

PHARMACY PRACTICE IN FOCUS: ONCOLOGY™

COVER FEATURE

In a Nod to Precision Oncology, the FDA Approves Revumenib

KEVIN LE, PHARMD, BCOP; AYAA KOBASSI, PHARMD CANDIDATE; EUGENIA KWON, PHARMD CANDIDATE; MAIDAH FAROOQ; AND AMIR ALI, PHARMD, BCOP

PRACTICE INSIGHTS

Advancements in the Management of Nonmetastatic Castrate-Resistant Prostate Cancer: A Review of Second-Generation Antiandrogens

RAYMOND DEMATTEO, PHARMD, BCOP; GRASHMA VADAKKEL, PHARMD, BCOP; AND STEPHEN ENG, PHARMD, BCOP

PRACTICE INSIGHTS

Navigating Steroid-Refractory GVHD Treatment: A Pharmacist's Guide to Medication Management

MOLLY SCHIFFER, PHARMD, BCOP

THERAPY SPOTLIGHT

Quizartinib in FLT3-ITD-Positive Acute Myeloid Leukemia: A New Era in Targeted Therapy

NICOLE BENTIVEGNA, PHARMD, BCOP; AND GABRIELA APONTE-MELENDZ, PHARMD

PEER REVIEWED

Precision Oncology: Expanding Therapeutic Horizons With Trastuzumab Deruxtecan

THOMAS BOKINZ, PHARMD; AND BRITNY BROWN, PHARMD, BCOP

Tarlatamab-dlle: A Beginning for Bispecific Therapies in Small Cell Lung Cancer

AVANI YENAMANDRA, PHARMD, BCOP

Targeting DLL3 in Small Cell Lung Cancer and Other Neuroendocrine Carcinomas

AUBREY R. LASKO, PHARMD, BCOP; AND CATHERINE B. MEADOR, MD, PHD

Equitable Representation in Triple-Negative Breast Cancer Clinical Trials

BRITNY BROWN, PHARMD, BCOP; MADISON SAVIDGE, PHARMD, MBA; AND OLIVIA ARUKWE, PHARMD

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TIMES
ONCOLOGY

PHARMACY PRACTICE IN FOCUS: ONCOLOGY™

ALSO IN THIS ISSUE

- 2 PUBLISHER'S NOTE**
Advancements and Challenges in Oncology: Addressing Disparities and Exploring New Treatment Frontiers
Mike Hennessy Jr
- 3 EDITORIAL ADVISORY BOARD**
- 4 EDITOR'S NOTE**
The Critical Role of Diversity in Cancer Clinical Trials
Zahra Mahmoudjafari, PharmD, MBA, BCOP, FHOPA, *Pharmacy Practice in Focus: Oncology* editor in chief

PEER REVIEWED

- 9 Equitable Representation in Triple-Negative Breast Cancer Clinical Trials**
Britny Brown, PharmD, BCOP; Madison Savidge, PharmD, MBA; and Olivia Arukwe, PharmD
- 14 Tarlatamab-dlle: A Beginning for Bispecific Therapies in Small Cell Lung Cancer**
Avani Yenamandra, PharmD, BCOP
- 18 Precision Oncology: Expanding Therapeutic Horizons With Trastuzumab Deruxtecan**
Thomas Bokinz, PharmD; and Britny Brown, PharmD, BCOP
- 24 Targeting DLL3 in Small Cell Lung Cancer and Other Neuroendocrine Carcinomas**
Aubrey R. Lasko, PharmD, BCOP; and Catherine B. Meador, MD, PhD

- 6 COVER FEATURE**
In a Nod to Precision Oncology, the FDA Approves Revenenib
Kevin Le, PharmD, BCOP; Ayaa Kobaissi, PharmD Candidate; Eugenia Kwon, PharmD Candidate; Maidah Farooq, PharmD Candidate; and Amir Ali, PharmD, BCOP

PRACTICE INSIGHTS

- 33 Advancements in the Management of Nonmetastatic Castrate-Resistant Prostate Cancer: A Review of Second-Generation Antiandrogens**
Raymond DeMatteo, PharmD, BCOP; Grashma Vadakkal, PharmD, BCOP; and Stephen Eng, PharmD, BCOP
- 39 Current Treatment Approaches for Relapsed/Refractory Diffuse Large B-Cell Lymphoma**
Jessica M. Lewis-Gonzalez, PharmD, BCOP; and Shashank R. Cingam, MD

- 44 Navigating Steroid-Refractory GVHD Treatment: A Pharmacist's Guide to Medication Management**
Molly Schiffer, PharmD, BCOP

- 47 Emerging Role of BRAF Inhibitors in Relapsed/Refractory Hairy Cell Leukemia Treatment**
Husna Rahim, PharmD, RPh; Sukeina Nasser, PharmD, RPh, CPh, PACS; Rezarta Lako, PharmD, BCPS; Richa Shah, PharmD, BCOP; Jessie Modlin, PharmD, BCOP; Avani Yensamandra, PharmD, BCOP; and Kevin Pang, PharmD

THERAPY SPOTLIGHT

- 50 Quizartinib in FLT3-ITD-Positive Acute Myeloid Leukemia: A New Era in Targeted Therapy**
Nicole Bentivegna, PharmD, BCOP; and Gabriela Aponte-Melendez, PharmD
- 52 New Therapy for Chronic Graft-Vs-Host Disease: Axatilimab**
Grashma Vadakkal, PharmD, BCOP; Melinda Cook, PharmD, BCOP; Kristian Casem, PharmD, BCOP; and Stephen Eng, PharmD, BCOP
- 55 Lisocabtagene Maraleucel Expands the Therapeutic Landscape for Relapsed/Refractory Non-Hodgkin Lymphoma**
Eve Hughes, PharmD; and Jordan Scott, PharmD

CLINICAL FORUM

- 58 Advancing Care for Metastatic Breast Cancer: Oncology Pharmacists Tackle Innovation, Biomarkers, and Operational Hurdles**
Alana Hippensteele, Lead Editor

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Publisher's Note

Advancements and Challenges in Oncology: Addressing Disparities and Exploring New Treatment Frontiers

DESPITE ADVANCEMENTS IN ONCOLOGY, Black women in the US face a disproportionately high burden of triple-negative breast cancer (TNBC), marked by higher incidence, poorer prognosis, and greater mortality rates than other racial groups. In the peer-reviewed literature review on page 9, authors Britny Brown, PharmD, BCOP; Madison Savidge, PharmD, MBA; and Olivia Arukwe, PharmD, demonstrate how clinical trial data leading to FDA approval of TNBC therapies from 2019 to 2023 show the underrepresentation of Black women, with median enrollment at just 6.5%, far below the US census proportion of 14.4%. Addressing this disparity requires prioritizing equitable enrollment, targeted recruitment, and systemic interventions to improve access and representation in clinical research.

Small cell lung cancer (SCLC) is a highly aggressive cancer with a poor 5-year survival rate of less than 10%. In the peer-reviewed literature review on page 24, authors Aubrey R. Lasko, PharmD, BCOP; and Catherine B. Meador, MD, PhD, discuss recent advances in SCLC treatment, including immune checkpoint inhibitors, which have modestly improved outcomes. However, treatment options for SCLC remain limited, especially in later-line settings. DLL3, a ligand expressed in 80% of SCLC cells, has emerged as a promising therapeutic target. This review highlights the development of DLL3-targeting therapies.

Targeting the DLL3 protein, tarlatamab-dlle (Imdelltra; Amgen Inc) has shown durable responses and manageable safety in clinical trials, although it requires careful monitoring for cytokine release syndrome and neurologic toxicities. In the peer-reviewed new drug review on page 14, author Avani Yenamandra, PharmD, BCOP, discusses tarlatamab's indication for extensive-stage SCLC with disease progression after platinum-based chemotherapy. The drug's mechanism of action and promising efficacy establish it as a critical second-line treatment option.

In the peer-reviewed literature review on page 18, authors Thomas Bokinz, PharmD; and Britny R. Brown, PharmD, BCOP, discuss the FDA's April 2024 approval of fam-trastuzumab deruxtecan-nxki (Enhertu; Daiichi Sankyo, Inc) for HER2-positive solid tumors. The approval marks a significant advancement in site-agnostic cancer therapy, expanding its use beyond specific cancer types to a broader patient population. Clinical trial data, including those of DESTINY-PanTumor02 (NCT04482309), demonstrate its efficacy across multiple tumor types, with notable responses in patients with gynecologic malignancies.

These peer-reviewed literature reviews underscore the advancements and persistent challenges in oncology. By prioritizing diverse enrollment, leveraging targeted therapies, and expanding site-agnostic approaches, the oncology community can work toward more inclusive and effective treatment strategies for all patients.

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The Critical Role of Diversity in Cancer Clinical Trials

Zahra Mahmoudjafari, PharmD, MBA, BCOP, FHOA

ABOUT THE EDITOR IN CHIEF

Zahra Mahmoudjafari, PharmD, MBA, BCOP, FHOA, is a clinical pharmacy manager in the Blood and Marrow Transplant Program in the Division of Hematologic Malignancies and Cellular Therapeutics at the University of Kansas Cancer Center in Kansas City, Kansas. Mahmoudjafari is a board-certified oncology pharmacist involved in several oncology-pharmacy organizations, such as the Hematology/Oncology Pharmacy Association (HOPA), currently serving as secretary on the HOPA board of directors. She has also been the chair or cochair of conferences such as Advanced Topics for Oncology Pharmacy Professionals and Oncology Pharmacists Connect. In 2022, she was the recipient of the American Society for Transplantation and Cellular Therapy Pharmacy Special Interest Group Lifetime Achievement Award and received the American Society of Clinical Oncology's 40 Under 40 in Cancer Award.

Mahmoudjafari has presented nationally on her experience with managing high-cost therapies and on clinical topics such as cell and gene therapies, acute and chronic graft-vs-host disease, and the management of fungal infections in hematopoietic stem cell transplantation. Mahmoudjafari completed her pharmacy training at the University of Missouri-Kansas City (UMKC) and her PGY-1 pharmacy practice residency at The Ohio State University Wexner Medical Center. She completed her PGY-2 oncology residency at Huntsman Cancer Institute at the University of Utah and most recently received her MBA from Henry W. Bloch School of Management, which is affiliated with UMKC.



As we embark on the new year, it is fitting to reflect on our progress in oncology and the challenges that remain. Among the most pressing issues in cancer care and research is the critical need for greater diversity in clinical trials. This is not merely an aspirational goal but an essential component of achieving equitable health care outcomes and advancing the science of oncology.

Cancer does not affect all populations equally. Significant disparities exist in cancer incidence, progression, and treatment outcomes across different racial, ethnic, and socio-economic groups. These disparities are often rooted in a complex interplay of genetic, environmental, and systemic factors. To address them effectively, we must ensure that the populations most impacted by cancer are adequately represented in clinical trials.

Historically, clinical trials have struggled with inclusivity. A 2020 analysis of US-based clinical trials revealed that only 8% of participants were Black, 6% were Asian, and 11% were Hispanic—despite these groups comprising approximately 13%, 6%, and 19% of the US population, respectively.¹ This underrepresentation is even more stark in oncology trials, where the burden of cancer disproportionately affects some of these same groups.² The result is a gap in our understanding of how treatments work across diverse populations, which can perpetuate disparities in care.²

The lack of diversity in clinical trials has far-reaching implications for the safety and efficacy of cancer treatments. Biological differences among populations can influence how drugs are metabolized, how tumors respond to therapies, and the likelihood of adverse effects. For example, genetic variations in drug-metabolizing enzymes such as CYP2D6 and CYP3A4 are more prevalent in certain racial and ethnic groups, potentially affecting the pharmacokinetics and pharmacodynamics of oncology drugs.^{3,4}

Without adequate representation of patient groups, these differences may go unrecognized, leading to less effective or harmful treatments for certain populations. Moreover, underrepresentation undermines the generalizability of clinical trial findings, making it difficult to develop guidelines that apply broadly to all patients. In an

era of precision medicine, where treatments are increasingly tailored to individual genetic and molecular profiles, the importance of including diverse populations in research cannot be overstated.⁵

To increase diversity in clinical trials, we must first address the barriers preventing participation. These multifaceted barriers include mistrust, logistical challenges, and eligibility criteria.⁶

As pharmacists, we are uniquely positioned to champion the importance of diversity in clinical trials. Our profession sits at the intersection of patient care, research, and advocacy, giving us a broad perspective on the barriers to participation and the strategies needed to overcome them. By engaging directly with patients, we can demystify the clinical trial process, address concerns, and advocate for their inclusion.⁷

The responsibility to improve diversity in clinical trials does not rest on a single profession or institution. It requires a collective effort across the health care ecosystem. As we embark on a new year, I urge all members of the pharmacy community to consider how they can contribute to this critical work.

For those in direct patient care, this might mean discussing clinical trials with eligible patients and addressing their concerns.⁷ For those in research, it means designing studies with inclusivity in mind and collaborating with diverse communities from the outset.⁷ For pharmacy leaders and educators, it involves advocating for policies that promote equity and incorporating these principles into training programs.^{7,8}

Looking ahead to 2025, we have an opportunity to make significant strides in this area. With advancements in telehealth and decentralized trial designs, we can reach patients in rural and underserved areas who were previously excluded from research. Innovative approaches to community engage-

ment, such as partnering with faith-based organizations or culturally specific advocacy groups, can also help bridge the gap.⁶⁻⁸

In closing, I want to thank you all for your dedication to the field of oncology pharmacy and the patients we serve. I hope this year is one of new beginnings, marked by progress, innovation, and a shared commitment to equity. Together, we can build a future where every patient—regardless of race, ethnicity, or socioeconomic status—has access to the best possible care and outcomes. 🌱

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In a Nod to Precision Oncology, the FDA Approves Revumenib

The approval marks a significant milestone in the treatment of a rare and aggressive subtype of acute leukemia.

Kevin Le, PharmD, BCOP; Ayaa Kobaissi, PharmD Candidate; Eugenia Kwon, PharmD Candidate; Maidah Farooq; and Amir Ali, PharmD, BCOP

ABOUT THE AUTHORS

Kevin Le, PharmD, BCOP, is a clinical pharmacist at the University of Southern California Norris Comprehensive Cancer Center in Los Angeles.

Ayaa Kobaissi is a 2025 PharmD candidate at the University of Southern California Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences in Los Angeles.

Eugenia Kwon is a 2025 PharmD candidate at the University of Southern California Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences in Los Angeles.

Maidah Farooq is a class of 2022 graduate from the University of California, Riverside, with a degree in biology.

Amir Ali, PharmD, BCOP, is a clinical pharmacist specialist at the University of Southern California (USC) Norris Comprehensive Cancer Center and an adjunct assistant professor of pharmacy practice at USC Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences in Los Angeles.

Revumenib (Revuforj; Syndax Pharmaceuticals) is a novel therapy recently approved by the FDA as the first of its class for treating relapsed or refractory (R/R) acute leukemia associated with specific *KMT2A* gene rearrangements (*KMT2Ar*), also known as mixed-lineage leukemia.¹ The drug is currently indicated for the treatment of R/R acute leukemia with a *KMT2A* translocation in adult and pediatric patients 1 year and older.² Revumenib received both breakthrough therapy and orphan drug designations from the FDA, emphasizing its potential to address a significant unmet need for this rare and aggressive cancer type. These expedited pathways recognize the drug's promising efficacy and safety profile in early trials and its potential to improve outcomes for patients lacking effective treatment options. Revumenib received FDA approval on November 15, 2024, and has been in the spotlight to assess its placement in standard of care. The novel mechanism of action of revumenib, a menin inhibitor, selectively targets the genetic drivers of *KMT2Ar* leukemia, distinguishing it from existing therapeutic modalities. With the emergence of this new therapeutic modality, pharmacists are integral to optimizing dosing and managing potential toxicities to ensure safe and effective treatment.³

Disease State Overview

Acute leukemia is a fast-progressing blood cancer originating in the bone marrow, where blood cells are produced and mature. The disease is marked by the uncontrolled proliferation of immature lymphocytes, a type of white blood cell, which disrupts the normal production and function of healthy blood cells. As leukemic cells multiply, they outcompete normal white

blood cells, red blood cells, and platelets, leading to complications such as increased susceptibility to infections, anemia, and bleeding disorders. The cancer's ability to circulate through the bloodstream enables it to spread rapidly to other areas, including the brain and various other organs. The term *acute* reflects the disease's aggressive nature, as it progresses quickly and becomes life-threatening without prompt treatment.⁴

It is estimated that more than 95% of patients with *KMT2Ar* acute leukemia have a *KMT2A* translocation, which is a type of rearrangement that occurs when part of one chromosome breaks and fuses to a different chromosome.⁴ It affects various types of leukemia in both pediatric and adult populations, accounting for approximately 10% of acute leukemia cases. This subset of leukemia presents significant treatment challenges, as standard treatment options such as traditional chemotherapy and hematopoietic cell transplantation often result in suboptimal outcomes, leading to relapse. The genetic abnormality contributes to an especially aggressive disease course, necessitating innovative therapeutic approaches to improve outcomes.⁵

Mechanism of Action and Clinical Context of Revumenib

Revumenib is an oral, small-molecule inhibitor that specifically targets menin, which is a protein that is essential for the pathologic interaction with the *KMT2A* protein. This interaction is a key driver of the leukemogenic process in *KMT2Ar* leukemia. By disrupting the menin-*KMT2A* interaction, revumenib interferes with the abnormal cellular signaling that fuels disease progression, offering a novel, targeted therapeutic

approach that is distinct from traditional therapies.⁶

Currently, standard treatment for *KMT2A*r leukemia involves intensive chemotherapy followed by hematopoietic stem cell transplantation. These approaches often yield suboptimal results, with high relapse rates and limited long-term survival. Until now, no targeted therapies have been available for *KMT2A*r leukemia. Its introduction marks a significant advancement, providing a new, precision-based treatment option for patients with this debilitating mutation.^{2,6}

Clinical Trial Review

Efficacy

R/R *KMT2A*r acute leukemia is associated with a poor prognosis, with less than 10% of patients achieving remission with existing therapies. In the AUGMENT-101 phase 1/2 clinical trial (NCT04065399) interim analysis, treatment with revumenib showed significantly higher remission rates compared with historical controls, with a complete remission (CR) and CR with a partial hematologic recovery rate of 22.8% (95% CI, 12.7%-35.8%) and an overall response rate of 63.2%. The efficacy profile across age subgroups, including varying ages, lineages, prior venetoclax (Venclexta; AbbVie) use, and different *KMT2A* translocation partners, demonstrates broad applicability while emphasizing the treatment's potential within precision oncology. These results stress the potential of revumenib monotherapy to clear leukemic blasts and allow patients to proceed to potentially curative allogeneic hematopoietic stem cell transplantation.⁶

Safety

Notable adverse events (AEs) to monitor with revumenib therapy include corrected QT interval (QTc) prolongation and differentiation syndrome. Specifically, revumenib contains a black box warning for differentiation syndrome, which is a severe reaction to anticancer therapy.² In the AUGMENT-101 phase 2 trial interim analysis, QTc prolongation occurred in 25.5% of patients (grade 3, 13.8%; grade 4, 0%) and differentiation syndrome occurred in 27.7% of patients (grade 3, 14.9%; grade 4, 1.1%), with a median time to onset of 10 days, ranging between 3 and 41 days. Interruption of therapy due to differentiation syndrome and QTc prolongation occurred in 7.4% and 11.7% of patients, respectively; however, treatment was manageable with supportive care and dose adjustments. It is also pertinent to note that no

treatment discontinuations occurred due to either QTc prolongation or differentiation syndrome. Furthermore, diarrhea, edema, febrile neutropenia, nausea, and vomiting are among the common AEs that occurred in more than 30% of patients.⁶ These findings highlight revumenib's tolerability and manageable safety profile, particularly in a population whose current therapies are used with palliative intent.

