specialty pharmacy’s staff are uniting around the focused goal of voicing and promoting the need for change to conditions that contribute to health inequities within specialty pharmacies and beyond.

**Moving Toward a More Equitable Future**
Research indicates cancer disparities are a result of determinants within and outside the health system including SDOH, racism, and discrimination. Although much remains to be done as we move toward achieving cancer health equity, it is important to remember that progress is being made toward that goal.

In the past 2 decades, the disparity in overall cancer mortality between Black and White populations has been reduced by half. Effective interventions addressing SDOH and promoting equity have been proven to reduce disparities while improving care for all patients.

Specialty pharmacies are positioned at a critical juncture for patients with cancer. By understanding the impact of SDOH in the context of cancer treatment, specialty pharmacies can help improve outcomes and move toward a more equitable future for all patients with cancer.

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**REFERENCES**
Conference Recap

Key Players Highlight Oncology Pharmacists’ Critical Role in Advancing the Field

Professionals address key challenges including structural racism and the hematology-oncology pharmacist great migration.

Alana Hippensteele, Managing Editor

Dismantling structural racism on a systems level is among several key challenges needing action from leaders in the oncology pharmacy field, explained keynote speaker Vibhuti Arya Amirfar, PharmD, MPH, during a session at the 2022 Advanced Topics for Oncology Pharmacy Professionals (ATOPP) Summit in July. Sessions at the summit also addressed challenges such as putting precision medicine into practice, comparing frontline renal cell carcinoma (RCC) regimens, addressing the hematology-oncology pharmacist great migration, and assessing the real-world impact of biosimilars on health care costs.

During the keynote address, Amirfar discussed the importance of building individual and systems resilience to dismantle structural racism in the pharmacy field. In an interview with Pharmacy Times®, Amirfar explained that she has found many individuals are tired of hearing about how they should build resilience individually to mitigate difficulties in their profession, such as burnout or situational stress at work. Amirfar said focusing on the systems themselves is critical, such as by assessing how to provide environments in which all team members not only survive but thrive.

In a session on the great migration of hematology-oncology pharmacists from the field, panelists Zahra Mahmoudjafari, PharmD, BCOP, DPLA; Alison Gulbis, PharmD, BCOP; and Kamakshi Rao, PharmD, BCOP, FASHP, discussed underlying causes of the migration beyond burnout. In an interview with Pharmacy Times®, Mahmoudjafari said her team’s research showed many emerging trends that have led to this migration, with some more obvious than others, such as a lack of support for oncology pharmacists to pursue board certification or attend conferences, as well as difficulties with patient ratios. Mahmoudjafari noted that her team was surprised to find these relatively attainable “low-hanging fruit” that institutions could implement quickly to retain staff.

During a panel discussion, panelist Alison Palumbo, PharmD, MPH, BCOP, provided real-world data comparing combination regimens used in treating frontline metastatic RCC. Although treatment of RCC has changed in recent years from immune checkpoint inhibitor monotherapies to combination regimens, Palumbo noted that there have not been head-to-head studies allowing oncology professionals to compare the new regimens, making it difficult to decide on an appropriate treatment for a particular patient. During the session, Palumbo and the other panelists aimed to provide oncology professionals with data to assist in such comparisons to aid in RCC treatment decisions.

In a session on the importance of implementing precision medicine programs into oncology practices, Andre Harvin, PharmD, MS, explained that although oncology professionals broadly understand the value of precision medicine in oncology, C suite executives at cancer centers may be harder to convince regarding return on investment (ROI) for such programs. In an interview with Pharmacy Times®, Harvin explained that oncology pharmacists are particularly well placed to define the why behind precision medicine in relation to ROI so that facts and data can resonate with C suite executives and all key players across the cancer care continuum.

Finally, during a panel discussion addressing the real-world impact of biosimilars on health care costs, moderator Jorge García, PharmD, MS, MHA, MBA, FACHE, explained that with rapid change in biosimilar payer benefit design, efforts to stay regularly updated on policy changes ahead of time have become critical for patient care in oncology. With the significant gain in clinical confidence in the demonstration process for biosimilars, García noted that the challenge remains in learning how to overcome roadblocks and manage opportunities that the evolution of biosimilars presents to oncology pharmacy practices.

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Digital Transformation, Shift to Home Care Delivery Have Significant Implications for Specialty Pharmacies

Oncology pharmacists must think critically about the digital experience they give patients.

JUSTIN LINDHORST, MBA

IN HEALTH CARE, digital transformation has quickly evolved from a corporate catchphrase to an operational necessity. A global pandemic, changing expectations, and growing research indicating the safety and efficacy of digital health technology are pushing health care to refine and advance digital capabilities.

Digital health represents a key component in helping patients safely manage therapy at home and in helping oncology-focused specialty pharmacies gather real-world data relevant to the interests of prescribers, pharmaceutical manufacturers, and payers. This article examines the rise of digital health, the changing site of health care in the United States, and the implications for oncology-focused specialty pharmacies.

The Rise of Digital Health and a Changing Site of Care

The digital health industry is booming. In 2021, digital health investments reached $29.1 billion—a 255% increase from 2019.¹ The industry is projected to reach $650 billion by 2026.² The proliferation of the smartphone, wearable devices, and the internet of things stands to significantly shape health care in the United States and around the world.

Patients have increasing digital health resources at their disposal. More than 350,000 digital health apps are available for download, 320 million wearable

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devices will ship globally this year, and 41.9% of US households are connected to smart home devices.\textsuperscript{3-5} More than ever, patients are using technology to monitor, measure, and manage their health.\textsuperscript{6} Although concerns about data and privacy linger, patients are increasingly willing to share digital health information with physicians, health insurers, and pharmacists to optimize their own care while increasing the ease of methods by which they receive that care.\textsuperscript{7}

Health care is moving closer to home. During the next 3 years, nearly $265 billion in services for Medicare fee-for-service and Medicare Advantage patients could shift from health care facilities to the home.\textsuperscript{1} Research demonstrates that digital health apps, wearables, and other monitoring devices are effective resources for home management of chronic health conditions.\textsuperscript{8} Studies involving oncology patients demonstrated a reduction in symptoms and increased survival time by using remote monitoring devices in the home.\textsuperscript{9}

Combining digital health with multidisciplinary support, hospital at home (HAH) programs seek to reduce length of hospital stays and unplanned hospital visits for patients with chronic health conditions. HAH oncology services are gaining traction in the United States, and research demonstrates oncology HAH support effectively improves treatment outcomes and lowers costs.\textsuperscript{10} Digital health and HAH programs will be a key tactic driving the site of care from the hospital to the home in years to come.

**Digital Health and Specialty Pharmacy**

Digital transformation and the changing site of health care delivery have significant implications for specialty pharmacies. Value-based contracting, digital companions for specialty drugs, and the expanding clinical role of pharmacists are among reasons why specialty pharmacies should evaluate, upgrade, and expand their digital health capabilities.

As health care moves toward value-based contracting and reimbursement models, digital health will play an increasingly important role in driving patient engagement, satisfaction, and the measuring of outcomes. In a value-based system, measurable outcomes and patient satisfaction both represent clinical quality measurements.

The digital revolution in communication, shopping, entertainment, and travel has set a high bar for the digital experience patients expect from health care providers. If their digital experience with a health care app is not on par with that of Amazon, Uber, Netflix, and other digital giants, patient expectations likely are not being met. Patients increasingly decide whether to keep or abandon a health care provider based on the provider’s digital capabilities.\textsuperscript{8} Specialty pharmacies not providing a digital experience in line with these expectations may see decreased patient engagement and satisfaction scores; such metrics are important in a value-based model of care.

In addition to overall digital experience, specialty pharmacies should prepare for the proliferation of digital companions and digital therapeutics. The next 5 years will see a growing number of specialty therapies targeting cancer reach the market.\textsuperscript{11} As new drugs are released, many pharmaceutical manufacturers are deploying digital companions to help patients manage complex therapies; these companions can also provide education and adherence support while collecting patient-reported outcomes related to therapy.\textsuperscript{12}

Digital therapeutics work by deploying evidence-based interventions to help unique patient populations manage, prevent, or treat specific health conditions.\textsuperscript{13} There are 35 to 40 FDA-approved digital therapeutics used for a growing range of mostly chronic health conditions, including cancer.\textsuperscript{14} Along with oversight from board-certified oncology pharmacists, digital companions and therapeutics will play an increasing role in helping patients manage complex therapies from home.

The ways in which pharmacists support patients are evolving. Integrating digital support into oncology medication therapy management programs provides an opportunity for clinical pharmacists to engage with patients, provide effective tools for managing therapy, and facilitate collection of valuable real-world data. Oncology pharmacists, technicians, and support staff should identify and develop competency in the use of digital health apps, companions, wearables, and therapeutics that are effective in supporting patients with cancer. With more apps and devices available, pharmacists can help patients
Identify, evaluate, and execute a tailored digital health strategy.

Health care often falls behind other industries in terms of digital maturity.15 Regardless, specialty pharmacies need to think critically about the digital experience they provide patients. As the site of health care moves from hospital to home, the role of the oncology pharmacist will evolve. Specialty pharmacies should consider how to best deploy digital health resources throughout the patient journey to improve communication, reduce barriers, facilitate medication access, gather real-world data, and promote positive outcomes.

References

Glioblastoma Multiforme (GBM) is an aggressive malignant brain tumor predominantly found in adults. Even with the latest advances in cancer therapeutics, the few drugs that have been able to cross the blood-brain barrier (BBB) and reach the tumor directly face the hurdle of the BBB being disrupted in the process. With only approximately 5% of patients living 5 years after diagnosis, professionals desperately need a solution.

With advancements in the understanding of what is necessary to treat GBM, treatment approaches have begun to change. Scientists historically have focused on developing new drugs to target malignant tumors. However, drug development can span decades, and as diagnoses of this disease continue, time is not on the side of oncology professionals. To address this dilemma quickly, scientists are shifting to advance methods of local drug delivery, finding new ways to administer therapeutics effectively while circumventing the BBB. With this paradigm shift of incorporating local drug delivery technology into GBM treatment, the field of oncology is set for monumental change.

Paradigm Shift to Local Drug Administration
The primary thrust in cancer research and treatment practice has evolved to a more personalized approach to treating tumors through precision medicine and therapy. We are moving into a “genomic era,” in which scientists look at genomic patterns in each tumor to tailor drugs for optimal results.

Effective drug administration remains one of the biggest challenges, despite recent advances in cancer care. Intravenous (IV) administration is not entirely effective for GBM treatment because many drugs still cannot penetrate the BBB, which limits efficacy. Despite this, the IV delivery method is still used with drugs that can be better localized in tumors based on pharmacokinetic data. The potential of delivering much higher levels of drug directly to the tumor location with sustained release during a roughly 3-week period while maintaining minimal systemic drug exposure represents a key shift in what is possible not only in treatment of GBM but more broadly in neuro-oncology.

Investigators looking to address this delivery dilemma have come to understand that packaging a drug with a formulation that can be inserted directly at the brain tumor site allows circumvention of the BBB. Drug delivery using this packaging formulation can better encapsulate the drug and allow us to protect it from the degradation that occurs with IV administration, enabling prolonged release.

About the Author
Mitchel S. Berger, MD, is the director of the University of California San Francisco Brain Tumor Center (BTC) and the principal investigator of the BTC’s SPORE Brain Tumor Program. He also serves on the PolyPid Scientific Advisory Board.
As new formulas undergo clinical investigation that would allow such prolonged release, the possibility for improved overall survival and clinical outcomes for patients with GBM becomes more real. These clinical trials have the potential to enable local drug delivery of chemotherapy directly at brain tumor sites at prolonged release rates, potentially reducing the tumor. Throughout 2022, these clinical trials are expected to progress, and during the next decade we can expect further development in additional investigations seeking new methods of crossing the BBB to advance treatment of GBM.

**Using Methylation Signatures to Target Specific Pathways**

A major recent development involves the number of new tools that allow oncology professionals to perform genomic classification of cancerous diseases, enabling identification of key mutations in genes that need to be targeted during treatment. By looking at genomic and epigenetic classifications, we can identify how the cells control gene activity. From there, we can look at the methylation profiles of genes, assessing how we can regulate cellular response to therapy.

The combination of methylation profiling with probiotic signatures and genomic classifications has allowed oncology professionals to identify the Achilles’ heel of many cancers with these specific pathways, which can drive invasion and ultimately reduce the ability of tumors to duplicate or divide.

**Repurposing Existing Drugs**

Because the process for bringing a drug to market can take 10 years or more, scientists have been looking at the methods by which existing drugs are administered. Recent research has showed that how the drug is administered may play a greater role in efficacy than previously thought. Now that we can uncover the genetic, epigenetic, or methylation signatures to assess pathways, we can identify existing drugs and those in phase 1 or phase 2 trials to repurpose and pair them with new local drug administration technologies for improving efficacy. As a result of these newly discovered molecular pathways based on genomic profiling and sequencing data, we can repurpose drugs that do not have a role in treating tumors and were not thought of as valuable in brain tumor treatment.

Taking it a step further, if we utilize FDA-approved drugs, we can halve the time it would take to prove a new drug’s safety and efficacy to get it into the hands of clinicians for their therapeutic toolbox. By embracing these new technologies, we have the potential to change the outcome in cancer care for GBM.

**Clinical Trials Recover From Impact of COVID-19**

As oncology evolves following the challenges of the COVID-19 pandemic, we have much to anticipate. Even before the pandemic, most patients in the United States did not participate in clinical trials because of daunting logistical complications. Problems remain, but there is more clarity regarding what we need to overcome to bring greater equality and access to the cancer clinical trial space for patients.

As we progress following the peak impact of COVID-19 on clinical trials, we must find a way to improve clinical trial structures so that all patients with GBM, especially those impacted by social determinants of health, can more easily receive care in the clinical trial setting. There is hope we will continue to see dedicated focus from those working in this space in years ahead, which will ideally bring more opportunities for patients with GBM to receive more affordable, advanced treatments.
As the COVID-19 pandemic wanes in 2022, the demand for innovation will increase. Pharmacists are expanding their scope of practice and filling gaps in care left by a shortage of well-trained oncologists and nurses.

Oncology pharmacists understand the need to gain expertise in virtual care and complex treatments to close education and information gaps caused by overwhelmed oncologists and other providers. They are also assuming the role of advocates for generic or lower-cost options for uninsured or underinsured patients.

A growing number of oncology pharmacists are also shifting into more high-value, patient-focused roles in response to trends that will continue to remodel the market in 2022 and beyond.\(^1\) These pharmacists will play a critical role in shaping the future of oncology pharmacy growth in a more strategic way. As a result, more oncology pharmacists will begin to embrace new revenue streams based on patients’ needs for proactive care coordination and convenience.

**New Oncology Drugs and Personalized Medicine**

The pharmaceutical industry continues to launch oncology therapies at a rapid pace. With over 21 new drugs approved to treat cancer in 2021, the industry broke its record of 20 cancer drug approvals, which was set in 2020.\(^2\) There has also been a fast acceleration of precision medicine, which gives oncology pharmacists the ability to choose a medication and dose based on patient-specific genomic factors.

Furthermore, clinical trial recruitment has shifted to the virtual world, which has sparked a rise in clinical trials that is likely to continue. This presents the possibility for more clinical trials and more participating patients gaining greater access to new treatment options.

**Oncology Specialty Pharmacy**

Oncology specialty pharmacies (SP) will continue to adopt innovative SP management programs that are designed to better support patient-based drug utilization plans, optimize oncology therapy selection, and maximize cost-management outcomes. As demand for evidence-based drug management strategies rises among health plans and prescription benefit managers, this trend will drive appropriate cancer therapy selection.

**Rise in Digital Care**

Heightened patient awareness and demand for virtual care are developing a shift toward greater reliance on digital technology across pharmacies that are striving to remain competitive. In acknowledgment of this shift, oncology patients have adjusted to telehealth and now expect more options, including remote, on-demand access to health care providers. This is enabling oncology pharmacies to adapt to tech-driven care delivery.

Over the next 5 years, the global pharmacy automation market is forecasted to grow at a compound annual growth rate of 7%, with no signs of stopping in the near future.\(^3\) Pharmacies are now tasked to provide more flexible, intelligent solutions.

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**ABOUT THE AUTHOR**

**DEA BELAZI** is the president and CEO of AscellaHealth.

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**FEATURED CONTENT**

**MARKET TRENDS**

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**Trends in Oncology Pharmacy Will Drive the Market Beyond 2022**

New drugs, virtual care, and a patient-focused approach are key during this period of transformation.

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**DEA BELAZI**
Industry-Wide Focus on Specialty Pharmacy
As SP gains greater focus across all stakeholders, expect expanded, specialized services to help patients with cancer better address not only the challenges associated with oncology specialty drug management, but also everyday lifestyle issues related to missing work, forgoing income, and reliance on family caregivers.

In 2022, emerging key trends impacting the market for oncology SP include the continued utilization and rising costs of specialty agents, emergence of ultra-high-cost specialty agents and cell/gene therapies for rare and orphan diseases, more focused management of the high-cost specialty drug patients to ensure adherence and optimize outcomes, and vertical integration of specialty pharmacies into health care organizations.

Additionally, greater focus on specialty pharmacy and further integration of its role into health care systems can better ensure specialty drugs are seamlessly accessed by prescribed patients and that drug therapies are monitored for efficacy and adherence to treatment.