The Pharmacist's Role

Pharmacists can play a pivotal role in the safe and effective administration of targeted therapies, such as revumenib. Prior to treatment initiation, it is essential to assess a patient's blood counts and electrolyte and liver enzyme levels, as well as perform a baseline electrocardiogram because of the potential risk of QTc prolongation. The dosing of revumenib, a cytochrome P450 (CYP) 3A4 substrate, requires adjustment based on concomitant therapy only with strong CYP3A4 inhibitors, such as voriconazole (Vfend; Pfizer Inc) and posaconazole (Noxafil; Merck). The recommended dose for patients requiring concomitant use of CYP3A4 inhibitors is 160 mg (95 mg/m² if <40 kg) every 12 hours in 28-day cycles. Of note, dose adjustments are not necessary for patients on moderate CYP3A4 inhibitors, such as fluconazole (Diflucan; Pfizer Inc) and isavuconazonium sulfate (Cresemba; Astellas Pharma Inc), emphasizing the critical role of pharmacists in optimizing treatment regimens. Furthermore, the package insert explicitly advises against concurrent use of both strong and moderate CYP3A4 inducers because of potential reductions in revumenib efficacy and increases in QTc prolongation.²

For patients not requiring strong CYP3A4 inhibitors, the recommended dose is 270 mg (95 mg/m² if <40 kg) every 12 hours in 28-day cycles. Revumenib is available in 3 tablet strengths: 25 mg, 110 mg, and 160 mg. This dosing regimen requires 2 separate dosage strengths, resulting in distinct prescriptions, which may potentially increase patient financial burden. Pharmacists play a crucial role in exploring cost-saving strategies and facilitating patient access to medications. Additionally, a key clinical pearl is counseling patients on the importance of administering revumenib on an empty stomach or with a low-fat meal (eg, meals with approximately 400 calories, 25% or less fat) to optimize absorption.²

Although revumenib has demonstrated a tolerable safety profile, vigilant monitoring is essential to identify signs and symptoms of differentiation syndrome, QTc

prolongation, and interactions with concurrent therapy that may exacerbate QTc prolongation. It is important for pharmacists to recognize the early signs and symptoms of differentiation syndrome for prompt management, as it can be life-threatening if left untreated. Key manifestations include pleuropericardial effusion, hypoxia, peripheral edema, fever, dyspnea, acute renal failure, and/or hypotension. Timely initiation of systemic corticosteroids is essential, along with therapy interruption if severe symptoms persist for more than 48 hours. Additionally, given the high incidence of nausea observed with revumenib, pharmacists can effectively prevent and address emetic episodes, drastically affecting patient quality of life. Monitoring potassium and magnesium levels is crucial in the setting of QTc prolongation. Pharmacists can be involved in correcting electrolyte abnormalities to prevent hypokalemia and hypomagnesemia, thereby reducing the risk of cardiac complications.^{2,3}


All in all, pharmacists are essential in ensuring optimal dosing, effectively managing potential toxicities, and making necessary adjustments based on patient-specific factors and drug interactions, ultimately enhancing treatment efficacy and patient safety.

Accessibility and Future Considerations

The approval of revumenib marks a significant milestone in the treatment of a rare and aggressive subtype of acute leukemia, offering renewed hope to patients and their families. For health care professionals, staying informed about the latest clinical applications of revumenib is essential. Pharmacists, in particular, can play a key role in oncology by facilitating optimized, individualized therapy. This includes educating patients on the drug's use and potential AEs, and ensuring adherence to treatment protocols in a safe manner, ultimately enhancing patient outcomes and advancing precision oncology.

In addition, preclinical and early-phase data suggest that combining revumenib with BCL2 inhibitors, such as venetoclax, FLT3 inhibitors, and hypomethylating agents, may result in higher remission rates. Ongoing trials, such as the phase 1/2 SAVE study (NCT05360160), are evaluating several treatment combinations, and studies combining revumenib with standard-of-care induction and consolidation chemotherapy are also being conducted.⁶

Treatment with revumenib has also shown promise in patients with *NPM1*-mutated (*NPM1m*) acute myeloid leukemia (AML), which is another challenging disease

lacking approved targeted therapies.⁷ Recent top-line results from the AUGMENT-101 trial's *NPM1m* AML cohort indicate that revumenib achieved significant clinical responses in R/R *NPM1m* AML, reinforcing its role in precision oncology.⁸ 

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LITERATURE REVIEW

Equitable Representation in Triple-Negative Breast Cancer Clinical Trials

Britny Brown, PharmD, BCOP; Madison Savidge, PharmD, MBA; and Olivia Arukwe, PharmD

AUTHORS

Britny Brown, PharmD, BCOP, is a clinical associate professor at the University of Rhode Island College of Pharmacy in Kingston and a clinical oncology pharmacist at Yale New Haven Health Smilow Cancer Center-Westery.

Madison Savidge, PharmD, MBA, is a PGY-1 pharmacy resident at the University of Maryland Medical Center in Baltimore, Maryland.

Olivia Arukwe, PharmD, is a PGY-1 managed care pharmacy resident at CVS Caremark in Dallas-Fort Worth, Texas.

DISCLOSURES

Britny Brown, PharmD, BCOP, reports grant support from Lilly.

PRÉCIS

Black women have higher rates of triple-negative breast cancer (TNBC) incidence and mortality than the general US population. Despite this, they are underrepresented in TNBC clinical trials.

ABSTRACT

BACKGROUND

Black individuals account for approximately 14% of the US population. Although Black women are less likely to be diagnosed with breast cancer, they are 40% more likely to die from breast cancer than their White counterparts. Despite lesser incidence of breast cancer overall, Black women are twice as likely to be diagnosed with triple-negative breast cancer (TNBC), highlighting the importance of their inclusion in TNBC clinical trials.

OBJECTIVE

We aimed to assess the representation of Black women in TNBC clinical trials.

STUDY DESIGN

This was a retrospective analysis of patient demographics in TNBC clinical trials.

METHODS

The Oncology (Cancer)/Hematologic Malignancies Approval Notifications search page within the FDA's website was used to identify newly approved TNBC therapies over a 5-year period from January 1, 2019, through December 31, 2023. The clinical trials leading to FDA approval were reviewed, and the racial demographics were extracted from each publication. Seven studies were included for analysis. Black representation was individually calculated as a percentage in each of the trials. To identify representation across studies, a median percentage and IQR were calculated.

RESULTS

Black individuals represented an average of 5.4% (321/5953) and a median of 6.5% (IQR, 4.0%-8.3%) of all women enrolled in 7 TNBC breast cancer clinical trials over a 5-year period.

CONCLUSION

Despite having a greater incidence of TNBC, Black women represented just over 5% of patients enrolled in recent clinical trials leading to FDA approval for the treatment of TNBC. Current representation is nearly 3-fold less than a conservative target of 14% (2022 American Community Survey) to match the US census population. These findings highlight the imperative need for strategies to achieve proportionate clinical trial enrollment for Black women with TNBC.

BACKGROUND

Despite significant advancements in oncology, cancer remains a pressing public health concern in the United States, ranking as the second leading cause of death after heart disease.¹ Notably, certain populations within the US, such as Black individuals, continue to bear a disproportionate burden of cancer. From 2000 to 2022, the Black population in the US grew substantially, from 36.2 million to 47.9 million individuals, representing 14.4%

of the US population.^{2,3} More than half (24.8 million) of Black Americans are women.² Triple-negative breast cancer (TNBC) is a subtype of breast cancer that is defined by a lack of expression in estrogen receptors, progesterone receptors, and HER2 receptors. It has a poorer prognosis, shorter time to relapse, and lower overall survival than other breast cancer subtypes because of its clinical features such as a high potential for invasion of surrounding tissues and a high rate of metastatic disease development.⁴ Although Black women have a lower rate of all breast cancer types compared with White women, Black women are 40% more likely to die from breast cancer.⁵ This disparity is partially driven by the disproportionate rate of TNBC in Black women. The rate of diagnosis in Black women is nearly 2-fold higher than other groups, with 24.5 out of 100,000 Black women being diagnosed vs 13.3 out of 100,000 White women and 14.5 out of 100,000 women of all races/ethnicities.⁶

Another driver of survival outcomes among Black women is lower rates of diagnosis at an early stage. Non-Hispanic Black women are more likely to be diagnosed with advanced stage 3 than stage 1 or 2 breast cancer when rates are adjusted for age; breast cancer subtype; Surveillance, Epidemiology, and End Results registry; and year of diagnosis (OR, 1.46; 95% CI, 1.40-1.53).⁷ When adjusted for confounders of socioeconomic status and health insurance status, the OR is almost halved (OR, 1.29; 95% CI, 1.23-1.35), emphasizing the importance of quality health care and access. Further, although rates of screening mammography are generally similar among Black and White women, Black women are 40% less likely to have appropriate imaging follow-up within 15 days of abnormal results.⁸

Although racial disparities in breast cancer survival and biology have been recognized for well over a decade, these disparities remain.⁹ Clinical trials are essential tools to characterize the utility of new anticancer therapies. Unfortunately, Black individuals are frequently underrepresented in clinical trials.⁵ For example, results of a survey from one pharmaceutical company revealed that only 16% of the company's cancer clinical trials achieved representation of Black participants at or above the US census level.¹⁰

As opposed to the common rhetoric that the historical untrustworthiness of the US health care system has affected clinical trial enrollment, interviews with Black patients with breast and ovarian cancers elucidated that access to quality health care and tertiary medical centers are the main contributing structural factors.¹¹ Moreover,

there are clinician, patient, trial, and institutional barriers that further impede racial and ethnic diversity in clinical trials.¹²

Prompted by these known disparities in clinical trial enrollment, the FDA released drafted guidance documents for the industry emphasizing the need to increase representation in clinical trials for racially/ethnically underrepresented groups by outlining strategies to expand eligibility and increase enrollment.^{13*} Plan recommendations include outlining the epidemiology of the disease state, known outcome disparities, and goals for enrollment based on disease epidemiology and/or previously established relevant data. Further, the document outlines the potential that greater-than-proportional enrollment may be necessary in some cases to detect significant differences in certain populations. Although these recommendations are presently in draft form, they are in alignment with the American Association of Cancer Research (AACR) recommendations from the AACR Cancer Disparities Progress Report 2024.⁵

Given the greater incidence of TNBC in Black women, enrollment in clinical trials should aim to match that of the US census level. The broad underrepresentation of Black individuals in clinical trials across cancer types is a cause for concern that this target is not being met in TNBC. Our study aims to characterize the representation of Black women in recent TNBC cancer clinical trials leading to FDA approval.

METHODS

Recent drug approvals using the keywords *breast cancer* were identified using the Oncology/Hematologic Malignancies Approval Notifications search page on the FDA's website.¹⁴ Specifically, any breast cancer therapies approved between 2019 and 2023 not specific to HER2-positive or hormone receptor-positive disease were included for analysis. One trial was excluded from the analysis due to missing racial demographic information.¹⁵

The clinical trial that led to the approval of each therapy was abstracted from the ClinicalTrials.gov database, and the clinical trial publication was located in the PubMed database. All of the included trials were the registration trials used for FDA review. The data collected for each included the trial name, national clinical trial number, therapy approved, approval date, indication, mechanism of action, countries represented, demographic information, total trial enrollment, and total number of Black participants. Given that there were only 7 data points, the data were assumed to be not normally distributed, and a median percentage and IQR were calculated.

^{13*}Since the initial draft and review of this publication, the aforementioned draft guidance has been removed from the FDA website under an executive order.

TABLE. TNBC Trials						
Trial name, year	Total enrollment	Black participants	Percentage of Black participants	Trial characteristics	Areas represented	Enrollment time frame
IMMU-132-01, 2019 ¹⁶	108	8	7.4%	Single group, phase 1/2	United States	2013-2017
OlympiA, 2022 ¹⁷	1836	48	2.6%	Randomized, phase 3	Europe or Israel (54.2%), Asia (27.1%), South America (1.5%), North America (13.9%), Australia (3.3%)	2014-2019
IMpassion130, 2019 ¹⁸	902	59	6.5%	Randomized, phase 3, double blind	Europe, Asia, North America, South America	2015-2017
KEYNOTE-522, 2021 ¹⁹	1174	53	4.5%	Randomized, phase 3	Europe or Israel, Asia, South America, North America, Australia	2017-2018
KEYNOTE-355, 2020 ²⁰	847	78	9.2%	Randomized, phase 3	Europe, Asia, South America, North America, Australia	2017-2018
ASCENT, 2021 ²¹	529	56	10.6%	Randomized, phase 3	Europe, North America	2017-2019
DESTINY-Breast04, 2022 ²²	557	19	3.4%	Randomized, phase 3	Europe or Israel (45.0%), Asia (38.7%), North America (16.3%)	2018-2021
All studies	5953	321	5.4%			
Median (IQR)	6.5% (4.0%-8.3%)					

TNBC, triple-negative breast cancer.

RESULTS

The median percentage of Black women enrolled in TNBC breast cancer clinical trials over the past 5 years was 6.5%, with an IQR from 4.0% to 8.3%. No studies leading to approval in the TNBC population over the past 5 years came within 20% of the population-matched target of 14.4% (Table¹⁶⁻²², Figure^{3,16-22}). Although initially there appeared to be a positive trend with the first 4 trials, the last 3 trials leading to FDA approval had a significant drop in representation, with Black participants representing less than 5% of the total study population (Figure). Of note, greater disparities in clinical trial enrollment among minority racial groups were previously observed during the COVID-19 pandemic period.²³

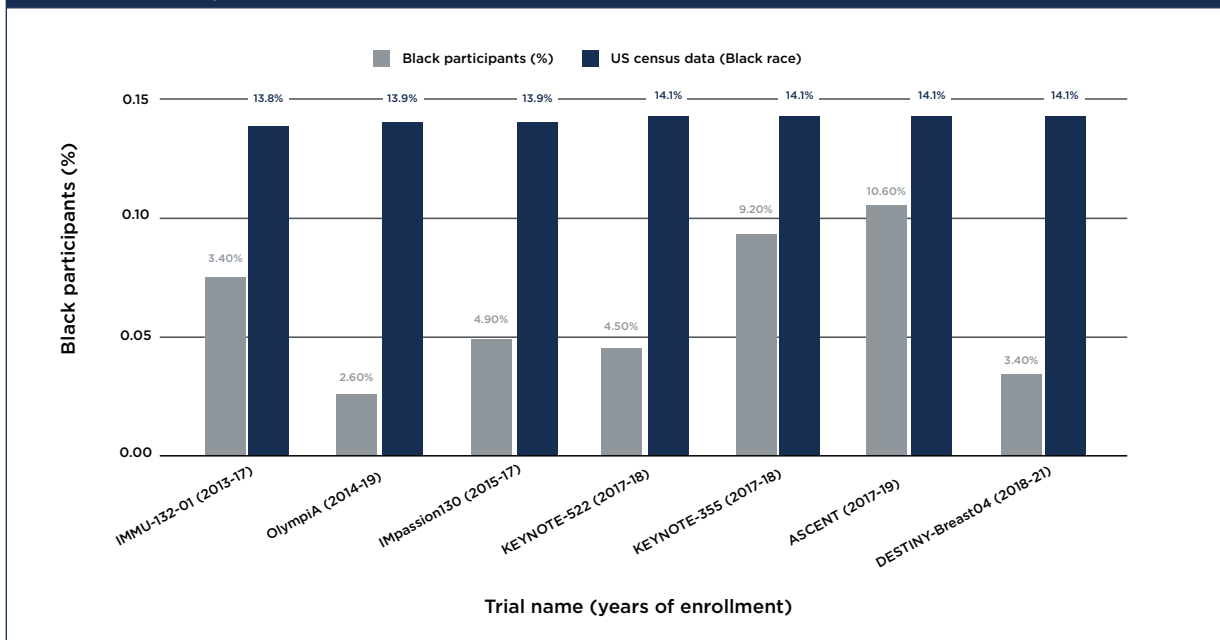
DISCUSSION

Despite significant strides in oncology, cancer remains a formidable public health challenge in the United States, particularly among racially and ethnically minority populations such as Black individuals. Black women face a disproportionately higher risk of TNBC diagnosis and mortality compared with other racial groups, reflecting broader health care inequities. The underrepresentation of Black individuals in clinical trials hinders efforts to identify effective therapies

for diverse populations. As the Black population continues to rise in the US (Figure) and outcome disparities persist, our findings emphasize the need for prioritization of equitable enrollment in TNBC clinical trials for people of diverse backgrounds. As suggested in FDA guidance, it would be of great interest to target recruitment of Black individuals to TNBC clinical trials higher than the US census level, given the considerably higher incidence and mortality rates.^{5,13}

Given our study strategy, our data are biased toward drug therapies that received FDA approval. It is possible that TNBC investigative agents that did not obtain FDA approval had greater Black representation in their clinical trials. It is also plausible that more aggressive underlying biology, propagated by environmental exposures and stress, in Black individuals results in TNBC that is more difficult to manage.²⁴ If true, this would lead to a publication bias toward trials with lower Black representation.

The relatively small number of trials included enrolled patients from up to 5 continents, not including Africa, and the US proportion of enrollment accounted for less than 20% of the trial population, when reported, except for just 1 study (IMMU-132-01; NCT01631552) that was conducted only in the US (Table).¹⁶⁻²² The

FIGURE. Black Representation in TNBC Clinical Trials^{3,16-22}

TNBC, triple-negative breast cancer.

*Black race was calculated using American Community Survey 1-Year Estimates for each year the clinical trial began enrollment, with the numerator of “Black alone or in combination of 1 or more other races” and denominator of the 1-year total population estimate.

lower proportions of Black individuals in countries outside the US likely had a large influence on their underrepresentation in the clinical trials highlighted herein. The greatest Black representation was noted in the ASCENT (NCT02574455) and KEYNOTE trials (NCT02819518, NCT03036488) (10.6% and 9.2%, respectively), although there did not appear to be any major design or geographical distinctions among these trials vs the others included in the analysis.^{20,21}

One of the 7 included trials investigated olaparib (Lynparza; AstraZeneca) in patients with *BRCA*-mutant disease.¹⁷ Historically, *BRCA* mutations are most prevalent in Ashkenazi Jewish women, with mutation rates approximately 50% in those genetically screened compared with 20% in Black women and 33% in White women.²⁵ The enrollment proportions did not reflect that of those affected, with 25 White individuals enrolled for each 1 Black individual.⁶

Our findings are consistent with previously published literature highlighting the underrepresentation of Black and Latinx individuals in cancer clinical trials.²³ A recent cohort study of a nationwide electronic health record database across 280 cancer clinics from 2017 to 2022 reported that Black individuals were less likely than White counterparts to participate in all clinical trials (4.4% vs 7.2%, respectively; HR, 0.57; 95% CI, 0.51-0.65)

and metastatic breast cancer clinical trials (5.0% vs 6.8%; HR, 0.67; 95% CI, 0.52-0.87). Similar to our findings, as demonstrated by the only trial that completed enrollment during the COVID-19 pandemic, DESTINY-Breast04 (NCT03734029), clinical trial representation disparities worsened during and after the COVID-19 pandemic. Inadequate clinical trial diversity may exacerbate health outcome disparities because of decreased access to novel treatment options; it also may limit generalizability to diverse populations.

There are many recommended strategies to improve clinical representation in diverse patient populations. Multiple interventions targeted toward increased enrollment and retention are the most likely to have the greatest efficacy.²⁶ Some examples include incorporating previously discussed FDA guidance, expansion of inclusion criteria, automated screening procedures using artificial intelligence technology, targeting of clinical trial sites serving greater proportions of racially/ethnically diverse individuals, education of clinical staff on cultural humility and implicit bias, and identification of community engagement and patient navigation resources and personnel at each trial site.^{5,12,26}

Pharmacists are encouraged to amplify these findings with patients and health care colleagues. On an individual level, pharmacists may seek training

to improve cultural humility and mitigate bias. Additionally, many oncology pharmacists have transitioned into industry-related fields over the past several years.²⁷ These professionals are well positioned and strongly encouraged to advocate for increased trial enrollment targets for Black individuals and other minority populations, especially those with known health disparities in the area of study.

CONCLUSION

Our study demonstrates clear underrepresentation of Black women in recent TNBC clinical trials, despite their nearly 2-fold increased likelihood of a TNBC diagnosis in the United States. The historical context of factors contributing to difficulty in equitable clinical trial enrollment has been well described. Our study provides a baseline data point for Black women's representation in TNBC trials. 🌍

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NEW DRUG REVIEW

Tarlatamab-dlle: A Beginning for Bispecific Therapies in Small Cell Lung Cancer

Avani Yenamandra, PharmD, BCOP

AUTHOR

Avani Yenamandra, PharmD, BCOP, is a clinical pharmacy specialist of hematology/oncology at MD Anderson Cancer Center at Cooper University Hospital in Camden, New Jersey.

PRÉCIS

Second-line and later treatment options for small cell lung cancer are limited. Tarlatamab offers a new approach to small cell lung cancer therapy, demonstrating long-lasting responses and tolerable adverse effects in pretreated patients.

DISCLOSURES

None.