Financial Considerations
A patient’s ability to pay for specialty medications will continue to be an issue, as specialty drug costs remain prohibitively high for many patients, adding barriers to patient accessibility. With patients’ out-of-pocket costs for specialty drugs increasing faster than gross domestic product growth over the past decade, a subsequent trend of note will be a greater reliance on customized co-pay assistance programs and innovative financial and technology solutions to help offset the high cost of cell/gene therapies and other novel agents, which can make a real difference for patients and payers.

Carving Out Specialty Drugs
Additionally, another consideration for the SP space that can impact the market is the carve-out of specialty drugs from the medical and pharmacy benefit, which can help to reduce costs, expand the availability of specialty drugs, and promote enhanced patient health outcomes. To accomplish these objectives, appropriate medication therapy management and utilization management programs can be customized and aligned for each plan sponsor.

Biosimilars
In 2022, biosimilars are poised to trend upward because of several additional blockbuster drugs losing patent protection. The rising burden of various chronic diseases, such as cancer, cardiovascular disease, and diabetes, will continue to fuel the biosimilar market, with affordability impacting market adoption.

Patient-First Approach to Pharmacy
In response to all these trends, a patient-first approach to oncology pharmacy—in which every care decision is made based on what is best for the patient—allows all stakeholders to connect seamlessly rather than operating independently. This results in a higher level of care continuity that strengthens communication, yields rich data for optimizing outcomes, and improves the overall patient experience.

Patient-first, specialty-focused care teams typically include care coordinators, pharmacists, nurses, and other specialists who are all focused on the disease state, patient community, and therapy. They deliver customized care coordination and telehealth solutions as an added layer that fosters discussion among the patient, oncology pharmacist, and other clinicians.

By incorporating assessments and interventions at key points in therapy, the care team can better manage adverse effects (AEs) and capture real-world evidence around the therapy, condition, and patient’s well-being. All these critical data are then compiled for outcomes reporting.

A patient engagement strategy also takes a multi-layered approach that includes various channels of communication, such as text, phone, and email. The strategy chosen for primary communication should be based on the customer’s preferences and what generates the best response for each patient.

In a world of shrinking options and sophisticated technology, the patient-first approach offers something that has gone missing in the US health care system: the human touch. By providing an elevated level of customized care, oncology pharmacists can help caregivers manage AEs and ensure patient feels heard.

When oncology pharmacists take a patient-first approach, they are able to cultivate a deeper relationship with patients and family caregivers, offering personalized information, care insights, and greater support that leads to improved outcomes and enhanced quality of life.
Prevent Diversion During Drug Disposal
Building a team to support best practices, medication safety, and staff education can reduce risks.

CRAIG KIMBLE, PHARM.D., MBA, MS, BCACP; TIFFANY DAVIS, PHARM.D.; CHRIS BOOTH, PHARM.D.; AND KEN MAXIK, MBA, BSPHARM

OPPORTUNITY FOR DIVERSION of controlled substances occurs at all steps in medication management. Health systems face many risks associated with diversion, including financial, legal, patient injury, and reputational.\(^1,2\) Affected parties include coworkers, patients, pharmacy staff members, and providers. To secure an effective diversion prevention program, pharmacy leaders should proactively engage essential interdisciplinary stakeholders, including individuals in charge of storing or disposing of controlled substances, the executive team, operating room staff, and patient care units. Input and shared decision-making with staff members should include discussions on decreased documentation burden, ways to lower diversion risk, peer oversight, and program value.\(^3\)

Risk Points
The American Society of Health-System Pharmacists (ASHP) Guidelines on Preventing Risk Diversion identify where in the supply chain diversion is most likely. These are the 5 essential phases where pharmacists should focus their efforts:\(^4\):

• **Drug procurement phase:** There is an opportunity for staff members to alter or delete records, gain unauthorized access to electronic controlled-substance ordering system and Drug Enforcement Administration (DEA) forms 222, or compromise a product container.

• **Preparation and dispensing phase:** Staff members might divert overfill, remove volume from a solution, replace one product with another, or replace a prepared drug with another product.

• **Prescribing phase:** Prescription pads could be targeted; prescribers might self-prescribe or prescribe controlled substances for family or friends. Issues with illegitimate or nonauthorized verbal orders may arise. Also, patients might alter written prescriptions. E-prescriptions have helped but do not eliminate risk.

• **Medication administration phase:** Products could be removed for a discharged patient, medications might be documented as administered but not provided to patients, or substitute drugs might be administered in place of the product.

• **Waste and removal phase:** Controlled-substance waste might be removed from unsecured waste containers, expired products might be diverted from holding areas, and waste in syringes might be replaced with saline.

Focusing on these risk points identified by the ASHP is important to ensure supply chain integrity.\(^4\) A comprehensive plan addressing all 5 phases with financial stewardship is important to assure adequate oversight.
Elements of a Good Prevention Program

First, administrative checks and balances help provide oversight and accountability. This includes the development of drug diversion teams. Teams should meet at set intervals to certify that controlled substance legal and regulatory requirements are met. Oversight should include general and random screens for handling of all controlled substances. The teams should ensure prompt audits and investigations, and results should be taken seriously. Automated intelligence provides teams with additional information with standard deviations to analyze efforts.

Second, teams should engage in health system-wide processes. This involves addressing components of human resources management (2 witnesses for medication waste), automation and technology (appropriate policy and procedures, including sign-outs), ensuring prompt event reporting and investigation, proactive monitoring (including scheduled and random counts), and camera surveillance. A good program makes it difficult to divert controlled substances while ensuring patient care.

Third, pharmacists should establish adequate user competencies, oversight, and training around chain of administration, custody, disposal, internal pharmacy supply chain, prescribing, returns, security and storage, and waste. An avenue for providing feedback and shared decision-making for these processes should be used.

A culture of collaboration in team efforts should include a variety of departments, including anesthesiology, human resources, medicine, nursing, and pharmacy, with support from the executive team. Ensuring transparent communication, goals, and perceived value with other disciplines is crucial to efficient controlled-substance management.

Medication Waste

Diversion and waste are significant problems, especially in areas where there is high use of drug products. The more waste produced, the greater the prospect for medication diversion. Reducing waste reduces diversion risk. The Third Consensus Development Conference on the Safety of IV Delivery Systems has a list of 10 items to ensure safe handling and reduce waste of intravenous products. Best practices include competencies, formal education, interdisciplinary efforts, legislative and regulatory frameworks, standardizing packaging sizes, training, and use of automation and technology where possible with appropriate policy and oversight. The DEA’s 2014 Final Rule on Disposal of Controlled Substances discusses disposal of a DEA registrant’s inventory. But it does not discuss disposal by health care facilities of partially administered syringes or single-dose vials (eg, medication waste) or how household users should handle waste disposal. The Environmental Protection Agency amended the Resource Conservation and Recovery Act in 2020 to require staff members to render wasted medication irretrievable. Product can no longer be poured down the sink into wastewater. This is now an added consideration.

Conclusion

Pharmacists should identify institutional practices supporting best practices, medication safety, and staff education to minimize drug diversion risks. Engaging key interdisciplinary stakeholders to gain support and improve the institution’s controlled-substance stewardship program is the goal essential to reducing the opportunity for diversion and ensuring a successful program.

REFERENCES

Targeted Therapy Allows Patients to Live With CML
Precise, more potent therapy can offer reduced toxicity.

Jameshia A. Below, PharmD, and Alexis Horace, PharmD, BCACP, AAHIVP

Developing Chronic Myeloid leukemia (CML) was once considered a death sentence. However, the introduction of targeted therapy transformed this cancer into a manageable, chronic condition.

As of February 2022, CML accounted for about 15% of all adult leukemia cases, according to data from the National Comprehensive Cancer Network. CML is a myeloproliferative disorder that originates in the stem cells and develops when a translocation involving chromosome 9 and chromosome 22 occurs. This translocation creates the Philadelphia (Ph) chromosome that results in fusion gene BCR-ABL.

CML is characterized by an uncontrollable growth of myeloid cells at different stages. There are 3 stages patients may present: the chronic phase, accelerated phase, and blast phase or blast crisis. Each is characterized by the number of immature cells detected in the bone marrow and presence of cytogenetic or molecular abnormalities. When the chronic phase remains untreated, it will eventually progress to the more aggressive accelerated phase or blast phase. Patients who progress to an accelerated or blast phase are treated similarly to patients with acute leukemia.

Most patients presenting with CML are asymptomatic and a positive diagnosis is made after a routine laboratory evaluation. Some characteristics seen in the complete blood count may include leukocytosis paired with a left shift and myelocyte bulge, blasts equal to or less than 2%, basophilia, and eosinophilia. Other symptoms in patients with CML include fatigue, weight loss, malaise, left upper quadrant fullness or pain, and bleeding issues in rarer cases. These signs and symptoms are usually the result of anemia or splenomegaly.

Prognostic Risk
CML prognosis has greatly improved since the development of tyrosine kinase inhibitors (TKIs). Prognosis has shown an association with several clinical characteristics. Many models have been developed to help determine the prognostic risk, including the Sokal index and the Hasford score.

The Sokal index predicts survival-based characteristics such as the patient’s age, spleen size on clinical examination, platelet count, and percentage of blasts in the peripheral blood. Depending on the Sokal score, patients are classified as having low-risk, intermediate-risk, or high-risk CML, which helps guide therapy selection. The Hasford score model includes similar variables but also accounts for the amount of eosinophils and basophils in the peripheral blood.

Treatment Goals
Current treatment goals vary based on the stage of CML. The overarching goal of therapy is eliminating Ph chromosomes in the bone marrow and achieving...
a major molecular response (MMR).

For chronic-phase CML, the treatment goals include maintaining hematologic, cytogenetic, and molecular remission; preventing progression to accelerated phase or blast crisis; and minimizing toxicity. The goal for patients with accelerated phase or blast crisis CML is to induce the disease into chronic phase.

Effectively assessing how patients respond to therapy can play a critical role in helping identify patients who are at high risk of disease progression or who may benefit from a change in therapy. The 3 types of responses to therapy are hematologic, cytogenetic, and molecular.8,9

**Targeted Therapy**

In the past few decades there has been a huge shift from traditional chemotherapy medications, which affect organ systems, to more specific targeted agents. The use of targeted agents provides a precise, more potent therapy with reduced toxicity.

First-line treatment of chronic-phase CML includes TKIs for BCR-ABL, such as imatinib (Gleevec; Novartis), dasatinib (Sprycel; Bristol Myers Squibb), nilotinib (Tasigna; Novartis), bosutinib (Bosulif; Pfizer), ponatinib (Iclusig; Takeda), and asciminib (Scemblix; Novartis), and the protein synthesis inhibitor omacetaxine (Synribo; Teva Pharmaceuticals).10 Studies have demonstrated superior rates of complete responses in TKIs, and they are positively transforming outcomes for patients who have received CML diagnoses.10,11

Nevertheless, patients may develop resistance to TKIs. Resistance to imatinib led to the development of second-generation TKIs such as dasatinib, nilotinib, and bosutinib. These agents are more potent inhibitors of BCR-ABL than imatinib and exhibit significant activity against all resistant mutations except T315I. The second-generation TKIs have produced a faster, deeper response compared with imatinib, but do not provide any decrease in mortality.12

The third-generation TKI ponatinib was developed to help combat T315I, which is commonly known as the gatekeeper mutation. Ponatinib has demonstrated activity against T315I mutations and BCR-ABL mutations that are resistant or intolerant to other TKIs. The decision to use ponatinib must be determined after a risk-vs-benefit assessment because of potential toxicities.13,14

Asciminib is an inhibitor that has multiple targets. It is a first-in-class BCR-ABL inhibitor specifically targeting the ABL myristoyl pocket. This agent shows activity against the T315I mutation and has the potential to overcome resistance to other approved TKIs.

In the ASCENBL trial (NCT03106779),15 asciminib was compared to bosutinib and showed a superior efficacy with an improvement in the safety profile. In this randomized, open-label, phase 3 trial, 233 patients with chronic-phase CML previously treated with 2 or more TKIs were evaluated. After 24 weeks, the MMR rate was 25.5% vs 13.2% for asciminib and bosutinib, respectively.15,16

**Toxicity Management**

The decision on a course of therapy for treating CML depends on the toxicity profile of the TKIs available. Treatment heavily relies on the monitoring of adverse effects (AEs) to enhance quality of life. Although most TKIs are generally well tolerated by patients when combined with adequate supportive care, the table highlights the precautions, medication-specific AEs, and monitoring parameters to consider for each TKI.

Myelosuppression may occur because of TKIs targeting the c-KIT receptors, which are responsible for the development of normal blood cells, mast cells, and melanocytes. It is important to monitor complete blood counts weekly for the first 2 months, then every month after for most TKIs.17 The amount of occurrence varies according to the agents, with the greatest rates of grade 3 or 4 neutropenia seen with dasatinib. Other AEs that occur more frequently include fatigue, myalgia, nausea, and vomiting.18

Cardiovascular toxicity is another common drug class effect. This condition is typically reversible with the administration of systemic steroids and circulatory support. The cardiovascular status of patients should be routinely monitored when administering any TKI. Decreased left ventricular function is another class effect, occurring more in dasatinib and ponatinib compared with the other TKIs. Although the rates of this AE are rare, the longevity of treatment combined with an aging population increases the risk. For this reason, patients should be monitored regularly for the development of heart failure.

There is also the risk of QT prolongation. Ponatinib provides the least risk of QT prolongation and is equal
**TABLE. TOXICITY PROFILES**

<table>
<thead>
<tr>
<th></th>
<th>First generation</th>
<th>Second generation</th>
<th>Third generation</th>
<th>STAMP inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TKI</strong></td>
<td>Imatinib</td>
<td>Dasatinib</td>
<td>Nilotinib</td>
<td>Bosutinib</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>400 mg once daily</td>
<td>100 mg once daily</td>
<td>300 mg twice daily</td>
<td>400 mg once daily or 500 mg once daily</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45 mg once daily</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>80 mg once daily or 40 mg twice daily or 200 mg twice daily**</td>
</tr>
<tr>
<td><strong>Precautions, adverse effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea, nausea, vomiting may occur; in such case, withhold therapy or reduce dose if needed</td>
<td>Bleeding-related events</td>
<td>Pancreatitis</td>
<td>GI toxicity</td>
<td></td>
</tr>
<tr>
<td>Perform hepatic enzyme tests monthly for the first 3 months, then whenever clinically indicated</td>
<td>Pleural and pericardial effusions</td>
<td>Hyperglycemia</td>
<td>Hepatic toxicity</td>
<td></td>
</tr>
<tr>
<td>Decline in eGFR noted; monitor renal function at baseline and during therapy, especially in patients with preexisting renal impairment; may consider dose adjustments based on current eGFR</td>
<td>Pulmonary arterial hypertension</td>
<td>Hepatotoxicity</td>
<td>Renal toxicity</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Electrolyte disturbances</td>
<td></td>
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<tr>
<td>Hemorrhage</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Clinical pearls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias associated with higher doses at ≥ 750 mg and dependent on stage of disease</td>
<td>Because of potential for severe G1 hemorrhaging, use with caution if patient is on antithrombotic or anticoagulant therapy</td>
<td>Use caution in patients with a history of pancreatitis and uncontrollable diabetes</td>
<td>Diarrhea, nausea, vomiting may occur; in such case, withhold therapy or reduce dose if needed</td>
<td></td>
</tr>
<tr>
<td>Monitor for cardiac disorders</td>
<td></td>
<td>Monitor hepatic function monthly or as clinically indicated</td>
<td>Perform hepatic enzyme tests monthly for the first 3 months, then whenever clinically indicated</td>
<td>Monitor liver function tests at baseline, then at least monthly or as clinically indicated</td>
</tr>
<tr>
<td>Decrease if GI discomfort occurs</td>
<td></td>
<td>Electrolyte disturbances need to be corrected before and during therapy; monitor periodically with routine laboratory work-up</td>
<td>Decline in eGFR noted; monitor renal function at baseline and during therapy, especially in patients with preexisting renal impairment; may consider dose adjustments based on current eGFR</td>
<td>Monitor liver function tests at baseline, then at least monthly or as clinically indicated</td>
</tr>
<tr>
<td>Imatinib should be taken with food, large glass of water</td>
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<td></td>
<td>Assess serum lipase and amylase levels monthly during treatment, or as clinically indicated</td>
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<td></td>
<td></td>
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<td></td>
<td>If lipase and amylase elevation are accompanied by abdominal symptoms, temporarily withhold asciminib</td>
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<td></td>
<td></td>
<td>Monitor blood pressure and manage with standard antihypertensive therapy; for grade 3 or higher hypertension, temporarily withhold, reduce dose, or permanently discontinue</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; CML, chronic myeloid leukemia; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; STAMP, specifically targeting the ABL myristoyl pocket; TKI, tyrosine kinase inhibitor.

*Dosing shown for chronic-phase CML.

**Dosing for chronic-phase CML with T315I mutation.
to or less than the risk level from bosutinib for patients. Dasatinib provides a greater risk of QT prolongation than bosutinib, whereas nilotinib provides the highest risk of QT prolongation among the TKIs. To monitor this risk, evaluating levels of electrolytes such as calcium, potassium, and magnesium in patients is recommended. Additionally, it is recommended to not administer TKIs with medications like cytochrome P450 3A4 inhibitors or foods that can prolong QT.\textsuperscript{17,18}

Among the other AEs, fluid retention and edema are also observed in patients when using TKIs. Fluid retention can manifest as the cause of pleural effusion, presenting as a dry cough or shortness of breath. Treatment with a short course of steroids and diuretics can mitigate this AE. Dose reductions may help to diminish the risk as well.\textsuperscript{17-22}

**Emerging Therapies**

Newer TKIs may be more attractive because of their higher rates of efficacy and faster, deeper response compared with imatinib. With the ongoing concern for development of resistance, clinical trials are being conducted to investigate new treatment options. Some BCR-ABL inhibitors in clinical trials are radotinib and flumatinib.

Radotinib is a second-generation BCR-ABL TKI that has a profile similar to that of imatinib. It is approved as a first-line therapy option for patients with chronic-phase CML in Korea based on the results of the phase 3 RERISE study (NCT03722420).

In RERISE, 241 patients with newly diagnosed CML were evaluated. Patients who received radotinib demonstrated significantly faster, higher rates of MMR compared with imatinib at 86\% vs 75\%, respectively. Overall efficacy results were comparable to long-term results seen with other second-generation TKIs. Radotinib had a well-tolerated safety profile and can be an appealing treatment option because of lower cost compared with other second-generation BCR-ABL TKIs.\textsuperscript{23}

Flumatinib is a BCR-ABL inhibitor that shows more potent activity compared with imatinib. The phase 3 randomized trial FESTnd (NCT02204644) compared the efficacy and safety of flumatinib with that of imatinib in 394 patients with newly diagnosed CML. The study revealed that at 6 months, the rate of MMR was significantly higher in patients receiving flumatinib than in those receiving imatinib at 33.7\% and 27.1\%, respectively. These results demonstrated that MMR was achieved more quickly among patients receiving flumatinib. During the trial, flumatinib also demonstrated significantly lower rates of AEs such as edema, pain in extremities, rash, neutropenia, anemia, and hypophosphatemia. These results may suggest that flumatinib can be an alternative for patients with previously untreated chronic-phase CML.\textsuperscript{24}

Other novel agents that show promising results include olverembatinib (HQP1351) and vodobatinib (K0706). Both novel drugs are third-generation TKIs that can be used to treat patients with CML who are resistant to imatinib and second-generation TKI therapies. PF-114 is a fourth-generation TKI that is effective against both BCR-ABL and T315I mutation similarly to ponatinib with potentially reduced cardiotoxicity.\textsuperscript{25}

**Treatment-Free Remission**

A potential new goal of CML therapy is treatment-free remission because of the long-term survival outcomes seen with the use of TKIs. Treatment-free remission is defined by the ability to maintain minimal residual disease that is undetectable or detectable at a stable low level after TKI discontinuation. Many individuals who have an optimal response can achieve life expectancy close to that of the general population.

Although treatment with TKIs is beneficial, they do come with prolonged use that can have an excessive cost and burden on patients. Recently, studies have shown that in a select group of patients with chronic-phase CML, TKIs can be safely discontinued. To be considered for TKI discontinuation, patients must meet strict criteria. Many studies are needed to safely make this an option for more patients in the future.\textsuperscript{26,27}
New Treatment Options Are on the Horizon for β-Thalassemia
Gene therapies in late-stage development may soon provide hope for a cure.

ADRIENNE BRENNAN, PHARMD, CSP

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β-TALASSEMIA IS A genetic disorder causing reduced production of hemoglobin, resulting in anemia. Symptoms can vary widely depending on whether an individual has β-thalassemia minor, intermedia, or major. In the most severe form, patients with β-thalassemia major, also known as Cooley anemia, become symptomatic in their early years of life.

β-Thalassemia is highly prevalent in the Mediterranean, Middle East, Africa, South Asia, and India but historically has been a rare disease in the United States. However, immigration to the United States from affected regions during the past 50 years has led to a 7.5% increase in prevalence of the disease in the US population. It is now estimated that approximately 1000 individuals in the United States have β-thalassemia major.

Treatment Landscape Today
β-Thalassemia has limited treatment options, with the disease mainly managed with red blood cell transfusions at regular intervals, generally every 2 to 4 weeks, and chelation therapy with a product such as deferoxamine (Desferal; Novartis) or deferasirox to remove excess iron from the bloodstream. Without transfusions and chelation therapy, patients with β-thalassemia may experience symptoms such as chronic fatigue, cardiac and liver disease, and pain. The only curative treatment for β-thalassemia major is a stem cell transplant.

In late 2019, luspatercept-aamt (Reblozyl; Bristol Myers Squibb) became the first drug approved for treatment of anemia in adult patients with β-thalassemia who require regular red blood cell transfusions. The approval of luspatercept-aamt was supported by the BELIEVE trial (NCT02604433), a phase 3 multicenter, randomized, double-blind, placebo-controlled trial enrolling 336 adult patients with β-thalassemia requiring routine red blood cell transfusions. Trial participants were randomized 2:1 to either luspatercept-aamt 1 mg/kg subcutaneously every 3 weeks with dose increases of 1.25 mg/kg as permitted, or placebo subcutaneous injections every 3 weeks. All patients were permitted to remain on best supportive care, such as transfusions, chelating agents, antibiotics, antivirals, antifungals, and nutritional support. The primary end point of 33% reduction or more from baseline in transfusion burden from weeks 13 to 24 was met, with 21.4% of patients in the luspatercept-aamt arm achieving this compared with 4.5% of patients in the placebo arm.

The most common adverse effects (AEs) associated with luspatercept-aamt include headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea, nausea, trouble breathing, and dizziness. Additionally, thromboembolic events and hypertension have been associated with luspatercept-aamt treatment. According to the Thalassaemia International Federation’s 2021 guidelines for the management of transfusion-dependent β-thalassemia, luspatercept-aamt could
be beneficial for reducing iron chelation therapy as a result of reduced transfusion burden, and may be best positioned as a treatment option for patients living in areas with poor access to blood transfusions, as well as those who were transfusion independent but now require transfusions. 

Gene Therapy Offers Promise

Although luspatercept-aamt has been a great advancement in the treatment of transfusion-dependent β-thalassemia, a need remains for therapies that can eliminate the need for transfusions and cure the disease. The known genetic origins of β-thalassemia make it an excellent candidate for gene therapy, and 2 gene therapies in late-stage development may soon provide hope for a cure.

Betibeglogene autotemcel (Zynteglo; bluebird bio) is a 1-time ex vivo gene therapy for adults, adolescents, and pediatric patients with all genotypes (β0/β0 and non-β0/β0) of transfusion-dependent β-thalassemia. Treatment with betibeglogene autotemcel involves extraction of the patient’s stem cells, introduction of functional copies of a modified form of the β-globin gene (βA[T87Q] -globin gene) into the stem cells via a BB305 lentiviral vector, and infusion of the modified cells into the patient. With a functioning βA(T87Q) -globin gene, the patient should then be able to produce their own functional gene therapy–derived adult hemoglobin and no longer need red blood cell transfusions. 

Currently, betibeglogene autotemcel is approved in the European Union, United Kingdom, Iceland, Liechtenstein, and Norway for patients 12 years and older with transfusion-dependent β-thalassemia who are eligible for stem cell transplant but do not have an available donor. Further, bluebird bio has submitted a biologics license application (BLA) to the FDA, supported by data from phase 1/2 and phase 3 trials. In the phase 3 NorthStar-2 trial (NCT02906202) investigating betibeglogene autotemcel, 23 adult and pediatric patients with non-β0/β0 genotypes were treated with betibeglogene autotemcel. In total, there were 22 patients who were eligible for evaluation, and 20 of them achieved transfusion independence, including 6 of 7 patients under age 12 years. The FDA also granted priority review of the BLA submission, and the expected action date is August 19, 2022, which gives a delay of 3 months from the original date of May 20, 2022, to allow the FDA time to review additional clinical data.

CTX001 is a gene therapy in phase 3 clinical trials, codeveloped by CRISPR Therapeutics and partner Vertex. Like betibeglogene autotemcel, it is a 1-time ex vivo treatment but targets an increase in production of fetal hemoglobin via CRISPR/Cas9 editing of the BCL11A gene in the patient’s cells. Interim data from 10 adult and pediatric patients with varying genotypes enrolled in the VX21-CTX001-141 trial (NCT05356195) demonstrated increased hemoglobin and fetal hemoglobin after administration of CTX001. During the trial, all 10 patients were able to stop transfusions within 2 months of treatment. CRISPR Therapeutics and Vertex plan to submit a BLA to the FDA in late 2022.

Potential Limitations of Gene Therapy for β-Thalassemia

Gene therapy is not without risk or safety concerns. There have been reports of myeloid malignancies following treatment with betibeglogene autotemcel for sickle cell disease, although the gene therapy has not been directly implicated in causing the malignancies. Even though patients with sickle cell disease and transfusion-dependent β-thalassemia have increased risk of developing myeloid malignancies irrespective of treatment with gene therapy, this remains an area of concern.

Durability of effect is also an unknown. In addition to safety concerns, cost may be a barrier to accessing gene therapy for patients with β-thalassemia. Betibeglogene autotemcel is priced at the equivalent of $1.8 million in Europe, and bluebird bio withdrew its approval in Germany after failing to agree on pricing with health authorities there.

The Role of the Specialty Pharmacy

Despite potential limitations, the possibility of not 1 but 2 gene therapies for β-thalassemia being available in the United States in the near future is an exciting advancement for patients and their families. Specialty pharmacists currently help patients with β-thalassemia manage their treatment with luspatercept-aamt and chelation therapy, assisting with medication education, AE management, proper dosing, and accessing co-pay assistance.
As gene therapies for β-thalassemia come to market and patients’ needs for luspatercept-aamt or chelation therapy diminish, specialty pharmacy still has an opportunity to play a key role in the care continuum of the patient. Pharmacists’ expertise in medication education may be essential when providing patients initial counseling on all aspects of their gene therapy. Specialty pharmacies also have infrastructure that could be useful for the dispensing of gene therapy to a medical center for administration, and clinical management programs could be used to track long-term outcomes information that will be important to payers and manufacturers.

**REFERENCES**

Current Treatment Modalities, Available Therapeutics for Prostate Cancer See Growth
The disease can often be detected and managed early before a patient experiences signs or symptoms.

PROSTATE CANCER is the second-most common cancer in American men and the second-leading cause of cancer death in the United States.1,2 In 2022 alone, the American Cancer Society estimates 268,490 new cases of prostate cancer in the country and 34,500 deaths.2

As men live longer, their chances of having prostate cancer increase.1,2 Although incidence of prostate cancer has nearly doubled over the past 20 years, early detection and improved treatment modalities have significantly decreased deaths associated with the disease.1

Background
Located below the bladder, the prostate is a walnut-sized gland in males that stores seminal fluid, a liquid that nourishes sperm.1,2 Almost all prostate cancers are adenocarcinomas that develop from these gland cells.2 Although the exact cause of prostate cancer remains unknown, the growth of cancer cells is known to be stimulated by the male hormone testosterone.1,2

Several factors may increase the risk of developing prostate cancer, including age (> 50 years); genetic predisposition/family history, such as BRCA1 or BRCA2 genes or Lynch syndrome (hereditary nonpolyposis colorectal cancer); and a high-fat diet.1,2 African American men are also twice as likely as non-Hispanic White men to receive prostate cancer diagnoses, whereas the disease occurs less frequently in Asian and Hispanic men.1,2

Prostate cancer can often be detected early before a man experiences signs or symptoms; some prostate cancers grow so slowly that they may never cause issues.1,2 Prostate-specific antigen (PSA) levels in a man’s blood and a digital rectal examination (DRE) are the current standards for initial screening.2,3

Approximately 80% of prostate cancers are diagnosed at an early, more treatable stage, with the survival rate for these patients at almost 100%.1,2 Abnormal findings in PSA or DRE may warrant biopsy to pathologically confirm a diagnosis of cancer.2,3 If cancer is confirmed, additional laboratory and imaging tests typically are performed to determine aggressiveness or staging of the cancer.1-3 Table 1 highlights the stages of prostate cancer.1,3

Treatment Modalities and Available Therapeutics
Treatment of prostate cancer is individualized; current options are based on factors including grade and stage of the cancer, as well as a patient’s health status and comorbidities, age, expected life span, and personal preferences.1,4 Localized prostate cancer ranges from indolent disease not needing treatment or disease requiring some treatment to aggressive disease calling for multimodal treatment.1,4 In older patients—
such as men with medical conditions precluding surgery or radiation or those with an early-stage, slow-growing tumor—providers may suggest “watchful waiting” to closely monitor disease progression rather than providing immediate treatment.¹,³

Surgery is the most common treatment option in cases where early-stage cancer is localized to the prostate and immediate surrounding tissue.¹,² Prostatectomy involves removal of the entire prostate gland, attached seminal vesicles, and nearby tissue.¹ A second type of surgery, transurethral resection of the prostate, involves removal of prostate tissue by inserting a tube through the urethra.¹

For early-stage prostate cancer, radiation therapy is the second-most-common intervention and is limited to cases where the cancer is localized to the prostate gland.¹,² Two types of radiation treatment designed to kill cancer cells are external beam radiation and brachytherapy, which uses implanted radioactive seeds.¹

Androgen deprivation therapy (ADT) is the most common treatment for more aggressive localized prostate cancer or for disease that has metastasized.¹,⁴ Because prostate cancer cells grow and feed on testosterone, ADT works by blocking its production or decreasing its effects in the body. However, in the treatment of prostate cancer, ADT is often accompanied by use of the following therapies³:

- Androgen blockade treatments including orchiectomy (surgical removal of the testicles, which produce testosterone) or use of medications to suppress hormone production
- Systemic hormone therapies, including luteinizing hormone–releasing hormone (LHRH) agonists, LHRH antagonists, antiandrogens, corticosteroids, estrogen, and androgen synthesis inhibitors
- Antiandrogen medications, which block receptors on prostate cancer cells from receiving testosterone
- Corticosteroids, such as prednisone, methylprednisolone, hydrocortisone, and dexamethasone, which can prevent the adrenal glands from producing testosterone
- Estrogens, which can stop the adrenal glands from producing testosterone, and androgen synthesis inhibitors, which can block androgen production

ADT is considered the first-line pharmacologic treatment for patients with advanced or metastatic prostate cancer, but many men with advanced disease eventually stop responding and are categorized as castration resistant.³,⁴ Castration-resistant prostate cancer (CRPC) is defined as a prostate cancer that progresses clinically, radiographically, or biochemically despite lowered levels of testosterone.⁴

There are 4 different patient-specific groups in advanced disease: metastatic castration-resistant prostate cancer (mCRPC), metastatic castration-sensitive prostate cancer (mCSPC), nonmetastatic castration-resistant prostate cancer (nmCRPC), and nonmetastatic castration-sensitive prostate cancer (nmCSPC).¹,³ For men who progress to CRPC, ADT with an LHRH agonist or antagonist is continued, but additional systemic therapies may be added depending on various

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**TABLE 1. Stages of Prostate Cancer¹³**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor description</th>
<th>Potential treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I/A/T1</td>
<td>Located within prostate but too small to be detected by DRE or imaging</td>
<td>Watchful waiting or, in some cases, surgery or radiation</td>
</tr>
<tr>
<td>Stage II/B/T2</td>
<td>Located within the prostate and detectable by DRE</td>
<td>Surgery, radiation, or hormonal therapy</td>
</tr>
<tr>
<td>Stage III/C/T3</td>
<td>Spread to the immediate surrounding tissue</td>
<td>Hormone therapy before and after surgery and/or radiation</td>
</tr>
<tr>
<td>Stage IV/D/M1</td>
<td>Metastasized and spread beyond the pelvic region</td>
<td>Hormone therapy before and after surgery and/or radiation and/or chemotherapy where hormone therapy is ineffective</td>
</tr>
</tbody>
</table>

DRE, digital rectal examination.
patient and disease characteristics. For aggressive cases, especially those where the cancer has spread outside the prostate, hormone therapy is often combined with chemotherapy, although chemotherapy may be used when hormone therapy is no longer effective. Chemotherapy tends to be harsh on patients because it attacks and destroys the rapidly dividing cancer cells, but also kills normal cells. Therefore, careful monitoring of patient response and side effects is crucial. 

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Lead company</th>
<th>Target</th>
<th>Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate (Yonsa)</td>
<td>Sun Pharmaceutical Industries Ltd</td>
<td>Cytochrome P450c17</td>
<td>05/2018</td>
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<td>Abiraterone acetate (Zytiga)</td>
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<td>Cytochrome P450c17</td>
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<td>Apalutamide (Erleada)</td>
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<td>Androgen receptors</td>
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<td>Bicalutamide* (Casodex)</td>
<td>AstraZeneca PLC</td>
<td>Androgen receptors</td>
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<td>Cabazitaxel (Jevtana)</td>
<td>Sanofi</td>
<td>Microtubules (tubulin)</td>
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<td>Darolutamide (Nubeqa)</td>
<td>Bayer AG</td>
<td>Androgen receptors</td>
<td>07/2019</td>
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<td>Degarelix acetate (Firmagon)</td>
<td>Ferring Pharmaceuticals</td>
<td>GnRH receptor</td>
<td>12/2008</td>
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<td>Docetaxel (Docofrez)</td>
<td>Sun Pharmaceutical Industries Ltd</td>
<td>Microtubules (tubulin)</td>
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<td>Docetaxel injection</td>
<td>Eagle Pharmaceuticals, Inc</td>
<td>Microtubules (tubulin)</td>
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<td>Docetaxel* (Taxotere)</td>
<td>Aventis Pharmaceuticals</td>
<td>Microtubules (tubulin)</td>
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<td>Enzalutamide (Xtandi)</td>
<td>Astellas Pharma, Inc</td>
<td>Androgen receptors</td>
<td>08/2012</td>
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<td>Estramustine phosphate sodium* (Emcyt)</td>
<td>Pfizer Inc</td>
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<td>Flutamide* (Eulexin)</td>
<td>Schering</td>
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<td>TerSera Therapeutics LLC</td>
<td>GnRH receptor</td>
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<td>Leuprolide acetate (Eligard)</td>
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<td>Leuprolide acetate (Lupron Depot)</td>
<td>AbbVie Inc</td>
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<td>Leuprolide mesylate (Camcevi)</td>
<td>Foresee Pharmaceuticals</td>
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<td>Mitaxantrone* (Novantrone)</td>
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<td>Olaparib (Lynparza)</td>
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<td>Myovant Sciences Ltd</td>
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<td>Rucaparib camsylate (Rubraca)</td>
<td>Clovis Oncology, Inc</td>
<td>PARP</td>
<td>05/2020</td>
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<td>Sipuleucel-T (Provenge)</td>
<td>Dendreon Corp</td>
<td>Immune system, PAP, stem cells/other cell therapies</td>
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<td>Triptorelin pamoate (Trelstar)</td>
<td>Verity Pharmaceuticals, Inc</td>
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<td>06/2000</td>
</tr>
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</table>

ERα, estrogen receptor α; GnRH, gonadotropin-releasing hormone; PAP, prostatic acid phosphatase.