INTRODUCTION

Small cell lung cancer (SCLC) is a highly proliferative malignancy and the most aggressive type of lung cancer, accounting for 15% of bronchogenic carcinomas worldwide.^{1,2} Although the overall incidence of and mortality rate for SCLC have decreased over the last several decades, the 5-year survival rate continues to be poor, at less than 10%.² SCLC is known to be responsive to chemotherapy and radiotherapy,¹ but more recent developments indicate that it is also responsive to immunotherapy, although less so than other types of cancer.¹ Patients with SCLC treated with platinum-based therapy in the first-line setting may be retreated with platinum-based therapy if the platinum-free interval has been more than 6 months¹; those with SCLC who are platinum resistant may be treated with agents such as lurbinectedin (Zepzelca; Jazz Pharmaceuticals, Inc), which has demonstrated a response rate of 35.2% or greater depending on the chemotherapy-free interval but a short duration of response (DOR; median, 5.3 months).³ Because the historical standard of care for SCLC (ie, chemoimmunotherapy) produces high initial response rates that are short-lived—particularly for extensive-stage SCLC—there remains an unmet need for more effective treatment options with durable responses, particularly once initial therapy has failed.³

In May 2024, the FDA granted accelerated approval to tarlatamab-dlle (Imdelltra; Amgen Inc) for the treatment of adult patients with extensive-stage SCLC with disease progression on or after at least 1 platinum-based chemotherapy. The approval was based on the agent demonstrating long-lasting responses in pretreated patients and made tarlatamab the first bispecific T-cell engager therapy for SCLC.⁴

MECHANISM OF ACTION

Delta-like protein 3 (DLL3) is an attractive therapeutic target because it is overexpressed in SCLC cells in 85% to 94% of patients with SCLC and minimally expressed in normal cells, and it acts as an inhibitor of the Notch signaling pathway,^{5,6} which is a neuroendocrine differentiation regulator in SCLC that causes cell proliferation when aberrantly activated.^{5,6} Tarlatamab is a bispecific T-cell engager that binds to DLL3 on the surface of cancer cells and to CD3 on the surface of T cells, leading to T cell-mediated lysis of DLL3-expressing cells.⁵⁻⁸ DLL3 testing via immunohistochemistry is not required for the use of tarlatamab in extensive-stage SCLC.⁵

DOSAGE AND ADMINISTRATION

Tarlatamab requires a step-up dosing schedule for the first cycle to reduce the incidence and severity of cytokine release syndrome (CRS), one of the major adverse effects (AEs) of this medication.⁵ **Table 1** shows the dosing schedule, recommended monitoring, and

TABLE 1. Tarlatamab Schedule, Dose, Monitoring, and Concomitant Medications⁵

Schedule ^a	Day	Dosage	Recommended monitoring	Concomitant medications
Step-up dosing schedule Cycle 1	1	1 mg	<ul style="list-style-type: none"> Monitor patients for 22-24 h in an appropriate health care setting. Recommend patients be accompanied by a caregiver and stay within 1 h of an appropriate health care setting for 48 h from the start of tarlatamab. 	<ul style="list-style-type: none"> Administer 8 mg IV dexamethasone within 1 h prior to tarlatamab administration. Administer 1 L IV NS over 4-5 h after tarlatamab infusion.
	8	10 mg		
	15	10 mg		
Cycle 2	1 and 15	10 mg	Observe patients for 6-8 h after infusion. ^b	NA
Cycles 3-4	1 and 15	10 mg	Observe patients for 3-4 h after infusion. ^b	NA
Cycle 5+	1 and 15	10 mg	Observe patients for 2 h after infusion. ^b	NA

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IV, intravenous; NA, not applicable; NS, normal saline.

^aTarlatamab treatment cycles are typically 28 days.

^bPatients who experienced grade ≥ 2 CRS, ICANS, or neurological toxicity during prior tarlatamab infusion require extended monitoring in a health care setting.

concomitant medications. The cycle repeats every 28 days, with tarlatamab 10 mg administered on day 1 and day 15, except for cycle 1.⁵

Tarlatamab is administered over 1 hour. Dexamethasone 8 mg is recommended prior to tarlatamab for cycle 1 day 1 and day 8 doses only, and 1 L of normal saline over 4 to 5 hours is recommended post infusion for days 1, 8, and 15 of the first cycle.⁵

CLINICAL DATA ON TARLATAMAB

Tarlatamab was first evaluated in the phase 1 DeLLphi-300 trial (NCT03319940) and demonstrated durable antitumor activity and a manageable safety profile.⁸ These findings led to the subsequent phase 2, open-label, international DeLLphi-301 trial (NCT05060016), on which the FDA based its approval of tarlatamab.⁴

The primary end point of the DeLLphi-301 trial was confirmed objective response (complete or partial response). Patients were eligible if they were 18 years or older and had histologically confirmed SCLC and an ECOG performance status of 0 or 1, and had received at least 2 prior lines of therapy. Patients with asymptomatic, treated, stable brain metastases were also included in the trial.⁹

DeLLphi-301 was conducted in 3 parts: Part 1 was a dose-comparison assessment of 176 patients who had been randomly assigned 1:1 to receive tarlatamab 10 mg or 100 mg. Investigators performed an interim analysis after 30 patients in each group were evaluable for objective response or had been followed for 13 weeks, whichever came first. After analyzing the data, a dose-selection

committee recommended the target dose of 10 mg for parts 2 and 3 of the trial. In part 2, additional patients were enrolled (n=12) at the 10-mg dose so that 100 patients (parts 1 and 2 combined) were reached. Part 3 was a safety substudy after part 2 enrollment completion that evaluated the reduced duration of inpatient monitoring (from 48 to 24 hours) following administration of the first 2 doses of tarlatamab.⁹

Patients enrolled in the study were predominantly former smokers, had a median age of 62.0 to 65.5 years, and had received a median of 2 prior lines of treatment. Twenty-three patients in the 10-mg tarlatamab group (parts 1 and 2) and 32 patients in the 100-mg tarlatamab group (part 1) had brain metastases. Median follow-up among those evaluated for antitumor activity and survival was 10.6 months in the 10-mg group and 10.3 months in the tarlatamab 100-mg group.⁹

The objective response rate (ORR) was 40% (97.5% CI, 29%-52%) in the 10-mg group and 32% (97.5% CI, 21%-44%) in the 100-mg group.⁹ Among patients with an objective response, the DOR—a secondary end point of the trial—was at least 6 months in 59% of patients, with objective responses ongoing at the time of data cutoff in 55% of responders in the 10-mg group and 57% of responders in the 100-mg group.⁹ Median progression-free survival was 4.9 months (95% CI, 2.9-6.7) and 3.9 months (95% CI, 2.6-4.4) in the 10-mg and 100-mg groups, respectively.⁹

Additionally, investigators performed safety and efficacy analyses by the presence or absence of baseline

brain metastases. The overall systemic ORR was 45.3% and 32.6% in patients with and without brain metastases, respectively. In the 10-mg tarlatamab group, the ORR was 54.5% in those with brain metastases and 36.4% in those without and any grade of immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 14% and 6% of patients with and without brain metastases, respectively; grade 3 or greater ICANS occurred only in patients in the 100-mg group and did not lead to tarlatamab discontinuation in any patient with brain metastases.¹⁰

ADVERSE EFFECTS

The most common AE during the treatment period of the DeLLphi-301 trial was CRS, which occurred in 51% and 61% of patients in the 10-mg and 100-mg tarlatamab groups, respectively,^{5,9} primarily at grade 1/2 (50% and 53%).⁹ Grade 3 CRS occurred in 1% and 6% of patients in the 10-mg and 100-mg groups, respectively, and required vasopressin.^{8,9} The median onset of CRS (all grades) was 13.1 hours (range, 7.8-27.4), with a median duration of 4 days (IQR, 2-6).⁹ The most common symptoms among patients with CRS were fever, hypotension, and hypoxia.⁹ Most patients with CRS were treated with fluids, acetaminophen, and glucocorticoids, with additional interventions such as supplemental oxygen, vasopressor support, and tocilizumab used as necessary for grade 3 CRS.^{5,9} Two patients in the trial's part 3 reduced-monitoring cohort (from which a significant portion of the recommendations for supportive care for CRS was derived⁵) received tocilizumab for grade 3 CRS.⁹

Neurologic toxicity including ICANS occurred in 47% of patients.⁹ Nine percent of patients experienced any grade of ICANS,⁵ and no patients in the 10-mg group (parts 1 and 2) experienced grade 3 or higher.⁹ Recurrent ICANS

TABLE 2. The Most Common ($\geq 20\%$) AEs of Tarlatamab in the DeLLphi-300, DeLLphi-301 Trials^{5,a}

AE	Any grade (%)	Grade 3 or 4 (%)
Fatigue	51.0	10.0
Pyrexia	36.0	0.0
Dysgeusia	36.0	0.0
Decreased appetite	34.0	2.7
Musculoskeletal pain	30.0	1.1
Constipation	30.0	0.5
Anemia	27.0	6.0
Nausea	22.0	1.6

AE, adverse effect.

^aBesides cytokine release syndrome.

occurred in 1.6% of patients treated with tarlatamab.⁹ During the DeLLphi-301 trial, most cases of ICANS occurred during cycle 1⁹; however, pooled safety population data from tarlatamab's prescribing information show that most patients experienced ICANS after the cycle 2 day 1 dose,⁵ which has also been this author's experience thus far. The median time to onset of ICANS from the first dose of tarlatamab in the pooled safety population was 29.5 days, with a median time to resolution of 33 days.⁵

Table 2⁵ shows other significant AEs of tarlatamab that occurred in patients with extensive-stage SCLC in the DeLLphi-300 and DeLLphi-301 trials. Laboratory abnormalities that worsened from baseline in patients from both trials included hyponatremia, hypokalemia, decreased lymphocytes, decreased neutrophils, and increased liver enzymes.⁵ **Table 3** highlights the AE differences between the 10-mg dose and the 100-mg dose of tarlatamab in the DeLLphi-301 trial⁹; of note, neutropenia or febrile

TABLE 3. Select Adverse Effect Differences Between Doses in the DeLLphi-301 Trial⁹

Adverse effect	Tarlatamab 10 mg (part 3: reduced inpatient monitoring) ^a No. (%)	Tarlatamab 100 mg (part 1) No. (%)
CRS	19 (55.9)	53 (60.9)
ICANS	2 (5.9)	9 (10.3)
Pyrexia	8 (23.5)	29 (33.3)
Anemia	9 (26.5)	22 (25.3)
Neutropenia	5 (14.6)	11 (12.6)
Lymphopenia	3 (8.8)	9 (10.3)
Hypotension	3 (8.8)	6 (6.9)
Transaminitis	11 (12.6)	30 (13.6)
Peripheral edema	1 (2.9)	3 (3.4)

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

^aThis cohort is most similar to the real-world patient population receiving tarlatamab because during part 3 of the trial, investigators evaluated the reduced duration of inpatient monitoring (from 48 to 24 h) following administration of the first 2 doses of tarlatamab.

neutropenia did not lead to treatment discontinuation in any patient.⁹

TARLATAMAB'S PLACE IN THERAPY

The National Comprehensive Cancer Network (NCCN) guidelines recommend tarlatamab as a second-line treatment option for platinum-sensitive extensive-stage SCLC (ie, an alternative to retreatment with platinum-based chemotherapy). It is also one of the preferred second-line options for patients with platinum-resistant extensive-stage SCLC. The NCCN guidelines note that these recommendations are based on the promising durability of response and acceptable safety profile of tarlatamab.¹¹

The FDA approved tarlatamab for patients with extensive-stage SCLC with disease progression on or after at least 1 platinum-based therapy, but the DeLLphi-301 trial enrolled patients with at least 2 prior lines of treatment. This raises the question: Who is the ideal patient for tarlatamab? The DeLLphi-301 trial included patients with a fairly robust performance status who were not chemotherapy naive. In clinical practice, providers need to take into account whether the patient, at the time of progression, is fit enough to handle tarlatamab. Additionally, patients who have received radiation, particularly whole-brain radiation, could be at risk for neurotoxicity depending on the time interval between the end of radiation and the start of tarlatamab. As we see more data on tarlatamab, perhaps some of our initial questions will be answered.

CLINICAL CONSIDERATIONS

Several bispecific therapies are utilized in hematology, with some variation in how to premedicate to mitigate the risk of and manage CRS or ICANS. For tarlatamab, due to the risk of CRS and neurologic toxicity, including ICANS, the package insert recommends monitoring patients in an appropriate health care facility for 22 to 24 hours after the first 2 doses.⁵ It is up to the institution what is the best course of action to do this safely. Moreover, clinicians may want to consider additional premedications (eg, acetaminophen, diphenhydramine, famotidine) plus dexamethasone to prevent or lessen the severity of CRS or ICANS, which have been successful with other bispecific therapies in other types of cancer.¹² Data are limited on the real-world toxicities of tarlatamab, but more will become available as additional patients are treated with the agent.


Tarlatamab has a significant risk of lymphopenia, and in solid tumor malignancies, antimicrobial prophylaxis is not typically used up front.^{5,9} We will need more clinical data

to know whether antiviral prophylaxis and *Pneumocystis jirovecii* pneumonia prophylaxis are necessary when lymphopenia occurs. Other hematologic abnormalities have been seen with this medication,^{5,9} but additional supportive measures are at the provider's discretion because they are not mentioned in the package insert.

LOGISTICAL CONSIDERATIONS

Because of the risk of CRS and ICANS with tarlatamab, it is up to the institution whether outpatient administration of tarlatamab for the first 2 doses is adequate.⁵ Some institutions are equipped with clinics that cater to patients on bispecific therapies and with staff who are adequately educated on the signs and symptoms of CRS and ICANS and on the proper procedures to follow when CRS or ICANS occurs. Other institutions may prefer inpatient administration of the first dose of tarlatamab and outpatient administration for dose 2 with inpatient observation. Patient safety as well as costs and revenue must be factored into these decisions. Another consideration is that some patients travel to be treated at a cancer center or high-acuity hospital but live in an area where the local hospital is not equipped to handle CRS or ICANS; therefore, it would be helpful to give these patients information on tarlatamab to provide to their local emergency department should an emergency arise.

CONCLUSIONS

Tarlatamab has a place in therapy as a second-line agent for SCLC, with a novel mechanism of action not previously seen in this disease state.¹¹ Future research on tarlatamab could include longer-term overall survival data and possible prospective trials for patients with small cell neuroendocrine cancers of the prostate because these cancers act similarly to SCLC. Findings from a phase 1b trial presented at the 2024 American Society of Clinical Oncology Annual Meeting on tarlatamab monotherapy in patients with metastatic de novo or treatment-emergent neuroendocrine prostate cancer showed a median progression-free survival of 1.9 months.¹³ Additionally, HPN328, a trispecific half-life-extended DLL3-targeting T-cell engager, demonstrated clinical activity and tolerability in patients with SCLC and other neuroendocrine cancers.¹⁴ The National Cancer Institute notes that regardless of the stage, the prognosis for patients with SCLC is "unsatisfactory" despite improvements in diagnosis and therapy over the past few decades.¹ Tarlatamab offers a new approach for treating this aggressive cancer and will hopefully shed light on the overall immunogenicity of SCLCs to allow more targeted agents to be developed. 

LITERATURE REVIEW

Precision Oncology: Expanding Therapeutic Horizons With Trastuzumab Deruxtecan

Thomas Bokinz, PharmD; and Britny Brown, PharmD, BCOP

AUTHORS

Thomas Bokinz, PharmD, is a PG-1 pharmacy resident at Stony Brook University Hospital in New York.

Britny Brown, PharmD, BCOP, is a clinical associate professor at the University of Rhode Island College of Pharmacy in Kingston and a clinical oncology pharmacist at Yale New Haven Health Smilow Cancer Center-Westerly.

DISCLOSURES

Britny Brown, PharmD, BCOP, reports grant support from Lilly.

PRÉCIS

The tumor-agnostic FDA approval of fam-trastuzumab deruxtecan-nxki for HER2-positive unresectable or metastatic solid malignancies exemplifies the importance of understanding the risks associated with targeted therapy and the need for proactive monitoring strategies.

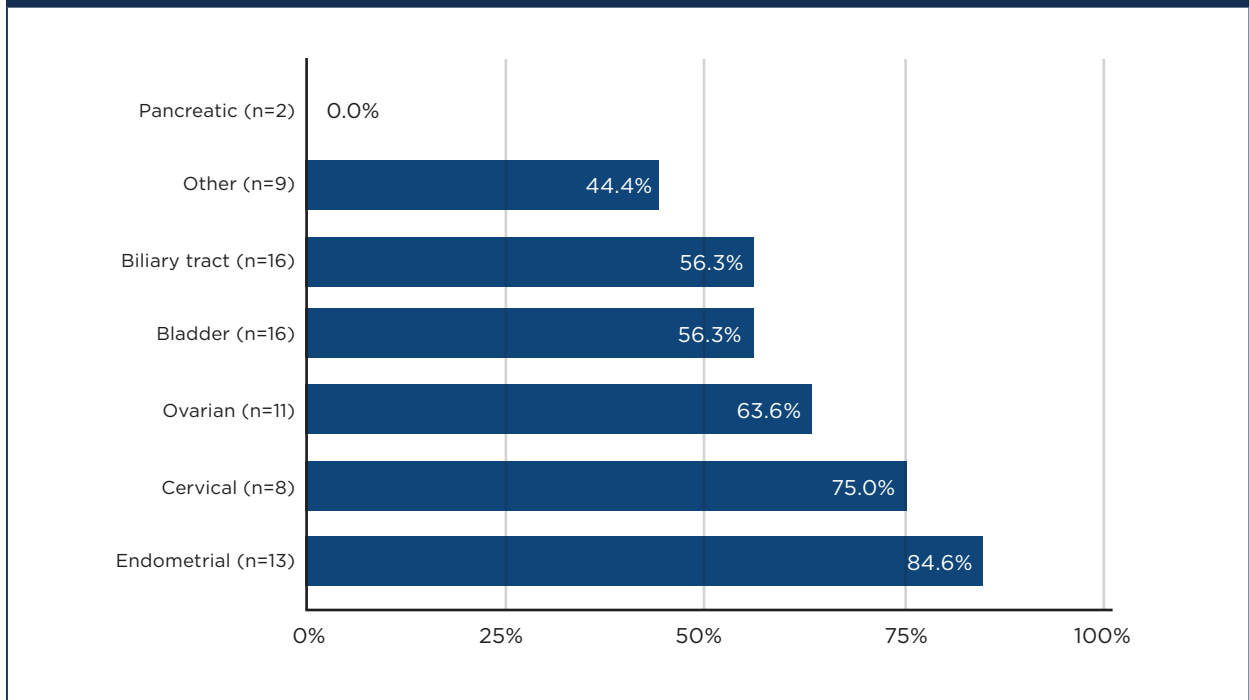
ABSTRACT

Precision medicine has revolutionized cancer treatment by targeting shared genetic markers and shifting oncology care away from traditional cancer type-specific approaches. The targeted therapy fam-trastuzumab deruxtecan-nxki (Enhertu; T-DXd; Daiichi Sankyo, Inc) received FDA approval on April 5, 2024, for adult patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC] score of 3+) solid tumors, expanding its former treatment landscape beyond metastatic breast, colorectal, gastric, and non-small cell lung cancers. The recognition of HER2 as a therapeutic target across various tumors has evolved since 2015, supported by clinical trials such as DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02. These trials demonstrated the efficacy of T-DXd across multiple tumor types, especially in cohorts with HER2 IHC 3+ expression. However, treatment with T-DXd can lead to unique and potentially fatal adverse events such as interstitial lung disease, highlighting the importance of patient monitoring and management strategies such as baseline assessments and regular imaging to detect complications early. Despite the potential risks, T-DXd offers an effective treatment option for patients with refractory solid tumors. As more therapies receive site-agnostic FDA approvals, understanding the risks associated with targeted therapy becomes crucial for proactive management and optimizing treatment outcomes.

INTRODUCTION

Since systemic cancer treatments were discovered in the 1940s, they have been targeted toward specific cancer types.¹ However, precision medicine has transformed the cancer landscape over the past 2 decades by identifying shared genetic and molecular markers (eg, genes, proteins, receptor expression) across tumor types. On April 5, 2024, the FDA approved fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu; Daiichi Sankyo, Inc) for adult patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC] score of 3+) solid tumors, making it the latest treatment to enter the space of site-agnostic approvals.² As of this writing, 8 other FDA oncology approvals (larotrectinib [Vitakvi; Bayer HealthCare Inc], entrectinib [Rozlytrek; Genentech, Inc], repotrectinib [Augtyro; Bristol Myers Squibb]; pembrolizumab [Keytruda; Merck Sharp & Dohme LLC], dostarlimab-gxly [Jemperli; GSK PLC], dabrafenib [Tafinlar; Novartis Pharmaceuticals Corporation], trametinib [Mekinist; Novartis Pharmaceuticals Corporation], and selpercatinib [Retevmo; Eli Lilly and Company]) share the site-agnostic space,² the first of which was pembrolizumab in 2017.

This latest T-DXd approval expands the agent's treatment landscape, which was previously limited to certain populations with HER2-positive breast cancer, HER2-positive gastric or gastroesophageal junction adenocarcinoma, HER2-low breast cancer, or non-small cell lung cancer (NSCLC) with an activating *ERBB2* (also known as *HER2*) mutation.³ However, because treatment with T-DXd can lead to unique and potentially life-threatening adverse events (AEs) such as interstitial lung disease (ILD),³ this site-agnostic FDA approval exemplifies the importance of understanding the risks associated with targeted therapy to proactively and effectively manage AEs and optimize treatment outcomes.

FIGURE. DESTINY-PanTumor02 ORR Based on Cancer Type With HER2 IHC 3+ Expression⁷

IHC, immunohistochemistry; ORR, objective response rate.

The HER2 tyrosine kinase domain is within the family of epidermal growth factor receptors and is encoded by the *ERBB2* gene. *HER2* and *ERBB2* are often used interchangeably to describe *ERBB2* mutations, which are distinct from *HER2* amplification (an abnormally high number of *ERBB2* gene copies) and HER2 overexpression (an abnormally high number of HER2 receptors on the surface of cancer cells).⁴

The introduction of HER2-directed therapies into the breast cancer treatment landscape significantly reduced relapse rates for patients with early breast cancer and improved survival rates for those diagnosed with advanced or metastatic disease.⁵ The recognition of HER2 as a therapeutic target across tumor sites dates to 2015. A study analyzing HER2 expression across nearly 38,000 patient samples found HER2 overexpression and/or *HER2* amplification in bladder carcinomas; extrahepatic cholangiocarcinoma; and gallbladder, cervical, uterine, and testicular cancers.⁶ Several clinical trials since have demonstrated the clinical efficacy of HER2-directed therapies, including those used as the basis for T-DXd's site-agnostic approval: DESTINY-PanTumor02 basket trial, DESTINY-Lung01 (NSCLC), and DESTINY-CRC02 (metastatic colorectal cancer).

DESTINY-PANTUMOR02 TRIAL

The open-label phase 2 DESTINY-PanTumor02 study (NCT04482309) evaluated treatment with T-DXd

(5.4 mg/kg every 3 weeks) in 7 tumor cohorts: endometrial (n=40), cervical (n=40), ovarian (n=40), bladder (n=41), biliary tract (n=41), pancreatic (n=25), and other (n=40). The most common cancer in the *other* tumor cohort was salivary gland cancer (n=19), followed by cancer types with a maximum of 3 individuals per group. The study enrolled patients with HER2-expressing (IHC 3+/2+) local or metastatic disease after at least 1 prior systemic treatment or those without alternative treatment options. Participants had a median of 2 prior lines of therapy, and investigators followed participants for a median of 12.8 months. The primary end point was objective response rate (ORR).⁷

The overall ORR was 37.1% (n=99; 95% CI, 31.3%-43.2%), with some degree of response noted in all tumor cohorts.⁷ The median duration of response (DOR) was 11.3 months (95% CI, 9.6-17.8), the median progression-free survival (PFS) was 6.9 months (95% CI, 5.6-8.0), and the median overall survival (OS) was 13.4 months (95% CI, 11.9-15.5).⁷ Participants with HER2 IHC 3+ expression experienced the greatest benefit from treatment (Figure),⁷ which may have influenced the FDA's decision to require IHC 3+ expression for the latest T-DXd indication. The response rates among gynecologic malignancies (ovarian, 63.6%; cervical, 75.0%; and endometrial, 84.6%) were particularly impressive and practice changing given the historically low response rates and higher mortality rates with

later lines of treatment in this patient population.^{7,8} Of note, only 2 patients with pancreatic cancer had IHC 3+ expression, and neither responded to treatment with T-DXd.⁷ Overall, T-DXd demonstrated efficacy and durable responses across numerous tumor types in DESTINY-PanTumor02, with the most robust responses observed in the biliary tract, bladder, ovarian, cervical, and endometrial tumor cohorts with HER2 IHC 3+ expression.⁷ The safety profile of T-DXd was consistent with its known profile (including ILD).⁷

DESTINY-LUNG01 TRIAL

DESTINY-Lung01 (NCT03505710) was a multicenter, 2-cohort, phase 2 study of T-DXd (6.4 mg/kg every 3 weeks) in patients with unresectable or metastatic, *HER2*-mutated, nonsquamous NSCLC refractory to standard therapy. The trial's primary end point was ORR. Patients were largely pretreated (median, 2 prior lines of systemic therapy), with 90% of patients having received any previous cancer therapy. Patients with *ALK*, *BRAF*, *ROS1*, or *EGFR* mutations who had received previous therapy targeted for those alterations could be enrolled in the trial, but the investigators did not report participants with these gene alterations by percentage.⁹

Among the 91 participants followed for a median of 13.1 months, the ORR was 55% (95% CI, 44%-65%).⁹ The median DOR was 9.3 months (95% CI, 5.7-14.7), the median PFS was 8.2 months (95% CI, 6.0-11.9), and the median OS was 17.8 months (95% CI, 13.8-22.1).⁹ Considering the median historical OS of 12.3 months in a heterogeneous population of patients with NSCLC receiving paclitaxel, carboplatin, and bevacizumab (Avastin),¹⁰ T-DXd provides a novel promising treatment option for patients with HER2-expressing tumors.

Due to the high rate of drug-related ILD/pneumonitis (27.5%) in the DESTINY-Lung01 trial,¹¹ the dose-optimization phase 2 DESTINY-Lung02 trial (NCT04644237) evaluated a 5.4 mg/kg dose (n = 102) with a 6.4 mg/kg dose (n = 50) via a 2:1 random assignment of patients with *HER2*-mutated metastatic NSCLC who were previously treated with a platinum-containing therapy. The trial had a primary end point of ORR and demonstrated comparable efficacy between the 2 doses.¹² The ORR was 49.0% and 56.0% for the 5.4 mg/kg and 6.4 mg/kg doses, respectively, with rates of

ILD/pneumonitis halved in the lower-dose group (12.9% vs 28.0%).¹² Results from the DESTINY-Lung02 trial established the justification for the recommended T-DXd dose of 5.4 mg/kg every 3 weeks.¹²

DESTINY-CRC02 TRIAL

The multicenter, phase 2 DESTINY-CRC02 study (NCT04744831) is assessing the efficacy of T-DXd (5.4 and 6.4 mg/kg) in patients with metastatic colorectal cancer and centrally confirmed HER2 expression. Participants were heavily pretreated, with a median of 3 lines of prior therapy in the 5.4 mg/kg arm and 4 lines in the 6.4 mg/kg arm, and the majority of patients in both arms (78.0% and 85.0%, respectively) had HER2 IHC 3+ expression. Confirmed ORR, the primary end point, was 37.8% (95% CI, 27.3%-49.2%) in the 5.4 mg/kg arm and 27.5% (95% CI, 14.6%-43.9%) in the 6.4 mg/kg arm, with only partial responses (PRs) in both arms. The median DOR was 5.5 months (95% CI, 4.2-8.1) and 5.5 months (95% CI, 3.7 to not evaluable) in the 5.4 mg/kg and 6.4 mg/kg arms, respectively, and the median PFS was 5.8 months (95% CI, 4.6-7.0) and 5.5 months (95% CI, 4.2-7.0), respectively. Safety favored the lower dose and was consistent with T-DXd's known safety profile.¹³

The results of this trial may challenge other treatment options for patients with heavily pretreated metastatic colorectal cancer, considering the historically low median PFS of 2.0 months for both regorafenib (Stivarga; Bayer HealthCare Inc) and trifluridine-tipiracil (Lonsurf; Taiho Oncology, Inc) in earlier trials.^{14,15} The OS benefit will be important to identify as DESTINY-CRC02 data mature, but in the interim, this trial demonstrates a significant advance for patients with heavily pretreated metastatic colorectal cancer.¹³

SIGNIFICANT AES ASSOCIATED WITH T-DXD

Because of T-DXd's mechanism of action as an antibody-drug conjugate with a topoisomerase 1 inhibitor payload, treatment with T-DXd is associated with unique AEs such as ILD, not otherwise seen with typical HER2-directed therapies, as well as other significant AEs, including nausea and vomiting, cytopenias, and cardiotoxicity, that require close monitoring and management. For example, as T-DXd has been studied and ultimately approved for 5 indications,³ we have become more

TABLE. T-DXd Rates of ILD/Pneumonitis in the Phase 2 DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 Trials^a

	DESTINY-PanTumor02 ⁷ (NCT04482309)	DESTINY-Lung01 ¹¹ (NCT03505710)	DESTINY-CRC02 ¹³ (NCT03505710)
Patients enrolled	N = 267	N = 91	N = 122 ^b
Cancer type	Endometrial, cervical, ovarian, bladder, biliary tract, pancreatic, other	NSCLC	Metastatic CRC
T-DXd dose	5.4 mg/kg	6.4 mg/kg	5.4 or 6.4 mg/kg
Frequency	Every 3 wk	Every 3 wk	Every 3 wk
ILD/pneumonitis, n (%)	28 (10.5)	25 (27.5)	LD: 7 (8.4) HD: 5 (12.8)
Grades 1/2	24 (9.0)	19 (20.9)	LD: 7 (8.4) HD: 4 (10.2)
Grade 3	1 (0.4)	4 (4.4)	0
Grade 4	0	0	0
Grade 5	3 (1.1)	2 (2.2)	1 (2.6) in HD arm

CRC, colorectal cancer; HD, high dose; IHC, immunohistochemistry; ILD, interstitial lung disease; LD, low dose; NSCLC, non-small cell lung cancer; T-DXd, fam-trastuzumab deruxtecan-nxki.

^aEfficacy of T-DXd in the subpopulation of patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors in these 3 trials led to the tumor-agnostic FDA approval of T-DXd for this patient population.³

^bLD arm: n = 83; HD arm: n = 39.

knowledgeable about its pulmonary toxicity.

In a pooled analysis of 9 T-DXd monotherapy studies that evaluated ILD/pneumonitis risk in 1150 heavily pretreated patients across multiple tumor types, including HER2-positive breast cancer, Powell et al found that the overall incidence of drug-related ILD/pneumonitis was 15.4%, with a median time to onset of 5.4 months and an overall rate of fatal events of 2.2%.¹⁸

In the DESTINY-PanTumor02 trial, 10.5% (n = 28/267) of patients developed ILD (**Table**), and 3 of these patients died, with rates of ILD and ILD-related deaths consistent with prior trials. The most common drug-related AEs in DESTINY-PanTumor02 across all 7 tumor cohorts were nausea (55.1%), anemia (27.7%), diarrhea (25.8%), vomiting (24.7%), fatigue (24.7%), and neutropenia (18.7%). Notably, this trial showed different rates of AEs across the 7 tumor cohorts.⁷

As previously mentioned, the 6.4 mg/kg dose in the DESTINY-Lung02 trial was associated with a greater drug-related risk of ILD compared with the 5.4 mg/kg dose (28.0% vs 12.9%, respectively). DESTINY-Lung02 trial investigators theorized that the higher ILD rate in the 6.4-mg/kg arm vs trials of other types of cancers treated with that same dose may be due to existing

BOX. DESTINY-Gastric01 Trial

Although DESTINY-Gastric01 did not play a major role in the site-agnostic approval of fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu; Daiichi Sankyo, Inc), it did lead to the agent's approval specific to gastric cancer. Therefore, we are providing an overview of this trial's findings to give readers a comprehensive understanding of T-DXd's use across tumor types.

DESTINY-Gastric01 (NCT03329690) was a multicenter, open-label, randomized, phase 2 trial that evaluated T-DXd (6.4 mg/kg every 3 weeks) vs physician's choice of chemotherapy (PCC; either paclitaxel or irinotecan) in patients with HER2-positive advanced gastric or gastroesophageal junction cancer who progressed on or after at least 2 previous therapies. Patients (N = 187) at participating sites in Japan and South Korea were randomly assigned 2:1 to receive T-DXd or PCC. The patient population was heavily pretreated (median, 2 previous systemic therapies), and 17% had received at least 4 prior therapies. The primary end point was objective response rate, which was 51% in the T-DXd group and 14% in the PCC group. Complete responses (CRs) and partial responses (PRs) were also observed at higher rates in the T-DXd group than in the PCC group (CR: 8% vs 0%, respectively; PR: 34% vs 12%). T-DXd also demonstrated longer OS, with a median of 12.5 months vs 8.4 months with PCC (HR for death, 0.59; 95% CI, 0.39-0.88; *P* = .01). The median PFS was 5.6 months in the T-DXd group and 3.5 months in the PCC group (HR for progression or death, 0.47; 95% CI, 0.31-0.71).¹⁶

The most common grade 3 or higher AEs in the T-DXd and PCC groups were decreased neutrophil count (51% and 24%, respectively), anemia (38% and 23%), and leukopenia (21% and 11%). Interstitial lung disease/pneumonitis occurred in 12 patients receiving T-DXd (grade 3/4 in 3 patients). One drug-related death due to pneumonia occurred in the T-DXd group (none in the PCC group). No patient in either group experienced left ventricular ejection fraction decline or heart failure.¹⁶

Efficacy outcomes were later confirmed in US and European populations in the single-arm, phase 2 DESTINY-Gastric02 study (NCT04014075) of patients with HER2-positive unresectable or metastatic gastric or gastroesophageal junction cancer who had progressed after first-line therapy with a trastuzumab-containing regimen. At a median follow-up of 10.2 months, 42% of patients had a confirmed objective response rate (the primary end point), supporting the use of T-DXd as second-line therapy for this patient population.¹⁷

lung damage caused by smoking, surgery, or radiation in patients with NSCLC. In addition, the difficulty distinguishing among respiratory symptoms and imaging lung abnormalities due to the disease itself vs ILD in patients with NSCLC may also lead to higher rates of ILD diagnosis.¹²

Not unique to T-DXd is the risk of cardiotoxicity, specifically left ventricular dysfunction, due to its trastuzumab component. Based on pooled safety information from 9 T-DXd trials, the rate of left ventricular ejection fraction (LVEF) decline was

3.8% at the 5.4 mg/kg dose in patients with HER2-positive and HER2-low metastatic breast cancer, *HER2*-mutant NSCLC, and other solid tumors, with 0.6% being grade 3.³

MONITORING AND MANAGEMENT STRATEGIES

Because T-DXd has proven to be effective across multiple cancer types but is associated with significant AEs, it is vital to monitor patients on T-DXd to avoid irreversible complications such as cardiomyopathy due to LVEF decline and pulmonary fibrosis secondary to ILD. Prior to initiation of therapy, patients require a baseline ejection fraction study as well as consideration for a high-resolution CT (HRCT) scan of the chest and a baseline reading of oxygen saturation levels.^{19,20} Consideration for T-DXd candidacy should take into account clinical trial exclusion criteria for ejection fraction minimums (eg, 50% in the DESTINY-PanTumor02 trial) and additional risk factors for the development of ILD, such as prior chest radiation, moderate to severe renal impairment, and a preexisting chronic lung condition that required recent corticosteroid use.²⁰

Patients identified as candidates for T-DXd treatment should be educated on signs and symptoms of ILD, such as worsening cough (especially dry cough), shortness of breath and dyspnea upon exertion, and fever. Suspected ILD may require radiographic imaging and a pulmonology consultation.²⁰

Expert consensus recommendations include taking a multidisciplinary approach with oncologists, pharmacists, and radiologists to monitoring and managing ILD. Monitoring recommendations include HRCT scans of the chest every 6 to 9 weeks for patients with respiratory symptoms and at least every 12 weeks for asymptomatic individuals. More frequent HRCT scans may be warranted in patients with Japanese ancestry, lower oxygen saturation levels, or renal impairment.²⁰

Strategies to minimize the risk and impact of T-DXd-related ILD are more

easily remembered with the 5 “S” rules, as follows²¹:

- 1. Screen:** Carefully select patients for T-DXd treatment and continue to screen throughout treatment.
- 2. Scan:** Use radiological scans to diagnose ILD, preferably HRCT scans of the chest at baseline and every 6 to 12 weeks.
- 3. Synergy:** Involve all members of the care team and the patient.
- 4. Suspend:** Interrupt T-DXd treatment if ILD is suspected and restart only in asymptomatic ILD that fully resolves.
- 5. Steroids:** Use corticosteroids, which are dosed based on ILD severity.

In addition, due to T-DXd’s high emetic risk, patients should receive appropriate prophylaxis and antiemetic medications for breakthrough nausea as well as psychosocial and nutritional support as necessary. Risk of neutropenia has been universally observed with T-DXd but may be dose dependent. For example, rates of grade 3 or 4 neutropenia were observed in 51% of patients receiving the 6.4 mg/kg dose of T-DXd for gastric cancer vs 16% of patients with metastatic breast cancer or NSCLC receiving the 5.4 mg/kg dose.³

CONCLUSION

T-DXd provides patients with metastatic, refractory solid tumors an additional effective treatment option. Given the recent positive results from the phase 3 DESTINY-Breast06 trial (NCT04494425) of T-DXd in HER2-low, hormone receptor-positive, metastatic breast cancer, it is anticipated that T-DXd use will be expanded to this patient population.²² Future studies will elucidate the safety and efficacy of T-DXd in other settings, such as for earlier-stage treatment of patients with HER2-positive breast cancer and in patients with HER2-positive breast cancer and active brain metastases.^{23,24} To overcome treatment resistance, combination therapies are of particular interest, with phase 1 trials underway of T-DXd in combination with other types of medications, such as immunotherapy and PARP inhibitors.²⁵

As more targeted therapies emerge with site-agnostic FDA approvals, it is imperative that we familiarize ourselves with the risks of these treatments to proactively and effectively mitigate negative safety outcomes and maximize treatment effects. 🌐

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LITERATURE REVIEW

Targeting DLL3 in Small Cell Lung Cancer and Other Neuroendocrine Carcinomas

Aubrey R. Lasko, PharmD, BCOP; and Catherine B. Meador, MD, PhD

AUTHORS

Aubrey R. Lasko, PharmD, BCOP, is a clinical oncology pharmacist in the Department of Pharmacy at Massachusetts General Hospital in Boston.

Catherine B. Meador, MD, PhD, is a clinical investigator at the Mass General Research Institute, an instructor in medicine at Harvard Medical School, and an attending physician in the Department of Medicine, Division of Hematology/Oncology, Massachusetts General Hospital in Boston.

DISCLOSURES

None.

PRÉCIS

DLL3 is an emerging therapeutic target in small cell lung cancer and other neuroendocrine carcinomas, with 1 FDA-approved therapy and several others under investigation.

ABSTRACT

Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy with high metastatic potential and limited therapeutic options. SCLC makes up approximately 15% of all lung cancer diagnoses, and patients with SCLC historically have had poor clinical outcomes because there are few effective treatments. Recent therapeutic advances, such as the addition of immune checkpoint inhibitors to first-line treatment, have marginally improved outcomes, but effective therapies, particularly in later-line treatment settings, remain limited. DLL3, a ligand in the Notch signaling pathway, is estimated to be expressed on the cell surface of 80% of SCLC cells, highlighting it as a potential therapeutic target. Several mechanistic classes of DLL3-targeting agents have been investigated, including antibody-drug conjugates, bispecific and trispecific antibodies, and chimeric antigen receptor T-cell therapy. This review will explore the DLL3-targeting therapies in development, with a focus on tarlatamab (Imdelltra; Amgen), a first-in-class DLL3 T-cell engager that recently received accelerated approval for and changed the landscape of SCLC treatment.

BACKGROUND

Small cell lung cancer (SCLC) accounts for approximately 15% of lung cancer diagnoses and is associated with an aggressive disease course and short-lived responses to treatment.¹⁻⁴ Approximately 250,000 new cases of SCLC are diagnosed globally every year, with the majority of these diagnosed as extensive-stage SCLC and not expected to be curable with treatment.⁴ Advances in the treatment of SCLC in recent years have included the first-line addition of PD-L1–blocking immunotherapy agents atezolizumab (Tecentriq; Genentech) or durvalumab (Imfinzi; AstraZeneca) to platinum-based doublet therapy and the second-line option of the alkylating agent lurbinectedin (Zepzelca; Jazz Pharmaceuticals).^{2,3,5} First-line immunotherapy and chemotherapy combinations resulted in similar median duration of response (DOR) to platinum doublet therapy (4.2 months for atezolizumab with chemotherapy; 5.1 months for durvalumab with chemotherapy) but have been noted to have a significant benefit in a subset of patients who respond, increasing the estimated 2-year survival from 11% to 22%.^{2,3}

Despite these new therapeutic options, median overall survival (OS) for patients with SCLC from the time of first-line treatment remains approximately 12 months, highlighting the unmet clinical need in this patient population. Broadly speaking, in contrast to non-small cell lung cancer (NSCLC), SCLC lacks recurrent oncogenic driver mutations that are considered therapeutically targetable. This has limited the development of highly effective targeted therapies and biomarker-driven treatment paradigms, such as those seen in subsets of NSCLC.⁶⁻⁸

Recently, however, transcriptional profiling has led to the discovery of novel molecular subsets of SCLC and potential therapeutic targets, leading to the push for development of therapies targeting proteins such as EZH2, TROP2, and DLL3.^{9,10} Of these, therapies targeting DLL3 have had the earliest success in clinical trials. Several DLL3-targeted agents

are either in development or have received accelerated approval from the FDA based on surrogate end points. These targeted agents include bispecific and trispecific antibodies, antibody-drug conjugates (ADCs), and chimeric antigen receptor (CAR) cellular therapy. Here, we present an overview of these agents, their mechanisms, and their current development status, with a particular focus on the recently approved DLL3 bispecific antibody tarlatamab (Imdelltra; Amgen) in SCLC.

DLL3 AND THE NOTCH SIGNALING PATHWAY

DLL3 plays a role in cellular differentiation and proliferation through the Notch signaling pathway.^{11,12} The Notch pathway can promote either oncogenic or tumor suppressor functions, depending on the cell and tumor type; in neuroendocrine tumors, it acts primarily as a tumor suppressor.¹¹ Notch1–4 receptor ligand activation and expression are dependent on transcription factors, including ASCL1, which is a key regulator of pulmonary neuroendocrine cell development in SCLC.^{11,12} ASCL1 expression has been correlated with higher DLL3 expression in these neuroendocrine carcinomas.¹¹ DLL3 is the sole ligand in the Delta/Serrate/Lag-2 family that consistently inhibits Notch signaling, preventing the Notch receptor localization to the cell surface.¹² This inhibitory effect of DLL3 in the setting of neuroendocrine tumors prevents the typical tumor suppressor function of Notch signaling.

DLL3 expression in normal tissues is primarily located intracellularly in the Golgi apparatus and cytoplasm.¹¹ In neuroendocrine carcinomas, however, DLL3 is abnormally overexpressed and detectable on the cell surface. In SCLC, 85% to 94% of patients have been shown to have positive DLL3 expression (defined as expression on $\geq 25\%$ of tumor cells), with similar expression across primary vs metastatic sites and at initial diagnosis vs disease recurrence.^{1,13} Elevated DLL3 expression has also been confirmed in other neuroendocrine tumors, including Merkel cell carcinoma, gastroenteropancreatic neuroendocrine neoplasms, small cell bladder cancer, and large cell neuroendocrine carcinoma.^{14–17} This aberrant expression promotes the growth of SCLC and neuroendocrine cells. Expression of DLL3 has not been shown to correlate to age, sex, stage of disease, or previous therapy.¹³ The inhibition of the Notch pathway tumor suppression function by DLL3 and the unique cell surface expression in neuroendocrine carcinomas including SCLC make DLL3 a viable and compelling target for antineoplastic treatment.