*Has approved generic competition.
cells. For men with bone metastases and CRPC, the addition of bone-modifying drugs such as denosumab (Xgeva; Amgen), zoledronic acid (Reclast; Novartis), or alendronate sodium (Binosto; ASCEND Therapeutics) is recommended.3,4

PARP inhibitors are another class of medications with products that have become valuable treatment options.5,6 PARP is a type of enzyme that helps repair DNA damage in cells.5,6 As a type of targeted therapy, PARP inhibitors work by preventing cancer cells from repairing, thus allowing them to die.5,6

**Table 2** illustrates currently approved therapeutics in prostate cancer and their respective targets.1

**Evolving Landscape, Latest Key Takeaways in Prostate Cancer**

The anticipated development of additional novel therapies in the near-term pipeline may continue to change standards of care in prostate cancer as well as expand the catalog of promising treatment options available to patients. **Online Table 3** shows the current investigative entities in the near-term pipeline for prostate cancer and their respective targets.

Because of its established efficacy across different patient-specific groups, recent and planned expansions into additional patient populations, and a lack of near-term generic competition, enzalutamide (Xtandi; Astellas Pharma US, Inc and Pfizer Inc), a next-generation androgen receptor (AR) inhibitor, stands as a market leader in prostate cancer treatment.1,5,6 Expansion opportunities in the future of enzalutamide for mCRPC patients include potential use in combination with PARP inhibitors.5,6

In the current phase 3 EMBARK trial (NCT02319837) for nonmetastatic hormone-sensitive prostate cancer (nmHSPC), enzalutamide is being studied in combination with leuprolide.1,5,6 This combination represents an opportunity to improve outcomes earlier in the treatment paradigm, but its uptake may be determined on justification of the clinical and financial considerations of enzalutamide treatment over existing localized options.

Since the 2018 US generic launch of abiraterone, use of blockbuster brand abiraterone acetate (Zytiga; Janssen Biotech, Inc) has declined, but the P450c17 inhibitor as part of standard regimens may expand to include several novel combinations.5,6 Rucaparib (Rubraca; Clovis Oncology) and olaparib (Lynparza; AstraZeneca) are being studied in the first-line treatment of mCRPC: rucaparib plus enzalutamide vs enzalutamide alone and olaparib with abiraterone against abiraterone alone.1,5,6 Most recently, the olaparib-abiraterone combination has shown top-line results with efficacy in patients regardless of homologous recombination repair status, opening a door for a label expansion opportunity.1,5,6 Niraparib (Zejula; GSK) and talazoparib (Talzenna; Pfizer) are being researched in combination with next-generation treatments.1,5,6 There is a relatively low prevalence of homologous recombination deficiency or BRCA biomarkers, which may limit the utility of PARP inhibitors with AR modulators, such as talazoparib with enzalutamide or niraparib with abiraterone in patients with mCRPC as first-line therapy options.5,6

Expansion into earlier lines of therapy and additional patient populations is ongoing, but the treatment paradigm has shifted in patients with nmCRPC and nmHSPC because of next-generation AR inhibitors darolutamide (Nubeqa; Bayer) and apalutamide (Erleada; Janssen Biotech, Inc).5,6 Bayer is seeking to expand the label for darolutamide for use in patients with high-risk localized disease and those with nmHSPC. Apalutamide may be differentiated with an aggressive development plan to include potential expansion to patients with nmCRPC who are chemotherapy-naïve in combination with abiraterone and treating patients with localized disease previously treated with surgery or radiation.1,5,6

Several checkpoint inhibitors are in development, but additional data from the ongoing trials will determine their future potential in prostate cancer. Pembrolizumab (Keytruda; Merck & Co, Inc) is being studied in combinations with olaparib, enzalutamide, and docetaxel for patients with mCRPC.1,5,6 Nivolumab (Opdivo; Bristol Myers Squibb) is being evaluated with docetaxel. Atezolizumab (Tecentriq; Genentech USA, Inc), a PD-L1 antibody, is in phase 3 trials with enzalutamide or cabozantinib (Cabometyx; Exelixis, Inc) for patients with mCRPC after failure with next-generation hormone therapy.1,5,6

In December 2020, oral GnRH receptor antagonist relugolix (Orgovyx; Myovant Sciences GmbH and
Pfizer Inc) was approved. Data from the phase 3 HERO trial (NCT03085095) may enable its use in patients with localized definitive therapy also requiring ADT, as well as offer an intermittent ADT option in patients with advanced HSPC with a goal of minimizing potential adverse effects (AEs).1,5,6

Gene therapy and cell therapy are overlapping fields of novel biomedical research with the goal of treating, preventing, or potentially curing diseases such as prostate cancer.7 Gene therapies function to correct genetic defects that may lead to growth of cancer cells, and may also treat diseases by replacing, inactivating, or introducing genes into the body, usually delivered through a viral vector.7,8 The transferred genetic material can increase disease-fighting proteins or reduce the levels of disease-causing proteins.

Cell therapies target the delivery of immune cells with the goal of eradicating the cancer cells.7,9 These therapies transfer modified live human cells into the body to restore or alter their functions and enhance their therapeutic potential.7,9 The cells used can come from the patient (autologous cells) or a donor (allogeneic cells).7,9

One example of cells originating from the patient is the chimeric antigen receptor (CAR) T-cell therapy.7,9 This type of cell therapy removes the patient’s T cells and genetically reengineers them. These reengineered cells can then express a specific surface receptor that recognizes antigens of malignant cells, allowing T cells to bind and attack the tumor.7,9

Bispecific T-cell engager therapy and CAR T therapies are being investigated as treatments for the prostate-specific membrane antigen (PSMA) or prostate stem cell antigen in patients with mCRPC, which typically overexpresses these types of antigens.7,9 Radiolabeled lutein antibodies directed toward PSMA are also being investigated as options for imaging and treatment.

One potential breakthrough treatment in development for mCRPC is 177Lu-PSMA-617. This treatment has 2 components: a compound targeting the cancer cell protein PSMA and a precise radioactive particle that destroys cancer cells.1 Healthy prostate cells do not contain PSMA, or do so at very low levels.1,5,6

Conclusion
It is normal for patients to want to start treatment as soon as possible after diagnosis; however, prostate cancer can grow very slowly, so patients have options. The array of therapeutic selections for patients with prostate cancer has expanded in recent years and choices depend on patient preferences, signs and symptoms, biomarkers, presence or absence of visceral disease, and potential AEs. Although selecting and sequencing optimal therapies for patients remains a challenge, newer study data arm patients and providers with information needed to make important treatment decisions. As practice standards evolve, specialty pharmacists can help develop individualized management plans for patients with prostate cancer involving the selection of optimal treatment strategies and approaches.
Great Strides Drive Progress Toward Precision Medicine in Lung Cancer Therapy

Disease management is moving toward holistic care of the patient in the long term.

MARILYN N. BULLOCH, PHARMD, BCPS, FCCM

LUNG CANCER IS THE THIRD-MOST-COMMON CANCER in the United States, claiming more lives annually than any other type of the disease. Although tobacco use is the leading cause of lung cancer, up to 20% of cases occur in patients who have never smoked but have a family history of the disease or were exposed to naturally occurring radon, workplace chemicals (eg, asbestos, diesel fuel), air pollution, or radiation treatment. Less than 25% of patients with lung cancer diagnoses survive more than 5 years, which is substantially lower than the 5-year survival rates for those with breast (89%), prostate (92.9%), or colorectal (65.7%) cancers.

There are 2 types of lung cancer: small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC). Each type is categorized into subtypes based on specific cancer cell characteristics (ONLINE TABLE). Although rates of lung cancer have steadily increased for decades, there has been a recent drop attributed to a decline in tobacco smoking and improvement in the number, type, and quality of the therapeutic options available for lung cancer treatment.

In 2021, the FDA approved 5 new medications for lung cancer and added the disease as an indication for 3 others already commercially available. All but 1 of these medications were for NSCLC, and 4 are oral therapies. There are niche considerations regarding use of each newly approved medication for lung cancer, representing a shift toward precision medicine in lung cancer treatment. The newly approved medications for NSCLC provide more focused oncologic therapy options that target actional biomarkers for mutations occurring in up to 40% of patients with the disease. The individual prevalence of these mutations in NSCLC is relatively low but often can result in more aggressive cancers with poor outcomes.

Advances in Management of NSCLC

To identify these biomarkers in patients with NSCLC, special testing must assess whether a patient’s cancer is likely to respond to one of these new agents. The duration of therapy with these agents also differs from traditional chemotherapy in that they are often given indefinitely until NSCLC progresses or the patient experiences an intolerable adverse effect (AE). Each medication also has a unique AE profile, although interstitial lung disease and pneumonitis are a concern with every agent that has been approved and/or received an indication for NSCLC since January 2021.

The 4 novel drugs and new indications for 3 existing agents for NSCLC in 2021 are each directed to different targets. Oral tepotinib targets MET exon 14 skipping alterations seen in 3% to 4% of metastatic NSCLC cases. Two drugs, the injectable bispecific antibody amivantamab-vmjw and the oral kinase inhibitor mobocertinib, are indicated for
patients with *EGFR* exon 20 insertion mutations.\(^4,6-7\)

Like *MET* exon 14 skipping alterations, these mutations affect 4% to 12% of the overall patient population in NSCLC.\(^4\)

Sotorasib is the first medication approved for any malignancy associated with the *KRAS* gene seen in approximately 3% to 13% of patients with NSCLC and *KRAS G12C* mutations.\(^4,8\) Two immune checkpoint inhibitors (ICIs), atezolizumab and cemiplimab-rwlc, received indications for NSCLC. These drugs work by binding to PD-1 or PD-L1, which ultimately removes inhibition of the immune response, upsetting peripheral tolerance.\(^9-10\) Lorlatinib was also granted a new indication for patients with ALK-positive tumors.\(^11\)

The discovery of oncologic-related mutations has propelled the lung cancer therapeutic pipeline. The introduction of medications that successfully target the mutations is even more impressive; having so many approved in a single year may not have been possible until recently.

Scientists spent more than 30 years trying to develop *KRAS*-targeted therapies.\(^12\) The *KRAS* gene was thought to lack a good area to which a drug could attach or anchor, due to its shape and surface.\(^13-16\)

Unfortunately, tumors driven by some of these mutations, such as *KRAS*, are not responsive to other medications, which may partially explain the high mortality rate of lung cancer to date.\(^14,16\)

What is interesting about many of the novel and pipeline therapeutics for lung cancer is that they do not appear to cure it but instead work to manage it as if it were a chronic disease such as heart failure or diabetes. For example, anti–PD-1 receptor binding decreases within 2 to 3 months after the last dose of ICIs.\(^17\)

For many patients, the use-limiting factor for these medications may not be disease progression but tolerability. Many of these medications can induce effects that would make them more harmful than helpful, which can be related to pharmacology. For example, the ICIs can produce immune-mediated reactions involving any organ system or tissue that can present during active therapy and even after treatment discontinuation.\(^9-10\) Others may produce severe effects less related to their oncologic mechanisms, such as mobocertinib-induced QTc prolongation or central nervous system effects from lorlatinib.\(^6,11\)

Some effects of these novel and pipeline therapeutics may be manageable with dosing modifications. Sotorasib has specific labeled dose reductions for patients experiencing hepatotoxicity or grade 3 to 4 adverse reactions.\(^8\)

The shift to chronic therapy requires renewed attention to drug-drug and drug-disease interactions. Tepotinib, mobocertinib, sotorasib, and lorlatinib all have drug-drug interactions involving cytochrome P450 3A4, and each of these except for mobocertinib also interacts with P-glycoprotein substrates.\(^5,6,8,11\)

Although lung cancer is less common in patients with reproductive potential, particularly women, it is not unheard-of. Patients with reproductive potential should use nonhormonal contraception throughout treatment with tepotinib, mobocertinib, amivantamab-vmjw, cemiplimab-rwlc, and atezolizumab; this should be continued for at least 1 week after the last dose in most patients.\(^5-7,9,10\) Women should extend contraception use for 1 month after mobocertinib, 3 months after amivantamab-vmjw, 4 months after cemiplimab-rwlc, and 5 months after atezolizumab.\(^5-7,9,10\) Given the similarities in pharmacologic properties of these pipeline medications, it is reasonable that few future medications would pose less of a monitoring requirement for interactions and safety.

**Therapeutic Developments in SCLC**

In contrast to the advances in management of NSCLC, therapeutic developments for SCLC have not been as successful. Trilaciclib was the only new medication approved for SCLC in 2021.\(^18\) However, the selective cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor is not a traditional chemotherapy agent. The 30-minute infusion is administered proactively to reduce the incidence of myelosuppression from a platinum/etoposide-containing or topotecan-containing regimen in patients with extensive-stage NSCLC.\(^18\) It works by maintaining G1 cell cycle arrest of the hematopoietic stem and progenitor cells to protect them from the cytotoxicity from chemotherapy.\(^18\)

However, the efficacy data of the trilaciclib are mixed.\(^19-20\) Although the majority of patients in 3 studies investigating trilaciclib for FDA approval...
were able to complete over 4 cycles of therapy, the drug only performed better than placebo in 1 study evaluating patients receiving a topotecan-containing regimen. However, in the phase 2 study, patients receiving trilaciclib were able to tolerate higher doses of chemotherapy and experienced fewer cycle delays ($P = .017$ and $P = .003$, respectively).

Another study reported that patients receiving trilaciclib experienced shorter severe neutropenia after cycle 1 (2 days vs 7 days; $P < .0001$). This study also reported that trilaciclib administration resulted in numerically fewer patients requiring the administration of granulocyte colony-stimulating factor agents, erythropoiesis-stimulating agents, platelets, and red blood cell transfusions, as well as less febrile neutropenia and fewer all-cause chemotherapy dose reductions.

Trilaciclib has a notable AE profile and can cause issues such as hypersensitivities; interstitial lung disease; pneumonitis; pneumonia-related deficiencies in blood calcium, potassium, and phosphate levels; fatigue; increased aspartate aminotransferase levels; and headache.

It does appear that for patients able to tolerate trilaciclib, the medication may be cost-effective. A pharmacoeconomic analysis showed a cost savings of $18,840 for patients administered trilaciclib, primarily from a reduced cost in neutropenia and thrombocytopenia management and higher quality-adjusted life.

There are limited but encouraging therapeutics in development for SCLC, primarily for patients who have tried other options that failed. A combination of olaparib, an oral PARP inhibitor, and temozolomide in patients who had previously failed SCLC treatment resulted in a 41.7% overall response rate, a 4.2-month median progression-free survival, and 8.5-month median overall survival. Olaparib has also demonstrated efficacy in animals with relapsed SCLC when used in combination with durvalumab, an anti–PD-L1 antibody.

Alisertib and other inhibitors of the Aurora A kinase, an important aspect in mitotic entry and cell cycle regulation, have shown promising results in early studies of patients who have not responded to first-line therapy. Fortunately, despite fewer novel approvals than for NSCLC, SCLC has historically been more responsive to more traditional chemotherapeutic options.

**Conclusions**

For years, lung cancer has remained one of the most frequently diagnosed cancers with a mortality rate that has long surpassed other malignancies. The recent scientific advancements in understanding how lung cancer grows and thrives has provided opportunities for these novel drug targets and therapeutics. The focus of these scientific advancements continues to be primarily directed toward lung cancers that do not or will not respond to long-standing oncologic therapies. The paradigm shift toward precision medicine introduces the concept of chronic cancer management in a field that has historically focused on remission.

Considering that many recently approved medications are oral therapeutics, with several in the drug pipeline, cancer management is progressing toward holistic care of the patient in the long term. The introduction of these chronic oncologic regimens into the patient’s medication profile will require individualized, diligent, and continuous monitoring for drug-drug interactions and AEs, which vary in scope and severity. However, for a disease with so few treatment options available historically, these important new approaches to therapy for lung cancer offer patients hope where none existed before.
Emerging Therapies Are Changing the Melanoma Treatment Landscape

Specialty pharmacists play critical role in supporting treatment adherence.