T-CELL ENGAGERS

Bispecific T-cell engagers (TCEs) are monoclonal antibody-based therapies that stimulate the activation of

T cells upon binding to their targets.¹⁸ The bispecific TCE antibody structure targets 2 distinct antigen binding sites, one a unique target on tumor cells and the other the CD3 receptor on T cells. TCE therapies are proving to be an effective treatment approach for patients with cancers that express unique antigens on the tumor cell surface, with multiple approvals in recent years in subtypes of leukemia, lymphoma, melanoma, and multiple myeloma.^{19–24} Because of the immune stimulation, administration of these agents may require inpatient monitoring, close follow-up with the health care team, and rapid supportive care management if cytokine release syndrome (CRS) and neurotoxicity occur.²⁵

Tarlatamab

Tarlatamab is a recently FDA-approved bispecific TCE that binds to DLL3 expressed on SCLC cells and CD3 expressed on T cells.¹ Binding at both antigen binding sites induces T-cell activation and cytokine production, and T-cell engagement and T-cell-mediated lysis are directed to the DLL3-expressing SCLC cells through a proximity-based effect. Tarlatamab also contains an immunoglobulin G crystallizable fragment domain on its molecular structure, which prolongs its half-life and allows for prolonged dosing intervals.²⁶

Tarlatamab was granted accelerated approval in the US on May 16, 2024, based on data from DeLLphi-301 (NCT05060016), a phase 2 open-label trial that enrolled 222 patients with relapsed or refractory (R/R) SCLC following at least 2 other lines of therapy.^{27,28} Patients received step-up doses of 1 mg on the first day of treatment, followed by 10 mg or 100 mg on days 8 and 15, and every 2 weeks thereafter.

Trial enrollment was divided into 3 parts: part 1, which randomly assigned patients to the 10-mg or 100-mg target dose cohorts; part 2, which was a dose expansion of the selected dose of 10 mg; and part 3, a substudy looking at the duration of required inpatient monitoring. There was no dose-response relationship identified between the 10-mg and 100-mg doses, but there was a higher rate of neurologic toxicity in patients who received 100 mg, leading to the selection of 10 mg as the target dose. Of the 100 patients who received the selected target dose of 10 mg in parts 1 or 2 of the study, 40% had an objective response with 2 (2%) complete responses, and a majority of patients who responded (59%) experienced a DOR of at least 6 months. The 10-mg cohort experienced a progression-free survival (PFS) of 4.9 months (95% CI, 2.9–6.7) and median OS of 14.3 months.¹

As seen with other TCEs, CRS was the most common adverse event (AE), occurring in 51% of patients who received the target 10-mg dose across parts 1 to 3 of the study.¹ One of these cases was a grade 3 event, and all

TABLE 1. Tarlatamab Treatment Overview^{1,27}

Indication	Treatment of adult patients with extensive-stage SCLC with disease progression on or after platinum-based chemotherapy		
Premedication and supportive care	C1D1 and C1D8: Dexamethasone 8 mg IV 1 hour prior to tarlatamab administration C1D1, C1D8, and C1D15: 1 L of normal saline IV over 4-5 hours		
Dosing schedule	C1D1: 1 mg IV C1D8: 10 mg IV C1D15 and every 2 weeks thereafter: 10 mg IV		
Expected incidence of CRS and ICANS¹		CRS % all grade (% grade 3 or 4)	ICANS % all grade (% grade 3 or 4)
	C1D1	40 (1)	1 (0)
	C1D8	28 (0)	2 (0)
	C1D15	6 (0)	2 (0)
	C2D1	2 (0)	3 (0)
Recommended monitoring	<p>Cycle 1, days 1 and 8:</p> <ul style="list-style-type: none"> Monitor for 22-24 hours from the start of infusion in an appropriate health care setting Patients should stay within 1 hour of an appropriate health care setting for 48 hours from the start of infusion <p>Cycle 1, day 15; and cycle 2, days 1 and 15:</p> <ul style="list-style-type: none"> Observe for 6-8 hours post infusion <p>Cycles 3 and 4:</p> <ul style="list-style-type: none"> Observe for 3-4 hours post infusion <p>Cycle 5 and subsequent:</p> <ul style="list-style-type: none"> Observe for 2 hours post infusion 		
Recommended dose reduction or treatment interruption criteria	<ul style="list-style-type: none"> No dose reduction is recommended If a dose is delayed by more than 2 weeks, refer to the package insert to determine whether the step-up 1-mg dosing should be repeated Consider treatment interruption for grade 3 or 4 neutropenia, anemia, or thrombocytopenia; febrile neutropenia or infection; or grade 3 hepatotoxicity Permanently discontinue for grade 4 hepatotoxicity or recurrent grade 4 neutropenia or thrombocytopenia 		

C1D1, cycle 1, day 1; C1D8, cycle 1, day 8; C1D15, cycle 1, day 15; C2D1, cycle 2, day 1; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IV, intravenous; SCLC, small cell lung cancer.

others were grade 1 or 2 (30% and 20% of patients treated, respectively) (Table 1^{1,27}). CRS occurred at a median of 13.1 hours after the most recent dose, and the most common symptoms of CRS included fever, hypotension, and hypoxia. Tocilizumab (Actemra; Genentech), an IL-6 receptor antagonist, was given in 5.3% of patients receiving the tarlatamab 10-mg target dose across all 3 study parts, and most cases were managed with supportive care, including supplemental oxygen, acetaminophen, and glucocorticoids. Neurotoxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), occurred in 8% of patients, and all cases were grade 1 or 2. Other common AEs included decreased appetite (29%), pyrexia (35%), constipation (27%), anemia (26%), dysgeusia (29%), and fatigue (23%). Treatment interruption or dose reduction due to AEs occurred in 13% of the 10-mg group, and treatment discontinuation was necessary in 3% of patients.

Tarlatamab's prescribing information recommends dexamethasone premedication and close observation for 22 to 24 hours following step-up dosing of 1 mg on day 1 and 10 mg on day 8 to prevent or facilitate the early identification of CRS and/or ICANS.²⁸ For gaps in treatment greater than 2 weeks, repeating the 1-mg step-up dose may be recommended depending on the patient's current treatment cycle. Patients and health care providers should be educated on early symptoms of CRS or ICANS, including fever, hypotension, tachycardia, hypoxia, and fatigue. Early supportive care and treatment with tocilizumab or corticosteroids should be administered if needed as per the prescribing information. If a patient experiences grade 2 or higher CRS or neurotoxicity, then extended monitoring is recommended with their next infusion, regardless of the treatment schedule.

Tarlatamab is being studied in a confirmatory phase 3 trial (DeLLphi-304, NCT05740566) vs other later-line

TABLE 2. Status of DLL3-Targeting Therapies in Clinical Development

	Development status	Clinical trials with brief description	Recruitment status
T-cell engagers			
Tarlata-mab (Imdelltra; Amgen)	Received accelerated approval from FDA	NCT03319940 (DeLLphi-300) ²⁷ : Phase 1 R/R SCLC	Active, not recruiting
		NCT05060016 (DeLLphi-301) ²⁸ : Phase 2 R/R SCLC	Active, not recruiting
		NCT05361395 (DeLLphi-303) ²⁹ : Phase 1 extensive-stage SCLC in combination with first-line treatment	Recruiting
		NCT05740566 (DeLLphi-304) ³⁰ : Phase 3 R/R SCLC	Active, not recruiting
		NCT06211036 (DeLLphi-305) ³¹ : Phase 3 extensive-stage SCLC in combination with first-line treatment	Recruiting
		NCT06117774 (DeLLphi-306) ³² : Phase 3 limited-stage SCLC following chemoradiation	Recruiting
		NCT04885998 ³³ : Phase 1 R/R SCLC in combination with AMG 404	Active, not recruiting
		NCT04702737 (DeLLpro-300) ³⁴ : Phase 1 metastatic de novo or treatment-emergent neuroendocrine prostate cancer	Active, not recruiting
BI 764532 (Boehringer Ingelheim)	Phase 1 and 2 clinical trials	NCT05963867 ³⁵ : Phase 1 R/R SCLC or NEC	Recruiting
		NCT04429087 ³⁶ : Phase 1 R/R SCLC or NEC, DLL3-positive	Recruiting
		NCT05879978 ³⁷ : Phase 1/2 SCLC or NEC in combination with ezabenlimab	Recruiting
		NCT05882058 (DAREON-5) ³⁸ : Phase 2 R/R SCLC or NEC	Recruiting
		NCT06132113 (DAREON-7) ³⁹ : Phase 1 NEC in combination with first-line chemotherapy	Recruiting
		NCT06077500 (DAREON-8) ⁴⁰ : Phase 1 extensive-stage SCLC in combination with first-line treatment	Recruiting
		NCT05990738 (DAREON-9) ⁴¹ : Phase 1 R/R SCLC in combination with topotecan	Recruiting
		NCT05916313 ⁴² : Phase 1 R/R glioma	
Bispecific and trispecific antibodies			
PT-217 (Phanes Therapeutics)	Phase 1 clinical trials	NCT05652686 (SKYBRIDGE) ⁴³ : Phase 1 R/R SCLC or NEC, DLL3-positive	Recruiting
HPN328/MK-6070 (Harpoon)	Phase 1/2 clinical trials	NCT04471727 ⁴⁴ : Phase 1/2 R/R SCLC or NEC	Recruiting
RO7616789/RG6524 (Roche and Chugai)	Phase 1 clinical trial	NCT05619744 ⁴⁵ : Phase 1 R/R SCLC or NEC	Recruiting
QLS31904 (Qilu Pharmaceutical)	Phase 1 clinical trial	NCT05461287 ⁴⁶ : Phase 1 R/R SCLC or other solid tumors, DLL3-positive	Recruiting
CAR T-cell therapy			
AMG 119 (Amgen)	Phase 1 clinical trial on an enrollment hold	NCT03392064 ⁴⁷ : Phase 1 R/R SCLC	Suspended
LB2102 (Legend Biotech)	Phase 1 clinical trial	NCT05680922 ⁴⁸ : Phase 1 R/R SCLC or large cell neuroendocrine lung carcinoma	Recruiting
DLL3-CAR-NK (Legend Biotech)	Phase 1 clinical trial	NCT05507593 ⁴⁹ : Phase 1 R/R SCLC	Unknown status

CAR, chimeric antigen receptor; NEC, neuroendocrine carcinoma; R/R, relapsed/refractory; SCLC, small cell lung cancer.

standard-of-care agents in SCLC, including lurbinectedin and topotecan.²⁹ Its use is also being explored in treatment of limited-stage SCLC following treatment with chemoradiation (phase 3 DeLLphi-306 [NCT06117774]), in combination with immunotherapy and chemotherapy

as first-line treatment of extensive-stage SCLC (phase 3 DeLLphi-305 [NCT06211036] and phase 1 DeLLphi-303 [NCT05361395]), and in neuroendocrine prostate cancer (phase 1 DeLLpro-300 [NCT04702737]), in addition to other trials (Table 2).²⁷⁻⁵⁰

BI 764532

BI 764532 (Boehringer Ingelheim) is another DLL3 TCE in clinical development. Similar to tarlatamab, BI 764532 is a DLL3-targeting TCE that binds to CD3 on T cells, inducing lysis of DLL3-expressing cells. Initial results from a phase 1 open-label, dose-escalation trial (NCT04429087) testing BI 764532 in patients with DLL3-positive advanced SCLC or neuroendocrine carcinoma were presented at 2023 World Conference on Lung Cancer.^{36,51} In this study, 107 patients received BI 764532 at 1 of 3 different dosing regimens for a maximum treatment duration of 36 months. Dosing is initiated with a fixed dose once every 3 weeks to avoid excess drug accumulation. Once the selected dose was determined, dosing frequency increased to once weekly. Of the total study population, 53 patients had a diagnosis of advanced SCLC. All patients had received at least 1 prior line of treatment, and 31% of patients had received at least 3 prior lines of therapy. At the time of presentation, the maximum tolerated dose had not yet been reached and dose escalation was still ongoing. Of the patients who received a dose of at least 90 mcg/kg and had a postbaseline tumor assessment, 10 of the 39 patients (26%) with SCLC and 3 of the 5 patients (60%) with large cell neuroendocrine lung carcinoma experienced a partial response. Responses were ongoing in 10 of the 13 responders, with a range in treatment duration from less than 1 month to 10.6 months. The most common AEs were those expected with a TCE and included any-grade CRS (48%), pyrexia (17%), and decreased lymphocytes (24%). Multiple phase 1 and phase 2 trials testing BI 764532 are ongoing, including the phase 2 DAREON-5 study (NCT05882058) for treatment of DLL3 expression-independent SCLC and other neuroendocrine carcinomas following at least 1 platinum-based regimen (Table 2).²⁷⁻⁴⁹

**ADDITIONAL BISPECIFIC AND TRISPECIFIC ANTIBODIES
PT217**

DLL3-targeted bispecific antibodies using alternative antigen targets to CD3 are being investigated as a therapeutic option in SCLC. One example is PT217, a bispecific antibody targeting DLL3 and CD47, which is also expressed on the surface of SCLC cells.²⁹ The normal function of CD47 on SCLC cells is to inhibit macrophage-mediated cell lysis. PT217 binding to the CD47 receptor blocks the negative regulation of macrophages and allows for the natural killer (NK) cell- and macrophage-mediated cell phagocytosis of cells that express DLL3.³⁰ PT217 has been granted a fast-track designation by the FDA and is being studied in the phase 1/2 SKYBRIDGE trial (NCT05652686; Table 2)²⁷⁻⁴⁹ in patients with SCLC and other neuroendocrine carcinomas expressing DLL3 who have previously been treated with all existing standard-of-care treatments.

HPN328/MK-6070

Trispecific antibodies, or trispecific T-cell engager (TriTE) molecules, bind to CD3 on T cells, the cancer-specific target, and human serum albumin, which is used to extend the serum half-life of the compound.^{52,53} A DLL3-targeted TriTE, previously known as HPN328 and now known as MK-6070, is being investigated for use in neuroendocrine carcinomas both as monotherapy and in combination with atezolizumab or investigational agent ifinatamab deruxtecan (I-DXd; Daiichi Sankyo and Merck).^{53,54} Interim results from the initial 3+3 dose escalation portion of the phase 1/2 study (fixed-dose escalation, early step-dose escalation, and dose optimization cohorts) included data from 97 patients (56 with SCLC, 18 with neuroendocrine prostate cancer, and 23 with other high-grade neuroendocrine neoplasms). At the time of data cutoff, 1 mg was determined as the maximum tolerated priming dose, and the maximum tolerated target dose had not been reached. Target doses of either 12 or 24 mg every 1 or 2 weeks are being studied in the dose optimization cohort. Forty-one of the 97 patients, whose data were presented at the 2024 American Society of Clinical Oncology Annual Meeting, received a target dose of MK-6070.⁵³⁻⁵⁵

Of these 41 patients in the dose optimization cohort, the objective response rate (ORR) was 39% in 28 patients with SCLC and 46% in 13 patients with other neuroendocrine neoplasms. CRS occurred in 63% of the 97 treated patients, with grade 3 or greater CRS seen in 3% of patients, and a majority of CRS events occurred following the first dose. ICANS occurred in 7% of patients, all grade 1 or 2. Other AEs included fatigue (37%), dysgeusia (36%), nausea (23%), and vomiting (21%). Treatment-related respiratory failure and pneumonitis led to death in 1 patient each, and 4% of patients discontinued treatment due to AEs. The recommended phase 2 dose of MK-6070 will be determined after further evaluation of monotherapy and atezolizumab combination cohorts. Primary completion of the phase 1/2 completion (NCT04471727) is estimated to occur in July 2025 (Table 2).²⁷⁻⁴⁹

RO7616789/RG6524 and QLS31904

Two additional bispecific and trispecific antibodies targeting DLL3-expressing cells are being investigated in phase 1 trials. RO7616789, also referred to as RG6524, is a trispecific TCE that targets DLL3 on tumor cells and CD3 and CD137 on T cells.⁴⁵ Concurrent binding to CD3 and CD137 synergistically stimulates T-cell function, redirecting T-cell activity to the DLL3-positive cells. QLS31904 is a TCE that binds to both DLL3 on tumor cells and CD3 on T cells.⁴⁶ Initial results from these 2 studies (NCT05619744; NCT05461287) are not yet available (Table 2).²⁷⁻⁴⁹

ANTIBODY-DRUG CONJUGATES

Utilizing a slightly different targeted therapy approach than that used with bispecific antibodies, ADCs were developed to enable delivery of cytotoxic therapy to cancer cells with a specific cell surface target. ADCs are comprised of a monoclonal antibody, a linker, and a cytotoxic agent.^{56,57} The linker component prevents early release and nontargeted delivery of the cytotoxic compound and is typically designed to cleave under specific conditions, such as a change in pH or via enzymatic degradation.⁵⁸ Cell surface antigens such as DLL3 that are specific to the tumor cells have been identified as effective targets for ADC development, for similar reasons as outlined above for bispecific and trispecific antibodies.⁵⁹ However, in practice, ADCs have thus far shown less clinical promise than other DLL3-targeted therapies.

Rovalpituzumab Tesirine

Rovalpituzumab tesirine (Rova-T; AbbVie) is an ADC comprised of a DLL3-targeted antibody (rovalpituzumab) linked to a cytotoxic pyrrolobenzodiazepine DNA crosslinking compound (tesirine).^{60,61} After Rova-T binds to cells with DLL3 expressed on the cell surface, the protease-dependent linker is cleaved and selectively delivers the cytotoxic payload to the DLL3-positive cells. Initial data from a phase 1 trial (NCT01901653) testing Rova-T in R/R SCLC demonstrated an 18% ORR (11 of 60 patients), including 38% (10 of 26 patients) of those with 50% or greater expression of DLL3 on tumor cells.³⁷ However, subsequent phase 3 studies TAHOE (NCT03061812; Rova-T vs topotecan in the second line) and MERU (NCT03033511; Rova-T maintenance vs placebo following first-line platinum/etoposide) were both terminated early for lack of efficacy at the prespecified interim analyses.^{60,61}

TAHOE randomly assigned 444 patients 2:1 to second-line therapy with Rova-T vs standard-of-care topotecan in DLL3-high advanced SCLC. Rova-T was administered at 0.3 mg/kg intravenously every 6 weeks for up to 4 cycles. The OS on the Rova-T arm was 6.3 months, compared with 8.6 months with topotecan. The most common AEs observed in the Rova-T arm included pleural effusion (29%), decreased appetite (25%), dyspnea (25%), fatigue (25%), nausea (23%), and pericardial effusion (20%). Grade 3 or higher events occurred in 64% of patients and included thrombocytopenia (9%), anemia (7%), dyspnea (7%), and pneumonia (6%). The MERU study randomly assigned 748 patients 1:1 to the established Rova-T dose of 0.3 mg/kg every 6 weeks or a double-blinded placebo arm. Rova-T led to a longer PFS than placebo by investigator assessment

(4 months vs 1.4 months) but no difference in OS (8.5 vs 9.8 months; HR, 10.7; 95% CI, 0.84–1.36). No difference in outcome was identified based on DLL3 expression. AEs were similar to those seen in the TAHOE trial and included pleural effusion (27%), decreased appetite (27%), peripheral edema (26%), photosensitivity (25%), and fatigue (25%). Based on the high rates of treatment discontinuation from AEs (13% in TAHOE and 20% in MERU) and the lack of clinical benefit, Rova-T was not carried forward in clinical development.³⁶

SC-002

Similar to Rova-T, SC-002 was another DLL3-targeted ADC with a pyrrolobenzodiazepine warhead designed to improve the safety and exposure profile associated with Rova-T. SC-002 contained a modified valine-alanine dipeptide linker and added 2 site-specific cysteine residues to standardize the drug-antibody ratio and improve the conjugation between the antibody and warhead.⁴⁰ A first-in-human phase 1a/1b dose escalation study (NCT02500914) enrolled 35 patients with SCLC and large cell neuroendocrine carcinoma.⁴⁰ Patients in the phase 1a dose escalation cohort were not required to have DLL3 expression, and they received SC-002 at dose levels from 0.025 mg/kg to 0.4 mg/kg every 3 weeks. DLL3 expression of 75% or greater was required for enrollment in the phase 1b dose expansion cohort.

Thirty-four patients were enrolled in phase 1a, and 1 patient was enrolled in phase 1b.³⁹ The maximum tolerated dose was determined to be 0.4 mg/kg every 9 weeks due to AEs of pleural effusion and photosensitivity reaction. In the treated population, SC-002 produced significant toxicity, including grade 3 or 4 AEs in 66% of patients and 1 grade 5 event of pneumonia possibly related to the study drug. Dyspnea and pleural effusion were the most common AEs; each occurred in 43% of patients. Study expansion was halted due to the systemic toxicity experienced by patients.