MARCIE MORRIS, PHARMD, CSP

Although melanoma accounts for approximately 1% of skin cancer diagnoses, it is responsible for a large portion of lives lost to the disease, with approximately 8000 deaths predicted to occur in the United States in 2022.1 A main reason for the high morbidity rate is that melanoma is much more likely to metastasize than other skin cancers.

Despite the high morbidity rate of melanoma, the disease accounts for only 5.6% of all new cancer cases in the United States, with the incidence of melanoma increasing steadily for several decades.1 Based on this statistic, the American Cancer Society estimates that 100,000 new melanoma diagnoses will occur in the United States in 2022.2

Current Treatments

The exact cause of malignant melanoma is unknown, but it is believed to be linked to excessive UV exposure from the sun and tanning beds. As such, most melanomas are highly preventable through limited UV exposure, use of sunscreen, and education about risk factors and warning signs. When detected before it has begun to spread, melanoma also has a 5-year survival rate of 99%.3

Furthermore, surgical resection is often a successful therapy for most patients with melanoma identified early. In more advanced stages, such as metastatic melanoma, patients have historically been treated with standard cancer treatments such as radiation and chemotherapy.1,2

Approved by the FDA in 1998, high-dose IL-2 was the first immunotherapy for metastatic melanoma. However, the potential for severe toxicities from IL-2 treatment has resulted in development of newer products with less toxic effects. Further, the treatment landscape of metastatic melanoma has changed immensely in recent advances in targeted therapies and immunotherapy (eg, checkpoint inhibitors) have been more effective than chemotherapy.2,4

Targeted therapy products work by treating melanoma cells directly, with the treatment targets often including mutated genes or proteins involved in regulation of cellular growth and division. Upon mutation, these cells grow and multiply at an uncontrollable rate, with the most common mutation being in the BRAF gene.1

Approximately 50% of all melanomas demonstrate a mutation in the BRAF gene. When this occurs, the MEK gene (and encoded MEK protein) interacts with the BRAF proteins aiding in cell growth.1

Drugs targeting the inhibition of MEK proteins are a common therapy for patients with malignant melanoma and BRAF mutations. Targeted therapies for inhibition of the BRAF and/or MEK proteins include binimetinib (Mektovi; Pfizer), encorafenib (Braftovi; Pfizer), dabrafenib (Tafinlar; Novartis), trametinib (Mekinist; Novartis), vemurafenib (Zelboraf; Genentech), and cobimetinib (Cotellic; Genentech). Additionally, combining a BRAF inhibitor and a MEK inhibitor is a common approach in treating a patient with a BRAF mutation who needs targeted therapy, as the...
combination often works better than monotherapy.\textsuperscript{1,2,4}

Advancements have been made with immune checkpoint inhibitors, now a pillar of treatment for advanced melanomas. Unlike targeted therapies, which go after melanoma cells directly, immunotherapy aims to improve the immune system’s ability to identify and destroy melanoma cells. PD-1 inhibitors pembrolizumab (Keytruda; Merck) and nivolumab (Opdivo; Bristol Myers Squibb) and CTLA-4 inhibitor ipilimumab (Yervoy; Bristol Myers Squibb) are included in this class of medications. These drugs actively block proteins involved in decreasing T-cell identification and destruction of melanoma cells. Further, blocking these proteins allows T cells to attack melanoma cells more effectively on their own. Additional immunotherapies such as melanoma vaccines and cell therapy utilizing tumor-infiltrating lymphocytes are being studied as well.\textsuperscript{1,2,4}

Updates in Melanoma Treatment
Effective immunotherapy options for treating advanced melanoma include combination ipilimumab/nivolumab, PD-1 inhibitor monotherapy, and most recently relatlimab/nivolumab fixed-dose combination. On March 18, 2022, the FDA approved nivolumab and relatlimab-rmbw (Opdualag; Bristol Myers Squibb) for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma. Nivolumab and relatlimab-rmbw is a combination immunotherapy treatment of the PD-1 inhibitor nivolumab with the novel LAG-3–blocking antibody relatlimab, the combination of which has been shown to increase T-cell activation.\textsuperscript{3}

The FDA approval of nivolumab and relatlimab-rmbw was based on data from the phase 2/3 RELATIVITY-047 trial (NCT03470922) in which nivolumab and relatlimab-rmbw more than doubled median progression-free survival compared with nivolumab monotherapy, at 10.1 months vs 4.6 months, respectively. There were no new safety events identified with nivolumab and relatlimab-rmbw compared to nivolumab alone.\textsuperscript{4,5}

When used in treatment, nivolumab and relatlimab-rmbw are given as a 30-minute intravenous infusion every 4 weeks or until disease progression. However, new and emerging treatments often come with a large financial burden, and nivolumab and relatlimab-rmbw continue this trend at a single infusion wholesale acquisition cost of $27,389 with an annual price tag of $328,668.\textsuperscript{1,5,6}

Role of Specialty Pharmacist
The specialty pharmacist is a key member of any patient’s health care team. They can provide patients and caregivers with medication and disease-specific education prior to and throughout therapy. They play a major role in adverse effect (AE) monitoring and management, along with supporting treatment adherence.

Early recognition and control of AEs can help to prevent unnecessary interruption of medication, thereby improving patient outcomes. Specialty pharmacists can also collaborate and facilitate communication between other segments of the health care team, such as dermatology and oncology, for the treatment of advanced melanoma. ■

\textbf{REFERENCES}
Differentiating Novel Treatment Modalities in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Introduction
The treatment landscape for management of relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) is rapidly expanding, with significant drug approvals in the past 5 years. Although these agents offer exciting opportunities for patients, the health care team must thoughtfully consider the clinical, logistic, and economic factors when deciding which new agent or regimen to recommend. Practitioners must be aware of prevention and management strategies for potential adverse effects (AEs), a key element for treatment selection; patient education; and institutional readiness for use of antibody-drug conjugates (ADCs) and chimeric antigen receptor (CAR) T cells in R/R DLBCL. In this article, the role of pharmacists in identifying and mitigating unique toxicities of these novel therapies along with site-of-care considerations associated with ADCs and CAR T-cell therapy will be explored.

What therapy is standard of care in R/R DLBCL?
Chemoimmunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has been the frontline standard of care for DLBCL for more than 15 years. Outcomes from the pivotal study adding rituximab to the CHOP regimen report 5-year progression-free survival (PFS) of 68% and overall survival (OS) of 80%.

Education Objectives
At the completion of this activity, the participant will be able to:
• Examine the role of the pharmacist in adverse effect recognition and management of antibody-drug conjugates (ADCs) and chimeric antigen receptor (CAR) T-cell therapies used in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL)
• Explore considerations for inpatient and outpatient treatment of R/R DLBCL

TARGET AUDIENCE: Oncology pharmacists, health-system pharmacists
ACTIVITY TYPE: Application
RELEASE DATE: July 27, 2022
EXPIRATION DATE: July 27, 2023
ESTIMATED TIME TO COMPLETE ACTIVITY: 1 hour
FEE: This lesson is offered for free at www.pharmacytimes.org.
sion-free (PFS) and overall survival (OS) of 54% and 58%, respectively.1 Despite the clear benefits for disease control and survival provided by R-CHOP, there are some patients who unfortunately either do not respond or experience relapse following frontline therapy. Results from the SCHOLAR-1 study illustrate the unmet need for effective therapies in refractory DLBCL.2 In this large-scale multicenter retrospective review of 636 patients, the objective response rate (ORR) to next-line therapy was a mere 26%, with only 7% of patients achieving complete response. A median OS of 6.3 months in this cohort underscores the importance of identifying new therapeutic strategies.

Until recently, the management of R/R DLBCL has been predicated primarily on a candidacy for autologous stem cell transplant (ASCT).3 Platinum-based salvage therapies such as rituximab, ifosfamide, carboplatin, and etoposide (R-ICE); rituximab, gemcitabine, carboplatin, and dexamethasone (R-GDP); or rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) are employed for young, fit transplant candidates. No clear frontrunner has been identified in randomized trials of these regimens; selection is therefore based on other factors such as AE profile or institutional preference.4,5 Patients demonstrating chemosensitivity proceed to ASCT, but this is only the case for approximately 50% of those initially considered eligible. Ultimately, for patients who make it to ASCT, the chance of cure remains 25% to 35%.3 Patients unable to proceed with ASCT due to age, comorbidities, or failure to respond to salvage therapy have had few viable treatment options before the recent barrage of FDA approvals, primarily ADCs and CAR T-cell products.

How do emerging monoclonal antibodies and antibody-drug conjugates fit into the treatment paradigm of R/R DLBCL?

Anti-CD20–based monoclonal antibodies (mAbs), such as rituximab, have long been considered integral in the treatment of B-cell malignancies, but additional cell surface targets are now proving to serve as effective targets as well. mAbs and ADCs targeting CD79b (polatuzumab vedotin-piiq) and CD19 (tafasitamab-cxix, loncastuximab tesirine-lpyl) have been approved in the past several years.6,8 Attached cytotoxic payloads on the targeted antibodies allow polatuzumab vedotin and loncastuximab tesirine to provide effective eradication of tumor-specific cells while potentially reducing risk of additional and cumulative toxicities of traditional cytotoxic chemotherapy. Dosing and administration of these agents are reviewed in the FIGURE, and key elements and outcomes of each of the registration trials for these 3 agents are reviewed in TABLE 1.2,6,7

Polatuzumab vedotin is an ADC targeting CD79b, a cell surface marker associated with B-cell receptor signaling with almost universal expression in patients with DLBCL.6 This antibody is equipped with monomethyl auristatin E (MMAE), a microtubulin inhibitor that is delivered directly to these malignant B cells. Although the magnitude of expression of CD79b varies across patients, no specific threshold appears necessary to see the improvements in response rate, PFS, and OS. Benefits also appear to be maintained across subgroups of patients with high-risk features. Successful application in R/R DLBCL has prompted evaluation of polatuzumab vedotin as initial therapy. Results from the phase 3 POLARIX study, wherein polatuzumab replaces vincristine in R-CHOP (pola-R-CHP), are now published and highlight an improvement in PFS with this novel combination.12

Loncastuximab tesirine is also an ADC, which targets CD19 and delivers a pyrrolobenzodiazepine (PBD) dimer payload.7 Unlike other newly approved agents, loncastuximab has been studied in patients who previously received CAR T-cell therapy. Of the 13 patients who received loncastuximab...
following a CAR T-cell product in the LOTIS-2 study, the ORR was comparable to that of the entire study population. Moreover, in a small cohort of patients who underwent CAR T-cell therapy after loncastuximab as part of the same study, there was no signal of CD19 loss following this ADC. Together, these data indicate that loss of CD19 expression may not be as likely a cause of treatment failure or relapse for either of these modalities.

Finally, tafasitamab-cxix is a traditional CD19-directed mAb with limited single-agent activity. Improved outcomes were seen for patients with sufficient baseline quantities of natural killer (NK) cells in a post hoc analysis of early-phase data. The potential for synergistic activity with lenalidomide, which is known to enhance NK cell activity as well as activity in B-cell non-Hodgkin lymphoma, led to the rational combination of these 2 agents. Long-term follow-up of the pivotal L-MIND study illustrates sustained activity with a median duration of response of 43.9 months, translating into a median OS of 33.5 months.

**How do CAR T-cell therapies fit into the treatment paradigm of R/R DLBCL?**

CAR T-cell therapy represents an opportunity for patients who are otherwise ineligible for ASCT. Three CAR T-cell products are currently approved for R/R DLBCL: axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel). Outcomes for the registration studies for each are summarized in **TABLE 2**. With the recent approval of axi-cel for use in first relapse and data anticipated for incorporating this agent in the front-line setting, CAR T-cell therapies are poised to drastically impact the treatment paradigm of DLBCL. An analogous evaluation of tisa-cel in the second line was unable

**TABLE 1. APPROVED NOVEL MONOClonAL ANTIBODIES AND ANTIBODY-DRUG CONJUGATES FOR RELAPSED/REFRACTORY DLBCL**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study population</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loncastuximab tesirine</td>
<td>LOTIS-2</td>
<td>Phase 2, multicenter, open-label, single-arm</td>
<td>R/R DLBCL following ≥2 prior regimens, including patients post-ASCT and post-CAR T-cell therapya (N = 145)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR = 48.3% • CR = 24.1% • PR = 24.1% mTTR = 41 days mPFS = 4.9 months mOS = 9.9 months</td>
</tr>
<tr>
<td>Polatuzumab vedotin</td>
<td>GO29365</td>
<td>Phase 2, multicenter, randomized comparing Pola-BR with BR</td>
<td>R/R DLBCL following ≥1 prior line(s) of therapy; transplant ineligible (N = 80)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>By independent review: CR • Pola-BR = 40% • BR = 17.5% • P = .26 mDOR • Pola-BR = 12.6 months • BR = 7.7 months mPFS • Pola-BR = 9.5 months • BR = 3.7 months mOS • Pola-BR = 12.4 months • BR = 4.7 months • HR, 0.42; P = .002</td>
</tr>
<tr>
<td>Tafasitamab-cxix</td>
<td>L-MIND</td>
<td>Phase 2, multicenter, open-label, single-arm combination of tafasitamab-cxix and lenalidomide</td>
<td>R/R DLBCL following 1-3 prior regimens; transplant ineligible (N = 81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR = 57.5% • CR = 40% • PR = 17.5% mTTR = 2 months mDOR = 43.9 months mPFS = 11.6 months mOS = 33.5 months</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplant; CR, complete response; DLBCL, diffuse large B-cell lymphoma; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; mTTR, median time to response; ORR, objective or overall response rate; PR, partial response; R/R, relapsed/refractory.

a Patients who received prior CD19-directed therapies needed biopsy-proven CD19 expression of the current relapse event before study enrollment.
An interim analysis of liso-cel in this setting illustrates superiority, with ORR = 86% vs SOC 48%; P < .0001. CR: liso-cel 66% vs SOC 39%; P < .0001. mPFS: liso-cel 14.8 months vs SOC 5.7 months; P = .0001. mOS: liso-cel NR vs SOC 16.4 months; P = .0257.

Differentiating among therapies is often provider and/or institution specific and may be based on familiarity, manufacturing metrics, and payer reimbursement in addition to traditional efficacy and safety parameters. Elements of the CAR design impact the overall kinetics of T-cell expansion and potentially AEs and disease outcomes. Tisa-cel and liso-cel rely on the 4-1BB co-stimulatory domain, which is associated with slower T-cell expansion with prolonged persistence, whereas axi-cel uses a CD28 in this capacity, leading to rapid expansion of T cells. Clinically, the rate of CAR T-cell expansion

<table>
<thead>
<tr>
<th>FDA indication(s) in DLBCL</th>
<th>Study</th>
<th>Design</th>
<th>Study population</th>
<th>Efficacy</th>
</tr>
</thead>
</table>
| Axi-cel                   | **2nd line:** DLBCL refractory to or relapse within 12 months of first-line CIT | **ZUMA-1** | Phase 2, multicenter, single arm | ORR = 82%  
• CR = 54%  
mTTR = 1 month  
mDOR = 11.1 months  
mPFS = 5.8 months  
mOS = not reached  
Manufacturing time*: 17 days |
| 3rd line and beyond: DLBCL following ≥2 lines of systemic therapy | | | | |
| **3rd line and beyond:** DLBCL following ≥2 lines of systemic therapy | **JULIET** | Phase 2, multicenter, open-label, single arm | R/R DLBCL following ≥2 prior regimens including rituximab and an anthracycline; including patients ineligible for ASCT (N = 111) | ORR = 52%  
• CR = 40%  
mTTR = 1 month  
mDOR = not reached  
mPFS = 6.8 months  
mOS = 21.1 months  
Time from enrolment to infusion: 54 days |
| **Liso-cel** | **2nd line and beyond:** DLBCL following ≥2 lines of systemic therapy | **TRANSCEned NHL 001** | Phase 2, multicenter, single-arm | ORR = 73%  
• CR = 53%  
mTTR = 1 month  
mDOR = not reached  
mPFS = 6.8 months  
mOS = 21.1 months  
Manufacturing time*: 37 days |
| **TRANSFORM** | Phase 3, multicenter, randomized, double-arm vs standard of care | Primary refractory to or relapsed ≤12 months after first line therapy (N = 184 [liso-cel 92 patients vs SOC 92 patients]) | ORR: liso-cel 86% vs SOC 48%; P < .0001  
• CR: liso-cel 66% vs SOC 39%; P < .0001  
mPFS: liso-cel 14.8 months vs SOC 5.7 months; P = .0001  
mOS: liso-cel NR vs SOC 16.4 months; P = .0257 |

ASCT, autologous stem cell transplant; CIT, chemoimmunotherapy; CR, complete response; DLBCL, diffuse large B-cell lymphoma; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; mTTR, median time to response; NR, not reached; ORR, objective or overall response rate; PD, progressive disease; R/R, relapsed/refractory; SD, stable disease.

*Time from leukapheresis to CAR T-cell delivery.

*Time from leukapheresis to CAR T-cell infusion.
appears to translate into differences seen in cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), with a longer time to onset for tisacel and liso-cel, explaining why these may be more attractive options for outpatient administration.

With the growing armamentarium of agents, is there guidance for the most appropriate way to sequence these agents?