Although both Rova-T and SC-002 were designed to infiltrate the DLL3-expressing cells, the levels of toxicity suggested normal cells were also being exposed to the cytotoxic warhead at higher than expected levels. Although the exact cause of these systemic toxicities is unknown, excess exposure to the cytotoxic compound may have occurred through several mechanisms.³⁹ Early separation or premature cleavage of the warhead and antibody can lead to nontargeted release of the cytotoxic compound. The warhead may also have been back-released from lysed tumor cells, leading to a possible bystander effect on nearby non-DLL3-expressing cells. Regardless of the specific mechanism of toxicity, the lack of success with Rova-T and SC-002 has been attributed to ADC design rather than DLL3 as a target.

Currently, there are no other DLL3 ADCs in the clinical trial stage of development.

CAR T-CELL THERAPY

CAR T-cell treatments are an adoptive cell therapy approved for use in hematologic malignancies including leukemia, lymphoma, and multiple myeloma. Once incorporated, CAR proteins are located within the cell membrane of T cells.⁴¹

The extracellular component is designed to target specific antigens on the cancer cell surface, and the intracellular domain transmits the activating signals following receptor-antigen binding. These receptors are synthetically created through the addition of a gene encoding the specific CAR to collected patient-specific T cells. The cells are then expanded in the laboratory setting, creating millions of CAR T cells expressing the synthetic protein. Prior to infusion of these engineered cells, a patient typically receives lymphodepletion chemotherapy to allow for engraftment and survival of the CAR T cells. CAR T-cell therapy is associated with potentially severe CRS and neurotoxicity due to the immune response following infusion of the cells.

In addition to bispecific and trispecific antibodies and ADCs, DLL3 has been considered as a potential target for CAR therapy. AMG 119, a DLL3-targeting CAR T-cell therapy, led to a partial response in 1 patient and stable disease in 2 patients out of the 5 treated.⁴¹ The phase 1 trial (NCT03392064) has since been on an enrollment hold (Table 2).²⁷⁻⁴⁹ A second DLL3-directed CAR T therapy, LB2102, is being studied in a phase 1 study (NCT05680922) currently enrolling patients, as is a CAR NK-cell therapy in another phase 1 trial (NCT05507593) (Table 2).²⁷⁻⁴⁹ Challenges to incorporating DLL3 as a CAR T or NK therapeutic target have been explored elsewhere and include poor cell trafficking into the tumor, an immune suppressive microenvironment, and tumor heterogeneity.^{43,44,49}

CONCLUSION

DLL3 is now a clinically targetable antigen in the treatment of SCLC with 1 FDA-approved therapy and several more in development (Table 2).²⁷⁻⁴⁹ To date, bispecific T-cell engager therapy leads the field with first approved DLL3-targeted agent tarlatamab based on its ORR of 40% and DOR greater than 6 months in a majority of patients.¹ Following its recent FDA approval, we await real-world data to continue to understand the efficacy and toxicity of this agent in patients with advanced SCLC. As reviewed above, outcomes of DLL3-

targeting ADCs Rova-T and SC-002 were limited by significant toxicity, and there are no additional DLL3-specific ADCs in development. Bispecific and trispecific antibodies have proved the most promising treatment option thus far, with several agents in early clinical trials. Outcomes data are eagerly awaited from CAR T and CAR NK therapies currently being studied to determine whether these will be efficacious and safe therapies for patients with neuroendocrine carcinomas.

Of particular interest in future studies will be a deepening understanding of DLL3 as a predictive biomarker for DLL3-targeted therapies. Tarlatamab was approved for treatment of histologically confirmed SCLC, and it does not require DLL3 expression. The majority of ongoing early-phase clinical trials for other DLL3-targeted agents also do not require DLL3 expression for enrollment. Although we know that the large majority of SCLC tumors express DLL3, a small subset of them do not. The DOR—or toxicity—from these agents as a function of DLL3 expression remains unknown. In the real-world setting, this is likely to remain a challenge due to the practicality of repeat tissue biopsies and the often-urgent need for treatment. Further study of the relationship between DLL3 expression and clinical outcomes, along with the possible incorporation of DLL3 expression into early pathology analysis if indicated, will be key to determining whether there is a specific subset of patients who are likely to receive the most benefit from these treatments.

One of the challenges of studying DLL3 as a predictive biomarker is the possibility of intratumoral heterogeneity of expression, or the potential for change in DLL3 expression levels between metastatic sites and/or over time in response to therapy. Future research efforts aimed at understanding the correlation of DLL3 expression with clinical outcomes as well as factors that affect DLL3 expression over time will allow for a more precise selection of patients for these therapies. In particular, as more DLL3-targeted therapies reach later stages of clinical development, it will be imperative to gain this more nuanced understanding in order to optimally sequence chemotherapy, immune checkpoint inhibitors, and DLL3-targeted agents in the treatment of patients with neuroendocrine carcinomas.

SCLC and other aggressive neuroendocrine carcinomas have remained difficult to treat despite recent advances, which is in part due to a paucity of effective treatment options. SCLC treatment lacks targeted therapies, especially when compared with the growing availability of oncogenic driver-based

treatments in NSCLC. Tarlatamab and the additional DLL3-targeted therapies in development help address this need, and the study of these in earlier-line settings or in combination with other treatments may bring greater change to current treatment recommendations. The relative rarity of other aggressive neuroendocrine carcinomas, such as solid tumors with small cell histology, will make treatment recommendations and sequencing more difficult. The studies of TCEs and other bispecific and trispecific antibodies in these tumors that are underway may assist in determining the most appropriate patient groups for these treatments.

Practical considerations for incorporating TCE treatments will remain a priority. Bispecific and trispecific antibodies and CAR therapy administration are currently limited due to the potential need for urgent supportive care, which can add additional considerations to treatment in a rural setting. These therapies are also often followed by inpatient monitoring, which creates a challenge for community oncology settings with no inpatient level of service. Optimizing postinfusion monitoring protocols and emphasizing early identification of CRS and ICANS symptoms by patients and caregivers will be paramount to allow for administration and observation across various care settings. Identifying risk factors for CRS and ICANS, which will allow for tailored monitoring recommendations, may also assist in bringing these therapies to a larger patient population. Despite these challenges, the approval of tarlatamab as the first DLL3-targeted therapy and the potential for future DLL3-targeted therapies are welcome additions to available treatment options for SCLC and other neuroendocrine carcinomas. 🌱

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Advancements in the Management of Nonmetastatic Castrate-Resistant Prostate Cancer: A Review of Second-Generation Antiandrogens

Treatment selection includes patient factors, cost, adverse effects, and drug interactions.

Raymond DeMatteo, PharmD, BCOP; Grashma Vadakkal, PharmD, BCOP; and Stephen Eng, PharmD, BCOP

ABOUT THE AUTHORS

Raymond DeMatteo, PharmD, BCOP, is a clinical pharmacy specialist at Memorial Sloan Kettering Cancer Center in New York, New York.

Grashma Vadakkal, PharmD, BCOP, is a clinical pharmacy specialist at Memorial Sloan Kettering Cancer Center in New York, New York.

Stephen Eng, PharmD, BCOP, is a clinical pharmacy specialist at Memorial Sloan Kettering Cancer Center in New York, New York.

ABSTRACT

The most common malignancy in men worldwide is prostate cancer, and the prognosis remains favorable with prostate cancer accounting for only 5.7% of all cancer-related deaths. In patients who have localized disease, treatment is dependent on age and risk factors. This can consist of observation or active surveillance, and in patients with intermediate- to high-risk disease, treatment includes androgen deprivation therapy (ADT), radiotherapy, and surgery. Though most patients typically respond to ADT, with responses lasting from months to years, long-term exposure to ADT eventually results in disease progression despite castration; this is referred to as castrate-resistant prostate cancer. Patients who have nonmetastatic castrate-resistant prostate cancer (nmCRPC) have a higher risk of developing distant metastasis, leading to worse clinical outcomes. The approval of second-generation antiandrogens, such as apalutamide (Erleada; Janssen Products, LP), enzalutamide (Xtandi; Astellas Pharma US, Inc), and darolutamide (Nubeqa; Bayer HealthCare Pharmaceuticals Inc), has significantly changed outcomes for patients with nmCRPC. Currently, there are no studies that directly compare these agents. This review aims to discuss each agent and considerations when choosing therapy in patients with nmCRPC.

Introduction

Prostate cancer is the second most common malignancy in men worldwide and accounts for 5.7% of all cancer-related deaths.^{1,2} Despite being one of the most common cancers in men, the prognosis remains favorable, with the 5-year relative survival being 97.1%. A majority of patients with prostate cancer (~80%) are diagnosed in the nonmetastatic setting, where the estimated 5-year survival is 100%.² Risk factors for developing prostate cancer include a family history of the disease, older age, race (African descent), exposure to environmental carcinogens, and smoking.¹ Initial suspicion of prostate cancer is based on an abnormal digital rectal exam (DRE) or an elevated prostate-specific antigen (PSA) level. A confirmatory biopsy is needed for a definitive diagnosis of prostate cancer, and once confirmed, pathologic assessment of the tissue and determination of lymph node involvement aids in risk stratification for localized disease.³

Pathophysiology

Prostate cancer is driven by activation of the androgen receptor (AR) via binding of its respective ligands' testosterone and dihydrotestosterone. Activation of AR results in nuclear translocation, which eventually leads to further downstream signaling to initiate cell proliferation and differentiation. The hypothalamic pituitary gonadal axis stimulates the secretion of testosterone from Leydig cells in the testes, which drives cellular proliferation of prostate epithelial cells. Gonadotropin-releasing hormone (GnRH), also known

TABLE 1. LHRH Agonists Used for Localized Prostate Cancer

Agent	Dose
Leuprolide (Lupron; AbbVie Inc) ¹¹	7.5 mg IM/SQ every month
	22.5 mg IM/SQ every 3 months
	30 mg IM/SQ every 4 months
	45 mg IM/SQ every 6 months
Goserelin (Zoladex; TerSera Therapeutics LLC) ¹²	3.6 mg SQ every month
	10.8 mg SQ every 3 months
Triptorelin (Trelstar; Verity Pharmaceuticals Inc) ¹³	3.75 mg IM every month
	11.25 mg IM every 3 months
	22.5 mg IM every 6 months

IM, intramuscular; LHRH, luteinizing hormone-releasing hormone; SQ, subcutaneous.

as luteinizing hormone-releasing hormone (LHRH), is released from the hypothalamus, which stimulates LH to be secreted from the anterior pituitary gland. LH induces the release of testosterone, which inhibits further GnRH and LH secretion via negative feedback. This pathway is crucial in understanding the pharmacologic agents used to treat localized disease, as LH and AR are the targets of several therapies used in this patient population.⁴

Initial Treatment for Localized Prostate Cancer

The initial approach to treating localized prostate cancer is dependent on age and risk factors. This determines if patients should undergo observation or activation surveillance, where no treatment is needed, and patients are followed for signs of progression via periodic DRE and PSA monitoring. If intermediate- to high-risk disease is present, several treatment modalities are utilized to induce remission, including androgen deprivation therapy (ADT), radiotherapy, and surgery. Because prostate cancer relies on testosterone to induce cell proliferation, ADT is used to suppress testosterone levels and achieve castration (defined as a testosterone level of <50 ng/dL) by preventing the release of testosterone through negative feedback.^{3,5}

Pharmacologic agents used to achieve castration are LHRH receptor agonists and antagonists. LHRH agonists (Table 1¹¹⁻¹³) include leuprolide (Lupron; AbbVie Inc), goserelin (Zoladex; TerSera Therapeutics LLC), and triptorelin (Trelstar; Verity Pharmaceuticals Inc), and they elicit their action by binding to LH receptors, leading to

TABLE 2. First-Generation Antiandrogens Used for Localized Prostate Cancer

Agent	Dose
Flutamide (Eulexin [®] ; Waylis Therapeutics LLC) ¹⁴	250 mg orally every 8 hours
Bicalutamide (Casodex; Astra-Zeneca Pharmaceuticals LP) ¹⁵	50 mg orally daily

^aEulexin has been discontinued in the US after reports of liver failure. According to the reports, evidence of hepatic injury occurred within the first 3 months and included elevated serum transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic failure.¹⁶

an initial surge in testosterone followed by depletion via downregulation of LH receptors and negative feedback. As a result, patients should be bridged with oral first-generation antiandrogens (Table 2¹⁴⁻¹⁶) starting several days before initiation of an LHRH agonist and for a minimum of 2 weeks after, to avoid tumor flare.⁶ First-generation antiandrogens bind directly to the AR, thereby blocking testosterone and dihydrotestosterone from eliciting their proliferative effects. First-generation antiandrogens can adequately suppress testosterone, but they have been shown to increase adverse effects (AEs) when used in combination with LHRH agonists for prolonged periods of time. Although data from 1 meta-analysis showed a potential benefit in 5-year overall survival (OS) with combined androgen blockage vs LHRH agonists alone, randomized prospective trials using combined androgen blockade are lacking, and therefore most patients are maintained on LHRH agonists alone once the risk of tumor flare has dissipated.^{3,7}

In contrast to LHRH agonists, LHRH antagonists (Table 3^{10,17}) bind directly to LHRH receptors in the anterior pituitary, resulting in rapid androgen deprivation without precipitating a surge in testosterone. Degarelix (Firmagon; Ferring Pharmaceuticals Inc) and relugolix (Orgovyx; Sumitomo Pharma America, Inc) are FDA-approved LHRH antagonists, with degarelix being a monthly intramuscular injection and relugolix being a daily oral alternative. These agents have a similar AE profile, with the exception of injection-site reactions being the most predominant AE with degarelix, and diarrhea being 1 of the most predominant AEs with relugolix.^{8,9} Relugolix is a major substrate of P-glycoprotein (P-gp) and is metabolized by CYP3A4; it is recommended to avoid coadministration with combined P-gp and strong CYP3A4 inducers.¹⁰

Acute and long-term AEs should be considered when patients are administered ADT. Short-term AEs of ADT include hot flashes, edema, sexual dysfunction, QTc

prolongation, mood swings, and injection-site reactions. Long-term AEs include gynecomastia, loss of muscle mass/strength, osteoporosis, dyslipidemia, cardiovascular disease, and acute kidney injury. Many of these AEs are reversible and can be avoided with appropriate supportive care and temporary cessation of ADT. The use of statins should be considered in patients at high risk of cardiovascular disease, and calcium/vitamin D supplementation can be implemented for those at risk of osteoporosis.³

Nonmetastatic Castrate-Resistant Prostate Cancer

Most patients achieve disease control with ADT, with responses lasting from months to years; however, the long-term exposure to ADT eventually results in disease progression despite castration. This clinical condition is known as castrate-resistant prostate cancer (CRPC), which can manifest either as metastatic or nonmetastatic in patients who have been receiving ADT for a prolonged period. Nonmetastatic CRPC (nmCRPC) is characterized by biochemical progression during ADT, despite a castrate serum testosterone level of less than 50 ng/dL and no signs of metastasis on radiographic imaging.¹⁸ Biochemical progression is defined by the Prostate Cancer Clinical Trials Working Group 3 as a 25% or greater increase in PSA level, with an absolute increase of 2 ng/mL above the nadir, which is confirmed by a second value taken at least 3 weeks or later.¹⁹ Patients who develop nmCRPC are at increased risk of progression to metastatic disease and worse clinical outcomes, thus necessitating further treatment.²⁰

Treatment of nmCRPC

The decision to escalate treatment in patients with nmCRPC depends on the aggressiveness of their disease. PSA doubling time (PSADT) has been used as a marker to determine if patients need additional treatment or if they can be observed. If PSADT is greater than 10 months, it is recommended that patients continue ADT with periodic monitoring because their disease is considered more indolent. For patients whose PSADT is 10 months or less, secondary hormonal therapy is recommended to be added to existing ADT therapy, as the AR may remain active despite castration levels of testosterone, thus increasing the risk of metastasis.³

Historically, no standard of care existed for patients with nmCRPC who progressed while receiving ADT. Strategies included maximizing androgen blockade with the addition

TABLE 3. LHRH Antagonists Used for Localized Prostate Cancer

Agent	Dose
Degarelix (Firmagon; Ferring Pharmaceuticals Inc) ¹⁷	Loading dose: 240 mg as 2 SQ 120-mg injections Maintenance dose: 80 mg SQ every 28 days
Relugolix (Orgovyx; Sumitomo Pharma America, Inc) ¹⁰	Loading dose: 360 mg orally on day 1 Maintenance dose: 120 mg orally daily

LHRH, luteinizing hormone-releasing hormone; SQ, subcutaneous.

of first-generation antiandrogens, but the data were extrapolated from the metastatic setting with unclear benefit being observed in the nonmetastatic setting. The advent of newer-generation antiandrogens has drastically changed the treatment landscape of nmCRPC. These agents have a higher binding affinity for AR than first-generation antiandrogens, while also impairing AR translocation to the nucleus and obstructing AR-mediated transcription. There are currently 3 FDA-approved second-generation antiandrogens that are used for patients with nmCRPC with a PSADT of 10 months or less.¹⁷ These agents have similar class effects to ADT, such as fatigue, hypertension, falls, fractures, and erythema, but also exhibit unique properties that can aid in their selection for these high-risk patients.²¹

Apalutamide

The first second-generation antiandrogen approved by the FDA for nmCRPC was apalutamide (Erleada; Janssen Products, LP), which was evaluated in the phase 3 SPARTAN trial (NCT01946204). This trial included patients with nmCRPC with a PSADT of 10 months or less during continuous ADT with or without local or regional lymph node disease and no signs of distant metastasis. Investigators randomly assigned 1207 men in a 2:1 manner to receive apalutamide 240 mg daily or placebo and ADT until radiographic progression. The median metastasis-free survival (MFS) was 40.5 months in the apalutamide arm vs 16.2 months in the placebo arm ($P < .005$). The study authors also found a statistically significant benefit in time to metastasis, progression-free survival, and time to symptomatic progression in the apalutamide arm.²¹ After a median of 52 months, the final OS analysis confirmed an improvement in OS with apalutamide plus ADT over placebo plus ADT (73.9 months vs 59.9 months; $P = .016$).²² AEs of interest associated

TABLE 4. Second-Generation Antiandrogens Used in nmCRPC

Agent	Dose	AEs of interest	Drug interactions
Apalutamide (Erleada; Janssen Products, LP) ²⁸	240 mg orally daily	Hypothyroidism Rash Falls Fractures	Substrate: CYP2C8 (major), 3A4 (minor) Induces: CYP2C19 (strong), CYP3A4 (strong), CYP2C9 (weak), P-gp (weak), OATP1B1 (weak), OATP1B3 (weak), UGT (weak)
Enzalutamide (Xtandi; Astellas Pharma US, Inc) ²⁹	160 mg orally daily	Seizures/mental impairment Cardiovascular events Fatigue Falls	Substrate: CYP2C8 (major), CYP3A4 (major) Induces: CYP3A4 (strong), CYP2C19 (moderate), and CYP2C9 (moderate)
Darolutamide (Nubeqa; Bayer HealthCare Pharmaceuticals, Inc) ³⁰	600 mg orally twice daily with food	Fatigue	Substrate: CYP3A4 (minor), P-gp (minor), UGT1A1, UGT1A9 Inhibits: BCRP, OATP1B1, OAT1B3

AE, adverse effect; nmCRPC, nonmetastatic castrate-resistant prostate cancer; P-gp, P-glycoprotein.

with apalutamide in the SPARTAN trial were fatigue, rash, falls, fracture, hypothyroidism, and seizure.²²

Enzalutamide

The phase 3 PROSPER study (NCT02003924) assessed whether enzalutamide (Xtandi; Astellas Pharma US, Inc) would benefit patients with nmCRPC who were at a higher risk of metastasis. Patients were included if they had a PSADT of 10 months or less, with a baseline value of at least 2 ng/mL, while receiving ADT, with no history of seizure or nodal/distant metastasis. During the trial, investigators randomly assigned 1401 patients in a 2:1 ratio to receive enzalutamide 160 mg daily plus ADT or placebo plus ADT until radiographic progression. The median MFS was 36.6 months in the enzalutamide group vs 14.7 months in the placebo group ($P < .001$). Time to PSA progression and first use of subsequent therapy statistically favored enzalutamide over placebo.²³ At a median follow-up of 48 months, the median OS was 67.0 months in the enzalutamide plus ADT arm vs 56.3 months in the placebo plus ADT arm.²⁴ AEs noted in the enzalutamide cohort included fatigue, falls, cardiovascular events, and mental impairment.²⁴

Darolutamide

Darolutamide (Nubeqa; Bayer HealthCare Pharmaceuticals, Inc) was the last second-generation antiandrogen the FDA approved in 2019. It differs from enzalutamide and apalutamide in that it has lower blood-brain barrier penetration, potentially leading to less central nervous system AEs.²⁶ This agent was studied in the phase 3 ARAMIS trial (NCT02200614),

which evaluated darolutamide 600 mg twice a day plus ADT vs placebo plus ADT in patients with nmCRPC with a PSADT of 10 months or less, with or without local or regional lymph node disease and no signs of distant metastasis. The trial included 1509 men who were randomly assigned 2:1; investigators found that darolutamide plus ADT improved MFS over placebo plus ADT (40.4 months vs 18.4 months; $P < .001$). Secondary end points that also significantly favored darolutamide included time to pain progression, time to first cytotoxic chemotherapy, and time to first symptomatic skeletal event.²⁵ An updated analysis confirmed a statistically significant improvement in OS for the darolutamide plus ADT cohort vs placebo plus ADT.²⁷ Fatigue was the predominant AE that was associated with darolutamide in the ARAMIS trial. The authors concluded that the incidence of hypertension, rash, dizziness, and cognitive disorders differed only slightly between the darolutamide arm and the placebo arm, which was mitigated with longer follow up.²⁶