A paucity of data exists to support precise sequencing algorithms for novel mAbs, ADCs, and CAR T-cell products in relapsed/refractory DLBCL. Multiple factors may impact the decision of how and when to use each of the aforementioned therapies. In the absence of head-to-head comparisons, factors to assist in decision making include CAR T-cell candidacy, disease behavior (eg, high-risk features, kinetics of disease progression), patient or provider preferences, tolerability, and cost. Emerging data for polatuzumab vedotin in the frontline setting or the recent approval for axi-cel as a second-line agent could help define a more universal pathway in R/R DLBCL.12,20 A cross-sectional survey was conducted by the American Society for Transplantation and Cellular Therapy of practicing lymphoma and cellular therapy physicians to assess preferred practice for patients post-CAR T-cell therapy. These data suggest that in the event of relapse post-CAR T-cell therapy, most responding participants assess for potential targetable antigens (eg, CD19) and/or biopsy to guide further treatment decisions, and then proceed with salvage alternate CAR T-cell therapy. However, there is variability among practitioners in routine surveillance post-CAR T-cell therapy, and also treatment at the time of relapse.25

Regardless of when CAR T-cell therapy is used in the course

### TABLE 3. SELECT ADVERSE EFFECTS FROM PIVOTAL STUDIES OF RELAPSED/REFRACTORY DLBCL6-9,15-17

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Pola-BR</th>
<th>Loncastuximab tesirine</th>
<th>Tafa-len</th>
<th>Axi-cel</th>
<th>Tisa-cel</th>
<th>Liso-cel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4 neutropenia</td>
<td>46.2%</td>
<td>26%</td>
<td>48%</td>
<td>78%</td>
<td>16%*</td>
<td>60%</td>
</tr>
<tr>
<td>Grade 3/4 febrile neutropenia</td>
<td>10.3%</td>
<td>3%</td>
<td>12%</td>
<td>31%</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Grade 3/4 thrombocytopenia</td>
<td>41%</td>
<td>18%</td>
<td>17%</td>
<td>38%</td>
<td>16%*</td>
<td>27%</td>
</tr>
<tr>
<td>Grade 3/4 anemia</td>
<td>28.2%</td>
<td>3%</td>
<td>7%</td>
<td>43%</td>
<td>16%*</td>
<td>37%</td>
</tr>
<tr>
<td>Grade 3/4 lymphopenia</td>
<td>12.8%</td>
<td>5%</td>
<td>3%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>7%</td>
<td>5%</td>
<td>6%</td>
<td>NR</td>
<td>NR</td>
<td>1%</td>
</tr>
<tr>
<td>Other notable adverse effects</td>
<td>Related to MMAE payload: PN</td>
<td>Related to PBD dimer payload: edema, effusion, rash, elevated GGT</td>
<td>Diarrhea, rash</td>
<td>Risk for VTE (consider ASA or other ppx)</td>
<td>Hemophagocytic lymphohistiocytosis/macrophage activation syndrome, hypogammaglobulinemia</td>
<td></td>
</tr>
<tr>
<td>Grade 3/4 CRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>13%</td>
<td>22%</td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to onset</td>
<td>2 days</td>
<td>3 days</td>
<td>5 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to resolution</td>
<td>8 days</td>
<td>7 days</td>
<td>5 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3/4 ICANS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>28%</td>
<td>12%</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to onset</td>
<td>5 days</td>
<td>6 days</td>
<td>9 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to resolution</td>
<td>By day 17 after axi-cel</td>
<td>14 days</td>
<td>11 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASA, aspirin; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; GGT, gammaglutamyl transferase; ICANS, immune effector cell-associated neurotoxicity syndrome; liso-cel, lisocabtagene maraleucel; MMAE, monomethyl aurastatin E; NR, not reported; PBD, pyrrolobenzodiazepine; pola-BR, polatuzumab vedotin, bendamustine, and rituximab; ppx, prophylaxis; tisa-cel, tisagenlecleucel; tafa-len, tafasitamab-cxix and lenalidomide; VTE, venous thromboembolism.

*Reported as any grade 3 or higher cytopenia resolved by day 28.
of treatment, providers must consider timing for therapy initiation at the time of relapse. The manufacturing process of CAR T-cell therapy takes weeks from initial leukapheresis, and there may be challenges in health care center space and availability.26 Bridging therapy may therefore be required to control a rapidly progressive lymphoma if CAR T-cell therapy is the ultimate goal. In such cases, use of pola-BR is not preferred immediately prior to leukapheresis due to bendamustine-associated lymphodepletion.27 Convenience of the loncastuximab administration schedule, along with the limited data for use both before and after CAR T-cell therapy, are attractive features that cannot be overlooked, though more data are needed to characterize the impact of how CD19-directed therapies are sequenced.28-29 Barriers for use of tafa-len, in comparison, include an initially intensive schedule for the intravenously administered antibody along with acquisition of lenalidomide through limited-distribution specialty pharmacies, REMS requirements, and the potential for nonadherence.28 However, this remains a viable option for long-term disease control, especially for older or infirm patients who would not be candidates for ASCT or CAR T-cell therapy.

What are some of the common AEs seen with emerging therapies, and how can pharmacists assist in management?

Hematologic AEs are associated with all novel therapies; rates are summarized in Table 3.6-9,15-17 These are manageable with strategies including dose interruption, reduction, and use of granulocyte colony-stimulating factors (G-CSFs).9-11 Also, despite pola-BR causing a higher rate of grade 3 cytopenias compared with BR, this did not translate to an increased rate in infections or transfusion requirement.6 For combination regimens, consideration must also be taken to identify the most likely causative agent when determining any necessary modifications to therapy. For example, in the L-MIND study of tafasitamab-cxix plus lenalidomide, nearly 50% of patients developed significant neutropenia and a significant proportion of patients required dose reductions of lenalidomide for AEs, though specific reasons for lenalidomide reductions are not explicitly stated.8 It is unclear if the cause of neutropenia here can be linked to lenalidomide alone or an effect of the combination, but secondary prophylaxis with G-CSFs was ultimately required in 44% of patients. Understanding AEs of partner agent(s) equips pharmacists with valuable information for treatment planning and patient education.

Infusion-related reactions (IRRs) are associated with mAbs, with minimal risk for many of the emerging agents.7,8,17 However, pharmacists play a key role in ensuring appropriate supportive care medications are prescribed and standardized premedications are a part of treatment plans. Antipyretics and antihistamines are recommended before both polatuzumab and tafasitamab-cxix, and steroids are also recommended for tafasitamab-cxix.9,11 Loncastuximab does not require specific premedications for prevention of IRRs, but patients receive a short course of low-dose dexamethasone (4 mg twice daily for 3 days, starting the day before infusion) for prevention of edema.7,10

Although there are many commonalities, each of these mAbs and ADCs are also associated with their own unique toxicities. For example, polatuzumab vedotin is known to cause peripheral neuropathy due to the MMAE payload.6-7 Although this is potentially reversible, alternative therapies are preferred for patients with existing uncontrolled neuropathy. The PBD dimer component of loncastuximab tesirine has been implicated in the development of edema, effusion, rash, and elevations of gamma-glutamyltransferase (GGT).7 Nonhematologic AEs such as rash and diarrhea were seen in L-MIND, all of which have been well-described with use of lenalidomide.8,20 Providers may also consider prophylaxis with aspirin or anticoagulation due to the known risks of thromboembolic events with lenalidomide.8

What is the role of the pharmacist in assessing AEs of cellular therapies?

CRS and ICANS are acute toxicities of special interest for treatments that promote immune function of host T cells, including CAR T-cell therapies.28 Both comprise a constellation of symptoms including fever, chills, shortness of breath, and hypotension among others for CRS and headache, confusion, and aphasia for ICANS. Tocilizumab, an IL-6 receptor antagonist, rapidly reverses CRS, and corticosteroids are a cornerstone of managing isolated ICANS. Prompt assessment and treatment of symptoms associated with CRS or ICANS are essential to reduce the potential need for intensive care. These risks led the FDA to require risk evaluation mitigation strategy (REMS) programs for all CAR T-cell products. Sites must also ensure 2 doses of tocilizumab are available for each patient before infusion of CAR T cells.28-30

Pharmacists are well-positioned for involvement in education, training, and protocol development for management of CRS and ICANS, including adapting guidance on use of tocilizumab, corticosteroids, and how to incorporate antiepileptic prophylaxis. All of these activities not only satisfy enrollment and continued compliance in REMS programs, but also provide a platform to optimize patient outcomes within an institution.
Staying abreast of clinical updates, such as the findings of cohort 4 of the ZUMA-1 study revealing that earlier use of corticosteroids and/or tocilizumab reduces progression to severe CRS and ICANS, allows the pharmacist an opportunity to initiate mechanisms to update strategies at their own institution. Likewise, establishing a system to guarantee adequate supply of tocilizumab requires pharmacy participation, especially in times of drug shortage where allocation between various indications may be necessary.

Similarly, an awareness of institutional experiences and global positions on management of CAR T-cell–related cytopenias renders a pharmacist an asset to the care team in assessing appropriate use of colony-stimulating factors, such as neutropenia and B-cell aplasia infection risk. Pharmacists are able to manage prophylactic antimicrobials through agent selection, therapy initiation, and discontinuation. Additionally, pharmacists can assist with development of institution-specific standard practices.

**With the potential for outpatient administration of CAR T cells, what are some considerations for the health care team?**

During initial development, CAR T cells were primarily administered in the inpatient setting. Despite the risks of CRS and ICANS, safe outpatient administration has garnered significant attention. This is predicated on the best interests of patients and institutions. Key factors in determining the viability of an outpatient administration model include appropriate infrastructure, including physical space and staffing; mechanisms for urgent triage; and potential financial impacts of hospitalization. Inpatient reimbursement is limited based on diagnosis-related group bundled payments, whereas outpatient administration allows institutions to bill for 6% above the average wholesale price. Outpatient administration shifts resource utilization and has the potential to improve reimbursement of these therapies. Through use of collaborative practice agreements or in areas where there is an ability to gain provider-level status, pharmacists could step in to make supportive care interventions in real time, which may alleviate a portion of any identified need for additional staffing. Even with these elements in place, timely assessment of potential CRS or ICANS also relies on patients remaining within a reasonable geographic area of the clinic for the first month following infusion.

Despite the potential benefits of outpatient administration of CAR T-cell therapies, there are considerations with payment in the event patients are hospitalized. For example, Medicare imposes reimbursement penalties for admissions within 72 hours of administration. Nevertheless, reimbursement structures for outpatient CAR T-cell administration may overcome the reduced payments for hospitalization of the occasional patient requiring admission in this 72-hour window. Small data sets describing the outpatient administration experience from various institutions illustrate that although the likelihood of admission is significant, the median time to admission is 4 to 5 days. Known factors that impact the predictability of incidence and time to onset of CRS and/or ICANS symptoms include product selection and patient disease features. Axi-cel is associated with shorter time to onset of CRS and ICANS, likely due to use of the CD28 co-stimulatory domain. Liso-cel and tisa-cel, which both use 4-1BB instead of CD28, are attractive CAR T-cell products for outpatient administration, as there is a lower incidence of CRS, and also a delayed time to onset. Significant disease burden, poor performance status, and elevated lactate dehydrogenase have been shown to confer greater risk for CRS/ICANS.

Recommendations for developing a successful foundation for outpatient administration of CAR T-cell therapy focuses on considering the needs to facilitate daily follow-up, training of staff, establishing clear policies and procedures, and identifying appropriate patients. Proximity to the infusion center, ability to comply with frequent visits, and clear understanding of concerning symptoms that require prompt evaluation and intervention are all integral when considering patients for outpatient CAR T-cell therapy. Pharmacists can reduce the burden of these potential barriers by assisting in the development of institutional guidelines, building standard orders for associated therapy elements (eg, lymphodepleting therapy, supportive care including tocilizumab), and generating patient and caregiver education.

**Conclusion**

Multiple novel therapeutic agents are now available for R/R DLBCL. Evidence to support optimal sequencing remains unclear, making it vital for pharmacists to understand differences in toxicity profiles. Approval of CAR T-cell therapy earlier in the treatment of DLBCL will increase the number of eligible patients. This may tip the scale for site of administration toward the ambulatory setting to accommodate more widespread use, forcing centers to devise plans for safe administration.
REFERENCES


POSTTEST QUESTIONS

1. Which option accurately pairs a novel therapy for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) with appropriate premedication(s) to prevent infusion-related reactions?
   A. Loncastuximab tesirine: dexamethasone
   B. Polatuzumab vedotin: acetaminophen, dexamethasone
   C. Tisagenlecleucel: dexamethasone, tocilizumab
   D. Tafasitamab-cxix: dexamethasone, famotidine

2. TR is a 45-year-old woman with DLBCL who received first-line therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone and has relapsed 8 months after completing therapy. As you counsel her in clinic prior to her hospital admission for axicabtagene ciloleucel (axi-cel), she asks why this treatment is appropriate for her. Your response is that axi-cel is:
   A. Preferred in patients who have relapsed disease within 12 months
   B. Preferred in patients with relapsed disease who have received autologous stem cell transplantation
   C. Preferred over other CAR T-cell therapies when administered as inpatient
   D. Associated with the lowest incidence of adverse effects

3. Which of the following therapies has the most evidence to support outpatient administration based on adverse effect risk?
   A. Axicabtagene ciloleucel
   B. Brexucabtagene autoleucel
   C. Idecabtagene vicleucel
   D. Lisocabtagene maraleucel
Introduction

The treatment landscape for hematologic malignancies is rapidly evolving. Chimeric antigen receptor (CAR) T cells are autologous, genetically modified T cells that can recognize and eliminate cells expressing a specific target antigen. ¹ CAR T cells have demonstrated significant activity in relapsed/refractory hematologic malignancies. ² Since August 2017, the FDA has approved 6 CAR T-cell constructs covering numerous indications, including relapsed or refractory B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, acute lymphoblastic leukemia, and multiple myeloma. ³⁻¹² The unprecedented outcomes of CAR T cells in later lines of therapy have led to the investigation of the administration of CAR T cells earlier in the treatment course as second-line therapy.

The incorporation of CAR T cells into treatment guidelines has led to new challenges, requiring management by a specialized team of experts. In this article, questions on the challenges of CAR T-cell therapy and the role that pharmacists have as part of the multidisciplinary team will be explored.

What are potential challenges the health care team may experience in caring for patients who are candidates for CAR T-cell therapy?

One of the biggest challenges that health care professionals are currently facing is the availability of manufacturing slots, which is impacted by the CAR T-cell product itself and the manufacturing company. Specifically, there is currently

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The initial panel discussion is available on-demand. To view the on-demand CE session, please visit pharmacytimes.org/CART-CC. The activity is available through May 23, 2023.
a shortage of available CAR T-cell therapy slots for patients with multiple myeloma, creating a challenge in determining which patients receive highest priority for treatment. Furthermore, supply chain constraints affecting the raw materials needed for manufacturing CAR T cells may impact the timing of administration. Manufacturers are assessing innovative methods to improve both the efficiency of the manufacturing process and turnaround times for the manufacturing of CAR T-cell therapies. In addition, the current centralized manufacturing models limit the capacity and turnaround time from apheresis to end of product development.

Institutions administering CAR T-cell therapy are required to have 2 doses of tocilizumab available in the event of cytokine release syndrome (CRS). The COVID-19 pandemic impacted the availability of tocilizumab, as the FDA issued an Emergency Use Authorization for tocilizumab for the treatment of COVID-19. This shortage strained the ability of hospitals to meet the Risk Evaluation and Mitigation Strategy (REMS) requirements of having 2 available doses of tocilizumab per patient. In light of this shortage, the FDA issued temporary guidance allowing institutions to have 1 dose available on site for immediate administration within 2 hours of CAR T-cell infusion and a second dose available within 8 hours of the first tocilizumab dose. Other measures that have been observed to alleviate the shortage include encouraging clinicians to enroll patients in clinical trials assessing prophylactic measures to prevent CRS or immune effector cell-associated neurotoxicity syndrome (ICANS), initiating earlier use of corticosteroids, limiting the administration of tocilizumab to 2 doses, rounding tocilizumab dose to the nearest vial size, and utilizing the patient’s ideal body weight to calculate the tocilizumab dose.

Financial challenges are also ongoing. This includes the total cost of care, which may impact accessibility of therapy for patients. Outpatient administration of CAR T cells has been found to be more economical compared with inpatient administration and is also associated with a reduced length of hospital stay. There is a need for institutions administering CAR T-cell therapies in the outpatient setting to have a robust infrastructure and a workflow allowing for safe administration of therapy, as well as appropriate means of patient monitoring and follow-up.

Recognizing that some of these challenges do not have immediate solutions, health care professionals continue to work to improve the process of manufacturing therapies, as well as methods of administration in order to enhance safety and efficacy outcomes of CAR T-cell therapies. Additional considerations when administering CAR T-cell therapy that require further studies include limiting lymphotoxic therapies prior to the administration of CAR T cells to enable successful collection of autologous T cells, identifying the optimal bridging therapy prior to the administration of CAR T cells, standardizing adverse effect grading systems and toxicity management, and providing continued education to all members of the medical team taking care of patients receiving CAR T-cell therapy.

How long is the manufacturing process for CAR T-cell therapy?

The production process of CAR T cells is lengthy and requires several steps. The process begins at the treatment center with cell collection from the patient via leukopheresis that is then cryopreserved and delivered to the manufacturing facility. At the manufacturing facility, T cells are activated via the T-cell receptor CD3 and costimula-
tory signals, such as CD28 or 4-1BB. Transduction of the CAR complementary DNA occurs via retroviral or lentiviral vectors. CAR T cells are then expanded ex vivo, cryopreserved, and delivered back to the treatment centers for administration to the patient. While this process is similar for all CAR T cells, the turnaround time differs, ranging up to 6 weeks, owing to the different CAR T-cell constructs as well as location of the manufacturer relative to the treatment center (TABLE 1).