Considerations When Choosing Second-Generation Antiandrogens in nmCRPC

Although no head-to-head randomized trials have been conducted to compare apalutamide, enzalutamide, and darolutamide in nmCRPC, evidence from meta-analyses have shed insight regarding comparative efficacy and safety across the second-generation antiandrogens (Table 4²⁸⁻³⁰). Wenzel et al performed a meta-analysis that pooled data from the SPARTAN, PROSPER, and ARAMIS trials focusing on OS and AEs. They found all 3 second-generation agents conferred a longer OS

than ADT, with darolutamide being ranked first for providing maximal OS benefit. They also reported that the rate of grade 3 or higher AEs did not differ between darolutamide and ADT, whereas enzalutamide and apalutamide exhibited a statistically significant higher likelihood of grade 3 or higher AEs than ADT alone.³⁰ Corroborating these findings, a 2021 network meta-analysis confirmed that all 3 second-generation antiandrogens have an OS benefit over ADT alone in patients with nmCRPC, with darolutamide having the best likelihood of improving OS.³¹ Enzalutamide and apalutamide also had significantly more grade 3 or higher AEs than darolutamide.³² Lastly, an indirect analysis found no difference in MFS between the 3 agents, but found darolutamide to have lower rates of AEs than enzalutamide and apalutamide.³²

Health care costs should also be taken into consideration when choosing second-generation antiandrogens. Although the average cost of each agent is approximately \$15,000 per month, AEs and their subsequent management can contribute to a high economic burden on patients.¹⁹ Shore et al evaluated the grade 3 or higher AE costs from SPARTAN, PROSPER, and ARAMIS and found the mean per patient AE costs were \$1021; however, the cost was \$387 lower for darolutamide than for apalutamide and enzalutamide.^{20,33-35}

Drug interactions should also be taken into consideration when choosing a second-generation antiandrogen for nmCRPC. Apalutamide can drastically decrease the concentration of drugs that are metabolized by CYP3A4 and CYP2C19, while influencing the activity of drugs that are substrates of CYP2C9, P-gp, OATP1B1, OAT1B3, and UGT. Furthermore, coadministration with strong CYP2C8 or CYP3A4 inhibitors can impact apalutamide by increasing the concentration of its active moieties.²⁸ Enzalutamide can decrease the concentration of drugs that are substrates of CYP3A4, CYP2C8, and CYP2C19, while being influenced by drugs that inhibit CYP2C8 and CYP3A4.²⁹ For darolutamide, potential drug interactions consist of interactions with P-gp and CYP3A4 inducers or inhibitors and substrates of BCRP, OATP1B1, and OATP1B3.^{20,30} It is also worth noting that relugolix is a substrate of CYP3A4, making it prone to drug interactions with second-generation antiandrogens. For this reason, there are insufficient data to use this agent with second-generation antiandrogens in high-risk patients with nmCRPC.³ Lastly, administration should be taken into consideration in accordance with patient preference. Darolutamide is a twice-daily medication that requires food for maximal absorption, whereas

apalutamide and enzalutamide are once-daily medications that can be taken with or without food.²⁸⁻³⁰

Conclusion

The treatment of nmCRPC has drastically changed with the approval of second-generation antiandrogens. Apalutamide, enzalutamide, and darolutamide are efficacious in treating this heterogeneous disease, with improvements seen in MFS and OS. Patients should be counseled on possible AEs associated with these agents, including hypertension, falls, fractures, and fatigue. Although no studies have directly compared the second-generation antiandrogens with one another, indirect comparison studies and meta-analyses have suggested darolutamide may provide optimal OS and a better safety profile. Patients should be screened for potential drug interactions before being initiated on second-generation antiandrogens due to their potential to impact the activity of enzymes involved in the metabolism of other drugs.²⁰

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Current Treatment Approaches for Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Relapsed treatment has evolved with CAR T, bispecific antibodies, and immunotherapies.

Jessica M. Lewis-Gonzalez, PharmD, BCOP; and Shashank R. Cingam, MD

ABOUT THE AUTHORS

Jessica M. Lewis-Gonzalez, PharmD, BCOP, is a clinical hematology-oncology and cell therapy pharmacist at the University of New Mexico (UNM) Comprehensive Cancer Center in Albuquerque, New Mexico.

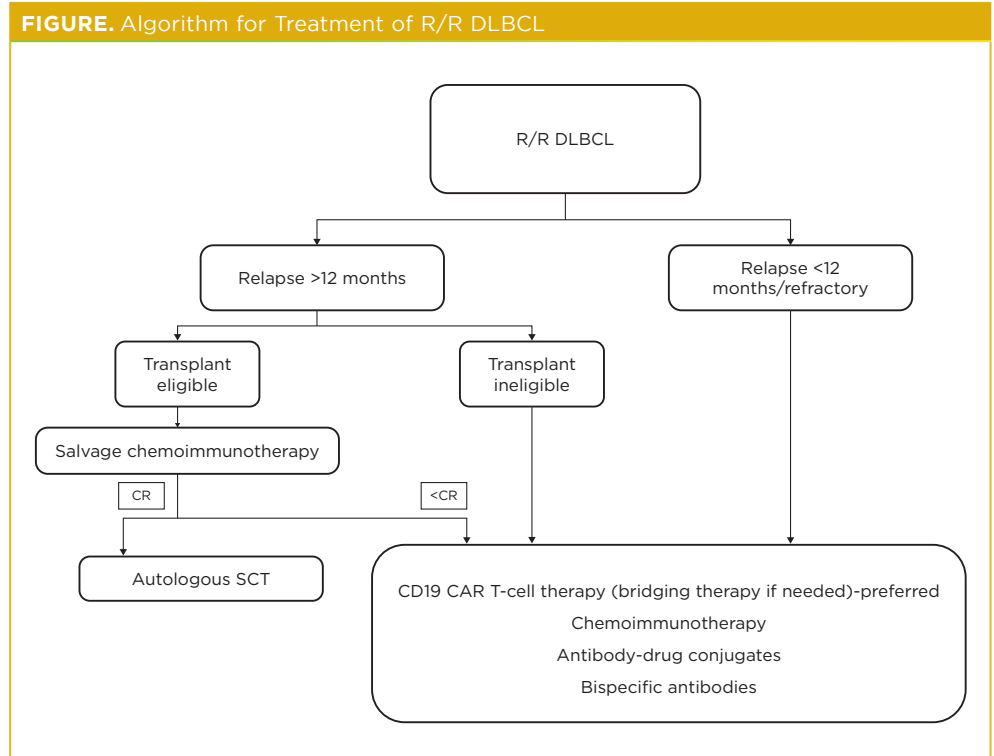
Shashank R. Cingam, MD, is a hematology-oncology and cell therapy physician at UNM Comprehensive Cancer Center in Albuquerque, New Mexico.

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Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphoma and accounts for approximately 30% of newly diagnosed cases each year globally.¹ Frontline chemoimmunotherapy leads to cures in about 50% to 60% of patients with DLBCL. However, historically, relapsed DLBCL was associated with poor outcomes, especially in patients who are chemotherapy resistant.²

Over the past decade, the treatment landscape for relapsed/refractory (R/R) DLBCL has significantly changed due to FDA

approvals of a number of immunotherapies and bispecific antibodies, as well as use of chimeric antigen receptor (CAR) T-cell therapies in earlier lines. In R/R DLBCL, the treatment algorithm is broadly categorized based on whether the disease is primary refractory, relapsed within 12 months of primary therapy, or relapsed after 12 months (**Figure**). Treatment options for R/R DLBCL have expanded to include novel agents in the third line and beyond. With numerous preferred treatments available, decisions are guided by careful consideration of the potential benefits weighed against the associated toxicities.



CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; R/R, relapsed/refractory; SCT, stem cell transplantation.

TABLE 1. Summary of Evidence for Salvage Chemotherapeutic Regimens^{4,6}

Regimen	Study (number in each treatment arm)	Response rate (%)	Transplant rate (%)	PFS (%)
R-ICE vs R-DHAP	CORAL (NCT00137995)	63.5%	51%	3-year: 31%
	(n = 202; n = 194)	62.8%	55%	3-year: 42%
R-DHAP vs R-GDP	NCIC-CTG LY.12 (NCT02910063)	45.2%	49%	3-year: 28%
	(n = 304; n = 306)	44%	52%	3-year: 28%

PFS, progression-free survival; R-ICE, rituximab, ifosfamide, carboplatin, etoposide phosphate; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; R-GDP, rituximab, gemcitabine, dexamethasone, cisplatin.

TABLE 2. Summary of Evidence for CD19 CAR T-Cell Products After 2 Lines of Therapy⁷⁻⁹

Approved CAR T-cell therapies	Study (number in treatment arm)	End point (%)	Common AEs, grade ≥ 3 (%)	Long-term follow-up
Axicabtagene ciloleucel (Yescarta; Kite Pharma)	ZUMA-1 (NCT02348216) (n = 111)	ZUMA-1 (NCT02348216) (n = 111)	Neutropenia (78%), anemia (43%), thrombocytopenia (38%), CRS (13%), neurologic events (28%)	At median follow-up of 63.1 months, median OS was 25.8 months; estimated 5-year OS rate was 42.6%.
Tisagenlecleucel (Kymriah; Novartis)	JULIET (NCT02445248) (n = 93)	ORR (52%)	Cytopenias > 28 days (32%), CRS (22%), neurologic events (12%), infections (20%), febrile neutropenia (14%)	At median follow-up of 40.3 months, median OS was 11.1 months.
Lisocabtagene maraleucel (Breyanzi; Juno Therapeutics)	TRANSCEND-NHL-001 (NCT02631044) (n = 344)	ORR (73%)	Neutropenia (60%), anemia (37%), thrombocytopenia (27%), CRS (2%), neurologic events (10%)	At median follow-up of 29.3 months, the median OS was 27.3 months.

AE, adverse effect; CRS, cytokine release syndrome; ORR, overall response rate; OS, overall survival.

Relapse at More Than 12 Months of Frontline Chemoimmunotherapy

Stem Cell Transplant

Salvage therapy followed by autologous stem cell transplantation (ASCT) is the standard of care for patients with relapsed DLBCL occurring at least 12 months after initial treatment and the goal of ASCT in this setting is cure. ASCT is superior to the alternative of chemotherapy alone and can cure approximately 20% to 50% of patients with relapsed DLBCL.^{3,4} The most significant determinant of successful cure after ASCT is the disease status at time of transplant. Patients with DLBCL who are transplanted with a PET-negative complete response (CR) have excellent disease-free survival (DFS) rates of approximately 80%, while those transplanted with residual PET-positive disease have DFS rates of 35% to 43%.⁵ **Table 1** lists evidence for the most commonly used salvage chemoimmunotherapy regimens before ASCT.^{4,6} Rituximab (Rituxan; Biogen and Genentech) plus dexamethasone, cytarabine, and cisplatin (R-DHAP) tends to have a higher risk of severe toxicities compared with rituximab plus ifosfamide (Ifex; Baxter Healthcare), carboplatin, and etoposide phosphate (R-ICE) and rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP), as demonstrated in both the CORAL (NCT00137995) and NCIC-CTG LY.12 (NCT02910063) trials.^{4,6} This makes toxicity management a key factor

in choosing the appropriate salvage regimen for individual patients.^{4,6}

CD19 CAR T-Cell Therapy

CAR T cells targeting CD19, which is expressed on malignant B cells, were found to have potent activity in clinical trials involving patients with R/R DLBCL, leading to approvals of 3 commercial CAR T-cell products after 2 lines of therapy (**Table 2**).⁷⁻⁹ Long-term follow-up data of these landmark trials show durable responses and offer a potential cure in a subset of patients. Patients may often require bridging therapy, if ongoing progression and/or impending organ damage before or after leukapheresis. Bendamustine should be avoided before leukapheresis because of its prolonged lymphotoxic effect.¹⁰

Primary R/R Under 12 Months From Frontline Therapy

CD19 CAR T-Cell Therapy

In patients with relapse within 12 months or refractory disease, results of the ZUMA-7 trial (NCT03391466) showed that axicabtagene ciloleucel (Yescarta; Kite Pharma) improved event-free survival (EFS) to 8.3 months compared with 2 months with standard of care (salvage chemotherapy followed by ASCT), whereas results of the TRANSFORM trial (NCT03575351) demonstrated that lisocabtagene maraleucel (liso-cel, Breyanzi;

TABLE 3. Summary of Evidence for Immunotherapy-Based Regimens in Second-Line and Subsequent Setting¹⁵⁻¹⁷

Regimen	Study (number in treatment arm)	Primary end point (%)	Common AEs, grade ≥ 3 (%)	Median duration of response in responders
Tafasitamab (Monjuvi; Incyte) + lenalidomide (Revlimid; Bristol Myers Squibb)	L-MIND (NCT02399085) (n=80)	OR (60%)	Neutropenia (48%), thrombocytopenia (17%)	21.7 months
Polatuzumab vedotin (Polivy; Genentech) + rituximab (Rituxan; Biogen and Genentech)	ROMULUS (NCT01691898) (n=39)	OR (54%)	Neutropenia (23%), anemia (8%), diarrhea (8%)	13.4 months
Polatuzumab vedotin (Polivy; Hoffmann-La Roche) + BR	GO29365 (NCT02257567) (n=40)	CR (40%)	Neutropenia (46.2%), anemia (28.2%), thrombocytopenia (41%), infections (23.1%)	12.6 months
Loncastuximab tesirine (Zynlonta; ADC Therapeutics)	LOTIS-2 (NCT03589469) (n=145)	ORR (48.3%)	Neutropenia (26%), thrombocytopenia (18%), increased GGT (17%)	13.4 months

AE, adverse event; BR, bendamustine and rituximab; CR, complete response; GGT, gamma-glutamyl transferase; OR, objective response; ORR, overall response rate.

TABLE 4. Summary of Evidence for Bispecific Antibodies in \geq Third-Line Setting^{18,19}

Regimen	Study (number in treatment arm)	Primary end point (%)	Common AEs, all grades (%)	Median duration of response
Epcoritamab (Epkinly; AbbVie and Genmab)	NCT03625037 (n=157)	ORR (63.1%)	CRS (49.7%), pyrexia (23.6%), fatigue (22.9%)	12 months
Glofitamab (Columvi; Genentech)	NCT03075696 (n=154)	CR (39%)	CRS (63%), neutropenia (38%), anemia (31%), thrombocytopenia (25%)	NR

AE, adverse event; CR, complete response; CRS, cytokine release syndrome; NR, not reached; ORR, overall response rate.

Juno Therapeutics) improved EFS to 10.1 months compared with 2.3 months with standard of care, respectively. Both trials demonstrated the significant benefit of CAR T-cell therapies in transplant-eligible patients and led to FDA approval in this population.^{11,12} However, ASCT can also be pursued in patients who achieve a PET-negative CR after bridging therapy.¹³ Liso-cel is also approved by the FDA for patients not eligible for hematopoietic stem cell transplantation due to comorbidities or age based on the results of the PILOT trial (NCT04359784).¹⁴

Other Second-Line and Subsequent Therapy Options

Immunotherapy-Based Options

Results of several recent trials have shown promising efficacy of targeting other B-cell markers with either antibody-drug conjugate (ADC) or naked antibodies. These can be used in patients who are ineligible for transplant or CAR T-cell therapy, as well as with subsequent relapses. Knowledge about ideal sequencing of these therapies is lacking. These regimens are reviewed in

Table 3.¹⁵⁻¹⁷ The L-MIND trial (NCT02399085) evaluated the combination of tafasitamab (Monjuvi; Incyte), a naked CD19 antibody, with lenalidomide, an immunomodulator, and reported that for patients enrolled in the trial, the most common reason for transplant ineligibility was age over 70 (46%).¹⁵ However, in the trial published by Sehn et al evaluating polatuzumab vedotin (Polivy; Genentech), a CD79b-targeted ADC delivering monomethyl auristatin E, a microtubule inhibitor, in combination with bendamustine and rituximab, the most common reasons identified as deeming a patient to be transplant ineligible were age (32.5%) and insufficient response to salvage therapy (30%).¹⁶ There are other key differences in patient considerations including dosing schedule, route of administration, and Risk Evaluation and Mitigation Strategy programs. The tafasitamab plus lenalidomide (Revlimid; Bristol Myers Squibb) regimen is a combination of intravenous (IV) therapy tafasitamab with the oral therapy lenalidomide. The dosing schedule for this regimen is completed on a 28-day cycle and starts with lenalidomide daily for 21 days, followed by 7 days off in combination for the first 12 cycles of therapy with


weekly tafasitamab for the first 3 cycles (the first cycle also has a day 4 dose), followed by twice-weekly tafasitamab.¹⁵ The polatuzumab vedotin plus bendamustine and rituximab regimen is administered IV on a 21-day cycle with treatment on days 1 and 2 of each cycle.¹⁶

In the subsequent therapy setting, the LOTIS-2 trial (NCT03589469) demonstrated the utility of loncastuximab tesirine, a CD19-targeted ADC, in multiple R/R DLBCL. The dosing schedule for this regimen was 1 dose of loncastuximab tesirine IV on day 1 of each 21-day cycle.¹⁷ As this drug can cause pronounced photosensitivity rash, patients should receive a recommendation to avoid prolonged sunlight exposure.

Bispecific Antibodies

The advent of using bispecific antibodies for the treatment of multiple R/R DLBCL has expanded the therapies available to these patients. These regimens are reviewed in **Table 4**.^{18,19} Patients receiving glofitamab (Columvi; Genentech) are to receive obinutuzumab 1000 mg IV 7 days before the first dose of glofitamab, a CD20×CD3 bispecific monoclonal antibody, aimed to debulk the tumor, followed by step-up dosing in cycle 1 before proceeding to full treatment dose of glofitamab IV on day 1 of a 21-day cycle.¹⁸ Epcoritamab (Epkiny; AbbVie and Genmab), a CD20×CD3 bispecific monoclonal antibody, also requires the use of step-up dosing in the first cycle, followed by subcutaneous doses on days 1 and 15 of each 28-day cycle moving forward.¹⁹ Of note, both glofitamab and epcoritamab have recommendations for hospitalization during the step-up dose period with observation for at least 24 hours post dose to monitor for the development of cytokine release syndrome. Patients receiving epcoritamab do not receive obinutuzumab as a lead-in to starting therapy as do those starting glofitamab.

Conclusion

There are many considerations when selecting the best regimen for a patient with R/R DLBCL. The primary consideration is if they are considered chemo resistant (relapsed < 12 months from frontline therapy, refractory disease, or not achieving CR after salvage therapy); for such patients, CAR T-cell therapy may be a preferred choice over ASCT. For patients relapsing after CAR T-cell therapy or ASCT, treatment must be personalized and informed by patient- and disease-specific factors, including prior therapy, disease biology, T-cell fitness, access to treatments, as well as comorbidities. For patients deemed to be ineligible for ASCT, considerations should focus on patient- and disease-specific factors, including prior therapy, disease biology, comorbidities, and dosing schedule. Participation in clinical trials should also be encouraged in patients with R/R DLBCL when available. 

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Navigating Steroid-Refractory GVHD Treatment: A Pharmacist's Guide to Medication Management

Pharmacists play a crucial role in medication management for these complex patients.

Molly Schiffer, PharmD, BCOP

ABOUT THE AUTHOR

Molly Schiffer, PharmD, BCOP, is a stem cell transplant and cellular therapy clinical pharmacy specialist at Yale New Haven Hospital in Connecticut.

Graft-vs-host disease (GVHD) is a major complication of hematopoietic stem cell transplantation (HSCT), manifesting as either acute GVHD (aGVHD) or chronic GVHD (cGVHD). aGVHD results from a donor T-cell-mediated attack on an immunocompromised host, whereas cGVHD mimics autoimmune diseases. Both forms lead to injury in host organs, with aGVHD primarily targeting the skin, the liver, and the gastrointestinal (GI) system; however, cGVHD can target most organ systems.^{1,2} The development of GVHD is influenced by multiple risk factors, including the use of unrelated or human leukocyte antigen-mismatched donors and peripheral blood stem cell sources.^{3,4}

The best strategy to mitigate the complications of GVHD is prevention, using both pharmacologic and nonpharmacologic methods. Nonpharmacologic strategies center on selecting the most histocompatible donor match. Pharmacologic approaches involve various immunosuppressive agents, such as calcineurin inhibitors, sirolimus, methotrexate, mycophenolate, posttransplant cyclophosphamide, and anti-human T-lymphocyte immune globulin. Despite these preventive measures, GVHD still occurs in 25% to 80% of patients, as reported in the literature.⁵

This article provides a concise review of aGVHD and cGVHD treatment methods, with an in-depth discussion of emerging therapies and the role of pharmacists in treating patients with GVHD.