What is the role of bridging therapy prior to CAR T-cell therapy? Is there a preferred regimen for use?

Following leukapheresis and prior to the infusion of CAR T cells, patients may receive bridging therapy, which works to maintain disease control or prevent disease progression while the CAR T cells are manufactured. Bridging therapy may also impact the clinical response to CAR T-cell therapy.

Several types of bridging therapy have been used in CAR T-cell trials, including immunotherapy, chemotherapy or targeted therapy, and radiation. A combination of these therapies is sometimes used to optimize patient outcomes. The goal of administering chemotherapy is to inhibit tumor cell proliferation and limit expansion of malignant disease. Immunotherapies exert their cytotoxicity via recruitment of immune effector cells, such as macrophages and natural killer cells or effector T cells. Radiation therapy is a debulking strategy delivered locally to the primary tumor or to specific metastatic sites.

While the choice of bridging therapy is currently not standardized, the optimal regimen is based on prior therapy the patient has received, disease burden, expected time to CAR T-cell infusion, adverse effects of chemotherapies used, patient comorbidities, and physician discretion.

What outcomes have been seen in real-world data?

Real-world data on the use of CAR T cells have been reported for axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tis-a-cel). In a real-world, prospective study for tis-a-cel, it was found that tis-a-cel demonstrated similar efficacy and even improved safety outcomes compared with what was observed in the ELIANA and JULIET trials. A real-world study of axi-cel found similar efficacy outcomes to that of the ZUMA-1 trial; this was also the case for patients with more aggressive disease and higher comorbidities, who may have been deemed ineligible for inclusion in the ZUMA-1 cohort. Compared with the real-world data, patients included in the clinical trials had relatively lower comorbidity status.

How do pharmacists impact a patient’s journey through CAR T-cell therapy?

Pharmacists play a significant role in optimizing the care and treatment outcomes for patients receiving CAR T cells. From an operational standpoint, pharmacists are involved in the creation of electronic order sets that include lymphodepletion chemotherapy regimens, doses, and duration of therapy for each specific CAR T-cell product. Pharmacists also ensure necessary supportive care medications are ordered, including antiemetics, intravenous fluids, prophylactic antimicrobials, seizure prophylaxis, and medications used for the management of infusion-related reactions. Pharmacists are also involved in reviewing, verifying lymphodepletion chemotherapy orders, and labeling of the CAR T-cell product. The labeling component may vary among institutions owing to differences in cellular therapy laboratory and pharmacy resources. Clinically, pharmacists are responsible for completing a detailed medication reconciliation prior to CAR T-cell administration as well as identifying drug-drug interactions.

In addition, pharmacists may be involved in education provided to the patient and their caregiver on the rationale for lymphodepletion chemotherapy and potential short- and long-
term toxicities of chemotherapy and CAR T cells. After CAR T-cell administration, pharmacists can be involved in monitoring for the development of any signs or symptoms of CRS and ICANS and can offer recommendations on the appropriate management of these toxicities.

All medical providers and pharmacists caring for patients receiving CAR T-cell therapy are required to enroll in a REMS program to reinforce that all members are aware of the complications of CAR T cells. This mandatory program ensures appropriate monitoring and management of the potentially severe toxicities associated with these therapies.

**TABLE 2. TRIAL SUMMARIES FOR REAL-WORLD DATA AND THE CORRESPONDING CLINICAL TRIAL DATA**

<table>
<thead>
<tr>
<th>CAR T-cell product (trial)</th>
<th>Design</th>
<th>Patient population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tisa-cel (ELIANA)</td>
<td>Phase 2, single-arm, open-label, international, multicenter</td>
<td>75 patients with R/R pediatric and young adult ALL received tisa-cel</td>
<td>Primary end point: • ORR (CR/CRi): 81% Secondary end points: • CR: 60%; CRi: 21% • RFS: 80% (6 mo); 59% (12 mo) • EFS: 73% (6 mo); 50% (12 mo) • OS: 90% (6 mo); 76% (12 mo)</td>
</tr>
<tr>
<td>Tisa-cel (JULIET)</td>
<td>Phase 2, single-arm, open-label, international, multicenter</td>
<td>111 patients with R/R DLBCL received tisa-cel</td>
<td>Primary end point: • ORR (CR/PR): 52% Secondary end points: • CR: 40% • Median DOR: NR • Median PFS: NR • Median OS: 12 mo</td>
</tr>
<tr>
<td>Tisa-cel data</td>
<td>Real-world, prospective study in United States and Canada</td>
<td>255 patients with R/R pediatric and young adult ALL received tisa-cel</td>
<td>Primary end point: • ORR (CR/CRi): 85.5% Secondary end points: • DOR: 78.1% (6 mo); 60.9% (12 mo) • EFS: 68.6% (6 mo); 52.4% (12 mo) • OS: 88.5% (6 mo); 77.2% (12 mo)</td>
</tr>
<tr>
<td>Tisa-cel data</td>
<td>Real-world, prospective study in United States and Canada</td>
<td>155 patients with R/R NHL received tisa-cel</td>
<td>Primary end point: • ORR (CR/PR): 61.8% Secondary end points: • CR: 39.5% • 12-mo DOR: 48.4% • 12-mo PFS: 26.4% • 12-mo OS: 56.3%</td>
</tr>
<tr>
<td>Axi-cel (ZUMA-1)</td>
<td>Phase 2, single-arm, open-label, international, multicenter</td>
<td>101 patients with R/R DLBCL received axi-cel</td>
<td>Primary end point: • ORR (CR/PR): 83% Secondary end points: • CR: 54% • Median DOR: 11.1 mo • Median PFS: 5.9 mo • Median OS: NR</td>
</tr>
<tr>
<td>Axi-cel data</td>
<td>Real-world, prospective, post-authorization safety study in the United States</td>
<td>1297 patients with R/R DLBCL received commercial axi-cel</td>
<td>Primary end point: • ORR (CR/PR): 73% Secondary end points: • CR: 56% • Median DOR: NR • Median PFS: 8.6 mo • Median OS: 21.8 mo</td>
</tr>
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ALL, acute lymphoblastic leukemia; axi-cel, axicabtagene ciloleucel; CR, complete response; CRi, complete response with incomplete hematologic recovery; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EFS, event-free survival; mo, months; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; R/R, relapsed/refractory; RFS, relapse-free survival; tisa-cel, tisagenlecleucel.
life-threatening CRS and neurotoxicities of CAR T cells. The REMS program also requires that centers authorized to administer CAR T cells have at least 2 doses of tocilizumab on site for each patient. This requirement has been temporarily amended due to a tocilizumab drug shortage.

### Conclusion

CAR T-cell therapy provides a promising therapeutic option, particularly for patients with advanced hematologic malignancies. A multidisciplinary team is integral to the success of CAR T-cell administration, both inpatient and outpatient. A focus on the clinical and logistical complexities of CAR T-cell therapy requires institutions to continue to outline and identify challenges and establish strategies to mitigate them to optimize patient safety and outcomes.

### REFERENCES


INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety.

Go to www.pharmacytimes.org/CART-CC to access the online version of this activity.

Click “Proceed,” then complete the online pretest.

Once completed, click “Next” until reaching the activity posttest.

Complete the online posttest and activity evaluation form.

After successful completion of the online interactive patient simulation, posttest, and activity evaluation, your credit will be uploaded into CPE Monitor. You must complete these steps before the activity expires in order to receive your credit.

You may view your credit within 48 hours at www.mycpemonitor.net.

NOTE: Your CE credit will be automatically uploaded to CPE Monitor.
POSTTEST QUESTIONS

1. Which phrase highlights a challenge for the multidisciplinary team when caring for patients receiving chimeric antigen receptor (CAR) T-cell therapy?
   A. Drug shortages with supportive care medications
   B. Limiting infusions to inpatient settings
   C. Geographic restrictions within 30 minutes
   D. Inadequate patient and caregiver education

2. Which action represents an opportunity for pharmacist involvement with outpatient administration of CAR T-cell therapies?
   A. Ensuring appropriate supportive care
   B. Standardizing cytokine release syndrome grading
   C. Assessing donor eligibility
   D. Recommending inpatient monitoring

3. QW is a 62-year-old man presenting for a consultation to consider second-line treatment with axicabtagene ciloleucel for relapsed diffuse large B-cell lymphoma. Which of the following is a potential challenge in his care?
   A. Outpatient administration is required for insurance coverage
   B. Requirement for inpatient admission
   C. Formulary restrictions with supportive care medications
   D. Drug shortages with supportive care medications
Pharmacists Reaching Out™ in Cancer Care: Examining Treatment Disparities in Oral Oncolytics

EDUCATIONAL OBJECTIVES
At the completion of this activity, the participant will be able to:
• Examine treatment disparities uniquely associated with oral oncolytics
• Explore clinical evidence outlining the negative impact of treatment disparities on patients receiving oral oncolytics
• Explain how factors such as complex administration, logistics, and reduced health care contact can create barriers for optimal treatment of patients prescribed oral oncolytics
• Identify barriers to oral oncolytic medication adherence for a patient with cancer based on patient- and disease-specific characteristics

TARGET AUDIENCE: Pharmacists
ACTIVITY TYPE: Application
RELEASE DATE: August 12, 2022
EXPIRATION DATE: August 12, 2023
ESTIMATED TIME TO COMPLETE ACTIVITY: 2.0 hours
FEE: This lesson is offered for free at www.pharmacytimes.org.

Background and Trends of Oral Oncolytics Approved by the FDA
Oral oncolytics are orally administered medications used to treat cancer; they generally include targeted agents, antimetabolites, topoisomerase inhibitors, and biologics, but not hormonal therapies. Oral oncolytics have become prominent in treating various cancers. Since the approval of capecitabine by the FDA in 1998, the utility and expansion of oral oncolytics in the treatment of diverse cancers have grown exponentially, with over 51% of chemotherapy agents approved in the past decade being oral oncolytics. More than a quarter of antineoplastic agents in the pipeline are estimated to be oral oncolytics. As shown in Figure 1, a total of 392 oral and intravenous oncolytics were FDA approved between 2011 and 2021, of which 51% (126) are oral oncolytics. Several oral oncolytics were approved for multiple indications, some in combination with intravenous oncolytics, and some with dosing variabilities depending on the indication.
Oral oncolytics offer improved quality of life (QOL) and are more convenient for patients than other forms of therapy. Usage also leads to less disruption with work and social activities, prevents painful injections and travel/logistics of infusion clinic appointments, while allowing patients to take more ownership of their therapy with self-administration. Additionally, in some cases, patients taking oral oncolytics may experience prolonged drug exposure that can translate into sustained therapeutic drug levels and improved drug efficacy.

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Overview of Treatment Outcomes in Patients on Oral Chemotherapy

Although all these factors are perceived advantages that have contributed to the increased use of oral oncolytics, studies have shown that patients prescribed oral oncolytics struggle with adherence and have high cancer-related symptom burden, low overall satisfaction, and low QOL.\(^5,6\) Jacobs et al published literature about 181 patients on oral oncolytics between December 2014 and August 2016 enrolled in a randomized study assessing adherence and symptom management at Massachusetts General Hospital Cancer Center. According to this study, the mean electronic pill cap adherence rate showed that patients took 85.57% of their oral oncolytics, with the most commonly reported cancer-related symptoms being fatigue (88.6%), drowsiness (76.5%), disturbed sleep (68.2%), memory problems (63.10%), and emotional distress (60.8%).\(^6\) These factors can inevitably lead to nonadherence, which contributes to poor clinical outcomes including prolonged treatment duration, increased treatment complexity, development of drug resistance, and increased toxicity.\(^7\) These data highlight the need to proactively address symptom burden, adherence challenges, and QOL among this patient population.

Disparities in Racial Representation in Clinical Trials

Despite the FDA’s approval of many oral oncolytics, patient populations from various racial and ethnic backgrounds representing the diverse US population are often not adequately represented or reported in clinical trials.\(^8\) Healthy People 2020 defines health disparity as a health difference that is intricately linked with social, economic, and/or environmental disadvantage.\(^9\) Racial disparities in health care can have a significant impact on patient outcomes and survival. According to the National Institute on Minority Health and Health Disparities, health disparity/ethnic minority populations are people of African American (AA), Hispanic/Latino, American Indian/Alaska Native, Asian American, Native Hawaiian, and other Pacific Islander descent.\(^10\) Ethnic minorities, especially AAs, have higher mortality for many cancers such as breast, prostate, and colon, at a rate of 28.0, 37.9, and 18.1 per 100,000 AAs, compared with 19.9, 17.8, and 13.4 per 100,000 White individuals, respectively.\(^11\) Many clinical trials focus on representing the US demographics without considering the increased cancer burden among minority populations.\(^12\) Unfortunately, while cancer rates are higher among ethnic minority populations, inclusion of minority populations in clinical trials remains low. This disproportionate representation in clinical research limits the ability of minority populations to fully benefit from biomedical research advances (including access to cutting-edge therapies), thus contributing to racial health disparities.\(^13\) Awareness of the current trend of cancer disparities and representation of minority populations, especially AAs, in clinical trials leading to

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**STAR*\(^*\)**

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*A drug may have multiple indications.*

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**FIGURE 1. TREND OF FDA APPROVAL OF ORAL VS INTRAVENOUS ONCOLYTICS, 2011-2021**

![Bar chart showing the trend of FDA approval of oral vs intravenous oncolytics from 2011 to 2021.](image-url)
the approval of oral oncolytics drugs in the United States becomes important.

Ajewole et al. conducted a retrospective review to evaluate the reporting of race and inclusion of AAs in clinical trials that led to the approval of oral oncolytics by the FDA from 2009 to 2019 in the United States. Results from the study showed that during the 2009 to 2019 timeframe, 142 clinical trials led to FDA approval of 81 oral oncolytics, among which 74 (52%) reported on at least 1 race. A total of 35,933 participants were enrolled in these 74 clinical trials, among which 25,684 (71.47%), 6061 (16.87%), 889 (2.47%), and 826 (2.30%) were White, Asian, AA, and Hispanic, respectively. As shown in Figure 2, AAs were also underrepresented in the clinical trials of the 3 cancer types (lung, breast, and prostate), with the highest disparity rates among the AA population. This disproportionate racial representation in clinical trials becomes more apparent when taking a closer look at the incidence rate of these 3 cancers among minority populations in the United States, as shown in Figure 3.

The authors concluded that there should be more AAs in cancer clinical trials to increase the generalizability of the results, improve outcomes, and eventually close the health disparity gap among ethnic minority populations.

Disparities in the Care Delivery Process: Intravenous Versus Oral Oncolytics

While there has been rapid growth in the approval and clinical utility of oral oncolytics in the United States over the past several years, this growth has not been accompanied with the commonly implemented and appropriate safety parameters with intravenous oncolytics. Administration of intravenous oncolytics occurs in a controlled (outpatient clinic, inpatient setting, or home-infusion) environment, with predetermined premedications, supportive care, laboratory monitoring, and surveillance. Scheduled infusion appointments allow for monitoring of patient adherence while allowing patient and/or family members/caregivers to interact with the multidisciplinary team. In contrast, oral oncolytics require patients and/or their caregivers to assume the majority of the control over their care. Treatment complexities, unique toxicities, drug interactions, patient responsibility for medication adherence and monitoring, reduced health care contact, and increased financial burden are all documented barriers to optimal care among patients receiving oral oncolytics.

In 2009, the American Society of Clinical Oncology and the Oncology Nursing Society published chemotherapy safety standards for ordering, preparation, and administration across...
the inpatient and outpatient settings for both oral and parenteral therapy. These standards are meant to guide day-to-day practice and most recently were updated in 2016 with specific guidance divided into 4 sections: (1) environmental policies and procedures; (2) treatment planning and patient education; (3) ordering, preparing, dispensing, and administering; and (4) monitoring after chemotherapy. One complication for patients on oral oncolytics is that while the use of these agents has increased, standardized safety measures as commonly accompanied with intravenous oncolytics has not been universally adopted across all institutions. According to a survey conducted across 42 comprehensive cancer centers in the United States, 10 centers had no infrastructure to monitor patient adherence. In 2010, the Quality Oncology Practice Initiative (QOPI) Quality Certification Program (QCP) was established by the American Society of Clinical Oncology to standardize cancer care in efforts to improve patient care and safety by identifying core measures for chemotherapy management. These standards include initial and ongoing oral chemotherapy adherence policy as well as chemotherapy toxicity evaluation and documentation policy. However, these standards are only required for institutions with QOPI certification, and hence are not mandated for all institutions/cancer centers. In 2010, a survey of 44 National Cancer Institute (NCI)-designated cancer centers showed that just 11 cancer centers had an oral chemotherapy education program for patients. Another study by Solomon et al conducted a chart review for 100 patients in a single academic medical center institution and reported that just 27% of patients received education by a clinical pharmacist. Toxicity checks were conducted by the providers at 30, 60, and 90 days for 80%, 65%, and 48% of patients, respectively. Treatment-related toxicities secondary to oral chemotherapy were reported by 79% of patients, with 55% classified as severe. Potential drug interactions were discovered in 55% of the patients. These apparent gaps in the care of patients on oral oncolytics create unique opportunities for clinical pharmacists to improve patient outcomes through patient education, assessment of medication adherence, and implementation of strategies to promote self-care for patients while preventing and/or managing treatment-related toxicities. Several institutions have successfully implemented pharmacist-driven solutions to address the growing need of oral oncolytic management including telehealth, comprehensive medication management, and oral oncolytic clinic programs. Such pharmacist-driven programs have been documented to have significant positive impact on patient outcomes, including increased patient education and medication adherence, improved self-care, toxicity identification/management, as well as overall clinical outcome. In addition to the barriers and challenges above, oral oncolytics are very expensive, with costs often exceeding $10,000 per month. The financial distress due to the high cost of oral oncolytics has been extensively described by clinicians, policy experts, and patient advocates. This financial burden poses a significant barrier for patients as well as insurers, leading to the potential breakdown of traditional cost-sharing strategies. Routinely, insured patients use charity assistance to
Supplement their coverage for oral oncolytics, which indicates a major deficiency in US health care policy.\(^{33}\) This variation in payments for oral oncolytics compared with intravenous oncolytics is a major contributor to disparities in use and adherence to oral oncolytics inevitably impacting overall patient outcomes.\(^{34}\) Medication reimbursement process in the United States depends on many factors, including age, type of insurance, and geographic location. Oral and intravenous oncolytics are not reimbursed in the same manner.\(^{20}\) Across several states, intravenous oncolytics are covered under a health plan’s outpatient medical benefit while oral oncolytics are covered under a health plan’s pharmacy benefit.\(^{35}\) There is a potential for patients to pay more for products obtained through pharmacy benefits because of cost-sharing arrangements such as deductibles and coinsurance, which require patients to pay a percentage of the drug price.\(^{34,36}\) Thus, a lack of parity in reimbursement of medications exists and leads to variability in out-of-pocket cost for oral oncolytics.\(^{37}\) To address discrepancies in coverage for oral versus intravenous oncolytics, 43 states and Washington, DC, have passed laws to improve affordability of orally administered anticancer medications over the past 12 years.\(^{34}\) These laws are under the Cancer Drug Parity Act of 2019, a bill that requires health plans that cover anticancer medications administered by a health care provider to provide no less favorable cost sharing for patient-administered anticancer medications.\(^{38}\) Despite the adoption of the cancer drug parity laws, the impact on out-of-pocket costs for oral oncolytics remains marginal.\(^{39,40}\) Additionally, this financial burden can be more significant for patients on Medicare Part D coverage, who are expected to pay high, uncapped out-of-pocket costs, particularly in the coverage gap and catastrophic coverage phase.\(^{41}\)

Ensuring patient access to oral oncolytics presents a unique set of challenges due to the significant cost of these novel agents, health care/payer policies, individual state regulations, distribution practices, and the reimbursement system. Across the United States, there are 2 major categories of pharmacy distribution models for oral oncolytics: medically integrated dispensing, previously called in-office dispensing services/retail pharmacies, or specialty/mail order pharmacies.\(^{42}\) Medically integrated dispensing allows for oncologists to dispense medications directly to their patients, which in theory allows for closer management of patients and overall care. Individual state regulations determine if a full retail pharmacy can be offered from within an oncologist’s practice; many states allow physician dispensing as an alternative to retail pharmacies while some do not allow such practices.\(^{43,44}\)
Specialty pharmacies can generally be categorized as practice based (associated with a health system or clinic) or as independent (nonpractice based). They can exist on site or separate from the oncology practice. Specialty pharmacy is not easy to define, especially in relation to oncology practice, because it consists of a wide range of business models that can include disease management or case management features. A specialty pharmacy has also been described as a model for managing the handling, dispensing, distribution, reimbursement, case management, and other services for patients with rare or chronic diseases. Medication distribution methods from specialty pharmacies are not standard and may include models such as mail order distribution (the traditional model for specialty pharmacy) or distribution from a community pharmacy. Pharmacy service models within the specialty pharmacy scope have been designed to fill the perceived gaps associated with pharmaceutical care provided by the traditional health care system. However, no universally accepted definition of specialty pharmacy exists, and the terms specialty pharmacy and specialty drug vary among health plans and pharmacy benefit programs. Specialty drugs can also be loosely defined as products used to treat chronic, high-cost, or rare diseases. Defining specialty pharmacy is also challenging because there are no mandatory certification standards for a specialty pharmacy, and specialty pharmacy practice beyond that of standard pharmacy practice is not regulated at a federal level, although some state regulations may exist. In an attempt to contain costs and ensure high-quality results for services, some payers require specialty pharmacies to achieve accreditation through accreditation entities, such as the Utilization Review Accreditation Commission (URAC), the Accreditation Commission for Health Care (ACHC), the Center for Pharmacy Practice Accreditation (CPPA), and the Joint Commission, in order to contract with them.

As shown in Figure 4, the US Pharmacy Distribution and Reimbursement System for Patient-Administered Outpatient Brand-Name Drug (including oral oncolytics) is very complicated with complex involvement of manufacturer, third-party payer/health plan, agreements (formulary, vendor, and service), fees/co-pay, pharmacy benefit manager, wholesaler, dispensing pharmacy, and drug shipment before the medication is delivered to the patient. In addition to this complicated process, the patient’s medication insurance and limited distribution models (where manufacturers limit the number of specialty pharmacies that can dispense its medications, a distribution strategy based on product characteristics, patient education, market reach, and administration/dispensing characteristics) primarily determine where a prescription for an oral oncolytic will be filled. Dispensing of oral oncolytics to patients from a remote specialty/mail order pharmacy has the potential to cause many problems from both the provider and patient perspectives. Significant delays in time to therapy start often occur. It is fairly typical for a patient to wait at least 1 to 2 weeks to receive their oral oncolytic from a specialty/mail order pharmacy.

### STAR

**What are some differences between the practice model for intravenous versus oral oncolytics?**
As shown in **Figure 5**, the practice model for oral oncolytics, especially those distributed through nonpractice-based specialty pharmacy, is complex and fragmented. This complexity and fragmentation unavoidably lead to disconnection between the oncologist and the multidisciplinary care team. Additionally, in the absence of integration of clinical services and integration between the dispensing/medical record software of specialty pharmacy and the patient’s electronic medical record in the cancer treatment facility, real-time access to pertinent laboratory/clinical values, accurate medication list, and weight changes among others is lacking. The unintended consequence of this fragmentation and disconnect is the isolation of patients on self-administered oral oncolytics and their caregivers with minimal oversight and support from the health care system. This fragmented process can be a barrier to optimal care for elderly or less technology-literate patients who often experience difficulties with establishing care in nonpractice-based specialty pharmacies, which often lead to delays in mail order delivery of oral oncolytics. The lack of in-person care coordination tends to lead to loss of follow-up, especially if specialty pharmacy is unable to reach patients by phone. Additionally, with the increase in telephone-related scams, patients are rightfully hesitant to discuss personal details or financial information over the phone in the absence of in-person care coordination. These barriers are less likely to occur with intravenous chemotherapy, thus increasing the complexity of the oral oncolytic care process. This disconnect offers a major disservice to the vulnerable patient population on oral oncolytics and can inadvertently lead to poorer clinical outcomes due to medication errors, toxicities, and miscommunication among the multidisciplinary care team.

Although specialty pharmacists can play a pivotal role in helping oncology patients navigate these obstacles to achieve a cytogenic response, remission, or cure, the dispensing of oral oncolytics by nonpractice-based independent specialty/mail order pharmacy poses unique challenges involving inadequate patient health literacy/patient education for the safe self-administration of these toxic medications, nonadherence that can lead to increased adverse effects due to unnecessary dose escalations, incomplete information about a patient’s drug regimen, including nonoral oncolytic and pharmacologic supportive measures, lack of recognition of drug-drug or drug-food interactions, failure in identifying serious adverse effects and how to manage them, and unfamiliarity with proper storage and disposal techniques. There may also be restricted formularies and supply chains that can delay treatment initiation, miscommunication between patients and/or health care providers about how to safely administer these medications, failure to communicate any schedule or dosage changes that may result from adverse effects or laboratory abnormalities, and financial toxicity.

**Disparities in Medication Waste Process and Management**
Irrespective of the extreme cost and financial toxicities associated with oral oncolytics, the prescribed and already dispensed dose (including dosing instruction, dosing frequency, number of tablets, and duration of administration) of oral oncolytics often change due to toxicity or discontinuation secondary to disease progression or death. Additionally, due to the complexity of the oral oncolytic drug distribution system, there is often a disconnect and communication gap between cancer clinics and dispensing pharmacy, thus allowing for continued dispensing and refilling of discontinued or adjusted doses of oral oncolytics. Patients can unintentionally accumulate unused oral oncolytics due to nonadherence, dose adjustments, and receipt of discontinued but still dispensed oral oncolytics. All these factors lead to the accumulation of unused oral oncolytics, which inadvertently results in waste of the products. Oral oncolytic wastage has undesirable cost implications for both patients and health insurers as well as detrimental effects on the environment.

**Barriers to Optimal Treatment Due to Disparities**
Chemotherapy regimens are growing increasingly complex with the advent of precision oncology and wide usage of multidrug regimens. This complexity poses additional challenges for patients on oral oncolytics where patients are responsible to comply with complicated dosing schedules, instructions, and frequency as well as supportive care for prevention and/or management of toxicities. This complexity becomes even more burdensome for patients on multimodal...
treatment regimens that might include combination of an oral oncolytic with intravenous oncolytics, immunotherapy, radiation, or another oral oncolytic.

Studies have shown that increased medication complexity correlates with low medication adherence across multiple disease states. Medication adherence involves a synergized effort and understanding between health care providers and patients in regard to the degree of conformity in day-to-day treatment with respect to dosing and frequency, including the duration of therapy and discontinuation. The patient’s role in medication administration is significantly more crucial when adherence to treatment regimens depends on proper self-management. Other challenges with oral oncolytics include patient safety and monitoring of adverse effects because patients often would not be taking these oral oncolytics in the inpatient/outpatient setting amid health care practitioners. Oral oncolytics require less oversight, symptom control monitoring, and support than standard chemotherapy infusions, leaving room for patients to miss doses and not stay as adherent to their treatment regimens. Research and data have shown that patients with cancer have reported lower rates of oral oncolytic adherence, as low as 16%, compared with patients under the supervision of clinicians delivering infusion. Decreased adherence leads to poor outcomes, including increase in morbidity and mortality, and underscores the importance of assessing medication adherence to oral oncolytics, identifying barriers, and improving measures for patients to receive optimal outcomes from these novel agents.

One study that looked at barriers to adherence to oral hormonal therapy in women with breast cancer found that among 328 participants who completed the survey, just 44.2% reported receiving instruction on the importance of taking oral medication as directed at every office visit. The most frequently cited factors for increasing compliance to oral medications were knowing adherence could improve clinical outcomes (88.7%) and better management of treatment-related adverse effects (60.2%). Based on the findings, the authors concluded that results of this survey suggest that treatment adherence could be improved if health care professionals discuss and emphasize the importance of taking oral medications as directed and the effect of adherence on clinical outcomes.

Drug-drug interactions are drug combinations that may result in therapeutic failure or potentially more serious adverse effects than from solitary administration. Drug interactions among patients taking oral oncolytics have been described in literature with reports of up to 55% potential drug interactions. On the other hand, drug-food interactions are ubiquitous among the broad class of oral oncolytics and contribute to enhanced treatment-related toxicities. Segal et al did a comprehensive review of literature on food and drug interactions for 58 oral oncolytics, including 49 oral chemotherapies, 7 hormonal agents, and 2 supportive care medications. Forty-one of these drugs were metabolized via the CYP450 enzyme pathway while drug-food interactions were noted for all 58 drugs. This study showed that oral oncolytics are associated with a significant number of medication and food interactions and recommended that it is essential for health care providers to evaluate patients’ diet and concurrent medications and provide accurate patient education, therapeutic monitoring, and, if necessary, alternative recommendations whenever oral oncolytics are prescribed.

**STAR**

Drug interactions can impact optimal outcomes for patients on oral oncolytics. What steps can a pharmacist take to address this?

**Conclusion**

The field of oral oncolytics is fast growing. It has changed the approach to care for many oncology patients and transformed the practice for many oncology health care providers. Although oral oncolytics offer the advantages of convenience, flexibility, and fewer disruptions of social and work-related lifestyles, it also comes with potential disadvantages such as

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reduced health care contacts, less frequent monitoring, and risk for nonadherence. While there are gaps and barriers that can contribute to treatment disparities and optimal outcomes for patients on oral oncolytics, these gaps and barriers are great opportunities for pharmacists to offer clinical services for this patient population. There are several resources available for pharmacists to help promote adherence, educate patients, assist with cost containment, and use technology to support patients on oral oncolytics. The field of oral oncolytics is also a unique clinical service area where pharmacists can develop integrated and collaborative practice in conjunction with oncologists, advanced practitioners, nurses, social workers, dietitians, patient navigators, community health workers, and other care team members to address treatment disparities, positively impacting the care and improving treatment outcomes for patients on oral oncolytics.

REFERENCES


27. Mathur AD, Maires TA, Andrick BJ. Impact of a pharmacist-led telehealth oral chemotherapy


**INSTRUCTIONS FOR EARNING CREDIT**

Begin the activity by reading the content in its entirety.

Go to [www.pharmacytimes.org/oral-oncolytics-disparities](http://www.pharmacytimes.org/oral-oncolytics-disparities) to access the online version of this activity.

Click “Proceed,” then complete the online pretest.

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POSTTEST QUESTIONS

1. Which statement is true about the costs of oral oncolytics compared with intravenous anticancer agents?
   A. All oral oncolytics are billed through medical benefits.
   B. Reimbursement is similar among anticancer agents regardless of route.
   C. Costs of oral oncolytics may be more when covered under pharmacy benefits because of deductibles and coinsurance.
   D. Patients with Medicare coverage have a limit on out-of-pocket costs for oral oncolytics.

2. Which of the following is true regarding the outcomes reported by Ajewole et al in a retrospective review that evaluated the reporting of race and inclusion of African Americans in US clinical trials?
   A. More than 85% of clinical trials that led to the FDA approval of oral oncolytics from 2009 to 2019 in the United States reported on at least 1 race.
   B. African Americans were proportionately represented in the clinical trials of the cancer types with the highest disparity rates.
   C. African Americans were proportionately represented in clinical trials that led to the approval of oral oncolytics by the FDA from 2009 to 2019 in the United States.
   D. Diversity and representation of minority populations in clinical trials is important to increase the generalizability of study results and to address gaps in health disparity.

3. Which outcome was observed in the study by Jacob et al on adherence and symptom management of patients prescribed oral oncolytics?
   A. More than 60% of patients reported no cancer-related symptoms.
   B. More than 75% of patients reported cancer-related symptoms of fatigue and drowsiness.
   C. 95% of patients reported high satisfaction with oral oncolytics.
   D. The mean electronic pill cap adherence rate for most patients was less than 15%.

4. Factors impacting clinical outcomes for patients receiving oral oncolytics compared with patients receiving anticancer infusions include which of the following?
   A. Frequency of health care provider face-to-face contact
   B. Risk of poor medication adherence
   C. Less complex medication administration schedule
   D. Ease of self-monitoring and reporting of adverse effects

5. Which factor impacts patient access to oral oncolytics?
   A. Health care/payer policies and state regulations
   B. Medication adherence
   C. Metastatic disease at diagnosis
   D. Potential drug-drug interactions

6. Which of the following is a reported advantage of oral oncolytics compared with intravenous therapies?
   A. Improved adherence
   B. Less disruption with work and social activities
   C. Less monitoring of laboratory values
   D. Less risk of adverse effects

7. In the absence of integrated technology between specialty pharmacy and oncology clinics, the dispensing of oral oncolytics can contribute the following challenges to optimal patient care, except?
   A. Inadequate patient health literacy/patient education for the safe self-administration of oral oncolytics
   B. Incomplete information about a patient's drug regimen
   C. Lack of recognition of drug-drug or drug-food interactions
   D. Identification of serious adverse effects and communication on how to manage them
POSTTEST QUESTIONS (continued)

8. Ms KP is the daughter of patient Mr TP, a 65-year-old man who recently passed away from complications of colon cancer. Ms KP called your retail pharmacy to inquire about disposing 3 full bottles of her father’s oral oncolytic drug capecitabine 500 mg that were found in his medication cabinet. After the phone call, your pharmacy student intern asked you about the possible causes of wastage of oral oncolytics. The following are possible causes of oral oncolytic wastage, except?
   A. Communication gap between cancer clinic and dispensing pharmacy regarding dose modifications of oral oncolytics
   B. Missed doses and low adherence rates of oral oncolytics
   C. Changes to dosing instruction, dosing frequency, and duration of administration
   D. Care coordination to prevent continued dispensing and refilling of oral oncolytics

9. KL is a 65-year-old non-English-speaking Korean man diagnosed with unresectable advanced BRAFV600 mutation-positive melanoma. His oncologist will be starting him on a regimen consisting of:
   • Cobimetinib (Cotellic) 60 mg PO once per day on days 1 to 21
   • Vemurafenib (Zelboraf) 720 mg PO twice per day on days 1 to 28

Secondary to disparities, KL is at risk of which of the following outcomes, except?
   A. Financial toxicity
   B. Missing his infusion appointments
   C. Nonadherence due to complexity of his multidrug treatment regimen
   D. Inadequate self-care management to prevent adverse effects

10. RB is a 55-year-old Latin American woman with full-time employment as a nurse practitioner, with good income and health insurance, who presents to clinic for a discussion of oral niraparib for treatment of her ovarian cancer. She lives 10 minutes away from the nearest cancer center. What is the most likely barrier to medication adherence to her niraparib?
   A. Adverse effects
   B. Health literacy
   C. Travel concerns
   D. Socioeconomic status