Standard of Care

GVHD remains a significant source of morbidity and mortality in patients with allogeneic HSCT. Treatment focuses

on reducing B- and T-cell activation, suppressing inflammation, and preventing fibrosis.⁶ Corticosteroids are the cornerstone of first-line treatment for both aGVHD and cGVHD, with approximately 50% of patients responding to therapy.⁷ For those who do not respond, additional lines of therapy are required.

In recent years, ruxolitinib (Jakafi; Incyte Corporation) has received FDA approval and is an National Comprehensive Cancer Network Category 1 recommendation for steroid-refractory aGVHD and cGVHD.⁸ However, a standardized approach to managing GVHD beyond corticosteroids and ruxolitinib remains elusive.

Several third-line agents are options, depending on patient-specific and institutional considerations. cGVHD treatment has seen an expansion in FDA-approved therapies, including ibrutinib (Imbruvica; Janssen Biotech, Inc and Pharmacyclics LLC), belumosudil (Rezurock; Kadmon Pharmaceuticals, LLC), and axatilimab (Niktimvo; Incyte Corporation). Other options, such as abatacept (Orencia; Bristol Myers Squibb), alemtuzumab (Campath; Genzyme Corporation), alpha-1 antitrypsin, calcineurin inhibitors, mTOR inhibitors, mycophenolate mofetil, and monoclonal antibodies targeting interleukin-2, interleukin-6, $\alpha 4\beta 7$ integrin, and tumor necrosis factor are available for both aGVHD and cGVHD.⁸

Emerging Therapies

Growing evidence highlights the potential of new and emerging therapies to address the unmet clinical needs in GVHD.

Axatilimab

Axatilimab, a colony-stimulating factor

1 receptor (CSF1R)-blocking antibody, has emerged as a promising treatment for cGVHD. The AGAVE-201 phase 2 trial (NCT04710576) evaluated 241 patients with refractory cGVHD randomly assigned to 3 axatilimab dosing regimens.⁹ The highest overall response rate (ORR; 74%) was observed with the lowest-dose group of 0.3 mg/kg every 2 weeks. Adverse effects (AEs) were primarily transient laboratory abnormalities, such as serum enzyme elevations and periorbital edema, linked to Kupffer cell depletion induced by the CSF1R blockade. Axatilimab received FDA approval in August 2024 for use in adult and pediatric patients with cGVHD after the failure of at least 2 prior systemic therapies.¹⁰

Baricitinib

Baricitinib (Olumiant; Eli Lilly and Company), a Janus kinase (JAK) 1/2 inhibitor, has demonstrated efficacy in preventing and treating GVHD.¹¹ As seen in mouse models, baricitinib differs from ruxolitinib in expanding regulatory T cells by preserving JAK3-STAT5 signaling, thereby preventing and treating GVHD. In a phase 1/2 study of 20 patients with refractory cGVHD, baricitinib (2 mg by mouth daily) achieved a 63% ORR at 6 months with a median time to OR of 1.4 months.¹² Responses were seen across most organs except the lungs. Common AEs included upper respiratory infections, neutropenia, hyperphosphatemia, and hypertriglyceridemia. Baricitinib's broader mechanism of action and lower anemia and thrombocytopenia rates may position it as a complementary or alternative therapy to ruxolitinib.

Ixazomib

Ixazomib (Ninlaro; Takeda Pharmaceuticals America, Inc), an oral proteasome inhibitor, has shown promise in steroid-refractory cGVHD. In a phase 2 trial, ixazomib (4 mg on days 1, 8, and 15 of a 28-day cycle) reduced the 6-month treatment failure rate to 28%, significantly lower than the historical 44% benchmark ($P = .01$).¹³ The study authors reported 6-month and 12-month overall survival rates of 92% and 90%, respectively. Most patients in this study had skin, eye, joint/fascia, mouth, or lung involvement; however, there was no evidence of any significant difference in efficacy among the various organs. Although this study was performed before the

FDA-approved agents such as ruxolitinib and ibrutinib, ixazomib demonstrated consistent efficacy across organ systems, offering a tolerable safety profile.

Teduglutide

Teduglutide (Gattex; Takeda Pharmaceuticals America, Inc), a glucagon-like peptide-2 (GLP-2) analog approved for short bowel syndrome, has shown potential for steroid-refractory acute GI GVHD.¹⁴ GLP-2 is an intestinal hormone secreted by L cells in the distal ileum and proximal colon that strengthens gut barrier function, promotes mucosal growth, and enhances blood circulation. A retrospective review of 3 pediatric patients with grade 3 to 4 GI GVHD treated with teduglutide (0.05 mg/kg subcutaneously daily) showed clinical improvement within 14 to 28 days. Although used alongside other systemic therapies, teduglutide represents a potential off-label, nonimmunosuppressive therapy for pediatric and adult GI GVHD, warranting further studies.

Pharmacists' Role in GVHD Management

Pharmacists are integral to the multidisciplinary care of HSCT patients, contributing to medication management, patient education, and quality improvement.¹⁵ Pharmacists' expertise guides therapeutic decisions, balancing efficacy, AEs, infectious disease risks, and patient-specific considerations in managing steroid-refractory GVHD.

Medication Management and Education

Following HSCT, patients often face complex medication regimens. Pharmacists play a vital role in educating patients and caregivers about proper medication use, thereby optimizing adherence and reducing anxiety. The transition of care between inpatient and outpatient is a critical chance for pharmacists to ensure the patients, caregivers, and members of the health care team have an accurate understanding of patients' current medication regimens.

Therapeutic Drug Monitoring

Accurate monitoring of immunosuppressive agents, such as calcineurin and mTOR inhibitors, ensures optimal GVHD prevention and treatment. Ensuring adequate serum concentrations of these medications correlates to clinical outcomes.

Additionally, antifungal prophylaxis often requires therapeutic drug monitoring to prevent opportunistic infections in immunosuppressed patients.

Quality Improvement and Research

Beyond direct patient care, pharmacists contribute to clinical research and quality improvement initiatives, ensuring compliance with Foundation for the Accreditation of Cellular Therapy accreditation standards.

Conclusion

As new therapies emerge for steroid-refractory GVHD, the role of pharmacists in optimizing patient outcomes through medication management, education, and evidence-based decision-making has become increasingly vital. Continued research into novel agents such as axatilimab, teduglutide, baricitinib, and ixazomib will expand treatment options, offering hope for improved quality of life and survival in this challenging patient population. 🌐

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Emerging Role of BRAF Inhibitors in Relapsed/Refractory Hairy Cell Leukemia Treatment

BRAF V600E inhibitors show improved outcomes in relapsed/refractory hairy cell leukemia.

Husna Rahim, PharmD, RPh; Sukeina Nasser, PharmD, RPh, CPh, PACS; Rezarta Lako, PharmD, BCPS; Richa Shah, PharmD, BCOP; Jessie Modlin, PharmD, BCOP; Avani Yensamandra, PharmD, BCOP; and Kevin Pang, PharmD

ABOUT THE AUTHORS

Husna Rahim, PharmD, RPh, is a medical communications specialist in Atlanta, Georgia.

Sukeina Nasser, PharmD, RPh, CPh, PACS, is a clinical pharmacist at Optum Health in Detroit, Michigan.

Rezarta Lako, PharmD, BCPS, is a pharmacist with Shields Health Solutions in Rochester, New York.

Richa Shah, PharmD, BCOP, is a leukemia clinical pharmacy specialist at Memorial Sloan Kettering Cancer Center in New York, New York.

Jessie Modlin, PharmD, BCOP, is an oncology pharmacist at St Luke's Health System in Boise, Idaho.

Avani Yenamandra, PharmD, BCOP, is a clinical pharmacy specialist at MD Anderson Cancer Center at Cooper in Camden, New Jersey.

Kevin Pang, PharmD, is a pharmacist at Cooper University Hospital in Camden, New Jersey, and is the manager of a clinical-stage authoring group.

Hairy cell leukemia (HCL) is a rare indolent type of chronic lymphocytic leukemia, making up fewer than 2% of all leukemias.¹ Historically, purine nucleoside analogues such as cladribine (Mavenclad; EMD Serono) and pentostatin (Nipent; Pfizer) have been the cornerstone of HCL treatment, achieving high response rates and durable remissions.² However, a significant proportion of patients relapse, with diminishing efficacy of purine analogues upon retreatment and the increased risk of cumulative myelotoxicity and immunosuppression.

The discovery of *BRAF* V600E as a driver mutation in roughly 90% of HCL cases represents a landmark advancement in understanding the disease's pathogenesis.³ As a result, targeted therapy with *BRAF* inhibitors, such as vemurafenib (Zelboraf; Genentech) and dabrafenib (Tafinlar; Novartis), has been incorporated into the National Comprehensive Cancer Network guidelines despite their lack of FDA approval for this disease state.⁴ *BRAF* inhibitors, both as stand-alone therapy and in combination with MEK inhibitors, constitute a substantial advancement in the treatment of patients with relapsed or refractory (R/R) HCL whose disease does not respond to standard therapy.

Vemurafenib

A multicenter, single-arm, phase 2 clinical trial (NCT01711632) first evaluated vemurafenib monotherapy in 36 patients with R/R HCL. For the initial course of treatment, patients received vemurafenib 960 mg twice daily for 3 to 6 months. Patients with relapsed disease could be rechallenged with vemurafenib 240 to

960 mg twice daily for a duration based on clinical response. The median age was 59 years (range, 34-80), and 83% of patients were men. Approximately 50% of patients had previously received 2 or more lines of treatment (range, 1-8). Median time from initial diagnosis to start of vemurafenib therapy was 10.5 years (range, 1-33).⁵

The primary objective was overall survival (OS) and relapse-free survival (RFS) after initial and subsequent treatment with vemurafenib. The 4-year OS rate was 82% (95% CI, 69%-98%), and the median RFS was 19 months (95% CI, 12.5-53.9) after the first course of vemurafenib and 12.7 months (95% CI, 4.2-not reached) after subsequent treatment. An increased probability of RFS was seen with a cumulative vemurafenib treatment dose greater than 230,000 mg compared with a lower cumulative dose of less than 150,000 mg (OR, 7.75 [95% CI, 2.23-26.87]; $P = .0013$). There was also an increased probability of RFS with treatment duration over 90 days compared with 90 days or less (OR, 2.48 [95% CI, 0.88-7.01]; $P = .08$), although it was not statistically significant.⁵

Key secondary end points included the impact of clinical variables on RFS and OS, overall response rate (ORR), and safety. Besides cumulative dosage of vemurafenib, no other clinical variables, including demographics, disease characteristics, disease duration, treatment history, and medical history, demonstrated a statistically significant impact on RFS or OS. The ORR observed in the 36 patients was 86%, with 33% achieving a complete response (CR). However, there was no significant difference in RFS for patients with a CR compared with those with a partial response.⁵

The overall incidence of adverse effects

(AEs) was similar between patients who received initial treatment vs those who received retreatment with vemurafenib. All AEs were grade 1 to 2, with the exception of 1 grade 3 rash and 1 grade 3 fever/pneumonia. The most common AEs that occurred in patients with initial vemurafenib treatment were arthralgia (57%), rash (29%), photosensitivity (36%), and fatigue (29%). During the retreatment therapy, 1 patient developed tonsillar squamous cell carcinoma and another patient with a history of melanoma developed metastatic melanoma. In both cases, vemurafenib was discontinued.⁵

Vemurafenib + Rituximab

A single-center, single-arm, phase 2 clinical trial (HCL-PG03) explored the combination of vemurafenib plus rituximab in a patient with R/R HCL harboring the *BRAF* V600E mutation. Patients underwent 2 induction cycles, which consisted of 4 weeks of oral vemurafenib 960 mg twice daily with intravenous rituximab (Rituxan; Genentech) 375 mg/m² administered on days 1 and 15, followed by a 2-week treatment break. After the second cycle, 4 additional doses of rituximab were given as consolidation therapy 2 weeks apart from one another. In the intention-to-treat analysis, 30 patients were included; these patients had a median age of 61 years, and 90% were men. The median lines of prior therapy was 3 (range, 1-14), and all patients had received a purine analogue. Additionally, 35% of patients were refractory to a purine analogue, 23% of patients were refractory to rituximab, and 23% of patients were refractory to a BRAF inhibitor.⁶

The primary end point was CR at the end of treatment. Key secondary end points included time to response, minimal residual disease status, progression-free survival (PFS), RFS, and safety outcomes. CR was achieved in 87% of patients. Among the 26 patients who achieved CR, 10 were previously refractory to a purine analogue, 7 were refractory to a BRAF inhibitor, and 5 were refractory to rituximab. Minimal residual disease was negative in the bone marrow aspirate and peripheral blood in 65% of patients with a CR. PFS from the start of treatment was 78% at a median follow-up of 37 months. RFS from the end of treatment was 85% at a median follow-up of 34 months. In a post hoc analysis, the 7 patients who were previously treated with a BRAF inhibitor achieved a longer RFS period with vemurafenib plus rituximab compared with BRAF inhibitor monotherapy (median RFS, >19.5 months vs 4 months, respectively).⁶

The most common AEs associated with rituximab were infusion-related reactions (29%) and transient neutropenia (16%). The most common AEs associated with vemurafenib were hyperbilirubinemia (77%), elevated pancreatic enzyme levels (58%), arthralgias or arthritis (55%), and rash (48%). Median dose intensity of vemurafenib was 92%, with dose reductions occurring 2 weeks in.⁶

Dabrafenib

The efficacy and safety of dabrafenib monotherapy in HCL was first evaluated in a single-center, pilot phase 2 trial of 10 patients with R/R HCL harboring *BRAF* V600E mutations. Patients received dabrafenib 150 mg twice daily for 8 weeks, followed by an additional 4 weeks of treatment if CR was not obtained. The median age was 62 years, and the median lines of prior therapy was 3.5. Nine patients had previously received a purine analogue, 6 patients received interferon, 3 patients received rituximab, 1 patient received rituximab plus pentostatin, and 2 patients received vemurafenib. Two patients had undergone a splenectomy.⁷

Disease response was defined as resolution of cytopenias, no palpable splenomegaly, and absence of leukemic hairy cells in bone marrow biopsy and peripheral blood smear. The ORR was 80%, and a CR was achieved in 3 patients (30%). One patient completed 8 weeks of dabrafenib and the remaining 9 patients completed 12 weeks of dabrafenib. Cytopenia recovery of platelets greater than or equal to 100,000/mm³, neutrophils greater than or equal to 1500/mm³, and hemoglobin greater than or equal to 11 g/dL occurred with a median time to recovery of 15 days (range, 6-36), 35 days (range, 11-58), and 51 days (range, 43-64), respectively. At a median follow-up of 64 months, the OS rate was 90%.⁷

Reported AEs included arthralgias in 7 patients, facial flushing in 5 patients, warts in 8 patients, and asymptomatic QTc prolongation in 2 patients. Four patients experienced decreased phosphate levels and 8 patients experienced increased liver/pancreatic function tests. Dose reductions due to treatment-related AEs occurred in 6 patients, with re-escalation in 4 patients to achieve a median dose intensity of 88% of the full starting dose. No grade intravenous AEs or permanent discontinuation of the drug were reported.⁷

Dabrafenib + Trametinib

MEK inhibitors are known to improve efficacy outcomes when added to a BRAF inhibitor

in numerous *BRAF*-mutated disease states, particularly melanoma.⁸ Trametinib (Mekinist; Novartis) is a MEK inhibitor that is commonly combined with dabrafenib for its synergistic activity. ROAR (NCT02034110), a multicenter, phase 2 basket study, assessed the efficacy and safety of dabrafenib plus trametinib in 206 patients with *BRAF* V600E mutation-positive rare cancers that were deemed untreatable with standard chemotherapy options.⁹

The 8 cohorts of rare, advanced cancers included in the study were HCL (n = 55), anaplastic thyroid cancer (n = 36), biliary tract cancer (n = 43), gastrointestinal stromal tumor (n = 1), small intestine adenocarcinoma (n = 3), low-grade glioma (n = 13), high-grade glioma (n = 45), and multiple myeloma (n = 19). Patients received dabrafenib 150 mg twice daily and trametinib 2 mg once daily until unacceptable toxicity, disease progression, or death. Interruptions and dose adjustments were allowed to manage toxicities and improve tolerability.⁹

Fifty-five patients with HCL were included in the basket trial. Enrolled patients had relapsed after at least 2 prior lines of treatment or were refractory to first-line therapy with a purine analogue. The median age was 66 years. Prior treatments included cladribine (94.5%), rituximab (63.6%), pentostatin (23.6%), interferon (21.8%), and moxetumomab pasudotox (20%) (Lumoxiti; AstraZeneca); 87.3% of patients received dabrafenib and trametinib for more than 12 months.¹⁰

The primary end point of ORR was 89.1% in the HCL cohort (95% CI, 77.8%-95.9%). A CR was achieved in 65.5% of patients. In patients with a response, the median duration of response (DOR) was not reached. The 24-month DOR rate was 97.7% (95% CI, 84.6%-99.7%), and the median time to first CR was 6 months. Median PFS was not reached, and the 24-month PFS rate was 94.4% (95% CI, 83.5%-98.1%). Similarly, median OS was not reached, and the 24-month OS rate was 94.5% (95% CI, 83.9%-98.2%). Median hemoglobin was normalized by week 8, platelets by week 4, and neutrophils by week 8.¹⁰

Across all disease cohorts in the basket trial, the most common AEs occurring in 20% or more of patients who received dabrafenib plus trametinib were pyrexia (54.9%), fatigue (42.2%), and nausea (41.7%). Neutropenia (7.3%), anemia (6.3%), and pneumonia (5.3%) were the most common grade 3 or higher AEs. The most commonly reported serious AE that was attributed to the study drug was pyrexia (9.2%).⁹

Reflective of the AEs experienced in other disease states, the most common any-grade AEs in the HCL cohort were pyrexia (58.2%), hyperglycemia (40%), chills (47.3%), dermatitis acneiform (38.2%), fatigue (34.5%), myalgia (32.7%), increase in aspartate aminotransferase (32.7%), peripheral edema (30.9%), and nausea (30.9%). Any-grade hematologic AEs included anemia (18.2%), neutropenia (10.9%), and thrombocytopenia (5.5%). Specifically in the HCL cohort, 63.6% of patients had a grade 3 or higher AE. The most common grade 3 or higher AEs were hyperglycemia (9.1%), pyrexia (7.3%), and pneumonia (7.3%). AEs leading to dose reduction occurred in 52.7% of patients, dose interruption in 69.1%, and permanent discontinuation in 21.8%. Cutaneous squamous cell carcinoma was reported in 16.4% of patients and basal cell carcinoma in 23.6%. Seven patients died during the study, 4 due to progressive disease.¹⁰

Conclusion

Historically used to treat cancers such as melanoma, the employment of *BRAF* inhibitors in R/R HCL represents a novel targeted approach. Clinical trials assessing vemurafenib, dabrafenib, and various combination regimens have consistently yielded significant response rates. These studies not only highlight the potential for improved patient outcomes, but also underscore the importance of personalized medicine in the management of HCL.

Notably, the combination of dabrafenib plus trametinib was studied in the greatest number of patients and showed exceptional rates of response. The DOR extended beyond 24 months for the vast majority of patients, signaling the potential for better long-term disease control.¹⁰ Despite these favorable outcomes, challenges with chronic therapy remain, such as managing AEs and anticipating mechanisms underlying drug resistance. The exploration of low-dose regimens, particularly for vemurafenib, may optimize therapy for those susceptible to dose-limiting toxicities.

Future research should focus on optimizing treatment duration, managing resistance mechanisms, and identifying patients with HCL most likely to benefit from regimens incorporating *BRAF* inhibitors. As personalized medicine advances, the goal is to extend survival and improve quality of life for patients with this rare but challenging hematologic malignancy. 🌐

Quizartinib in FLT3-ITD-Positive Acute Myeloid Leukemia: A New Era in Targeted Therapy

The drug solidifies its place as a first-line treatment option in AML.

Nicole Bentivegna, PharmD, BCOP; and Gabriela Aponte-Melendez, PharmD

ABOUT THE AUTHORS

Nicole Bentivegna, PharmD, BCOP, is a clinical pharmacy services manager and NCODA medically-integrated oncology pharmacy residency program director at Florida Cancer Specialists & Research Institute and Rx To Go, LLC, in Fort Myers, Florida.

Gabriela Aponte-Melendez, PharmD, is a clinical staff pharmacy resident at Florida Cancer Specialists & Research Institute in Fort Myers, Florida.

FLT3 mutations are present in approximately 25% to 30% of acute myeloid leukemia (AML) cases, leading to aggressive disease and poor outcomes.¹ FLT3 inhibitors encompass a diverse group of agents that target mutations in the *FLT3* gene, which are implicated in the development of AML (**Online Table**).

First-generation inhibitors, such as sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals Inc) and lestaurtinib (CEP-701; Teva Pharmaceuticals and Tocris Bioscience), were initially utilized in other cancers but showed limited efficacy in AML.² Midostaurin (Rydapt; Novartis Pharmaceuticals Corporation), another first-generation FLT3 inhibitor, is approved in combination with chemotherapy during induction and consolidation phases in patients with newly diagnosed *FLT3*-mutated AML, showing improved overall survival (OS) compared with standard treatment.³ Second-generation inhibitors, such as gilteritinib (Xospata; Astellas Pharma US, Inc) and crenolanib (ARO-002; Arog Pharmaceuticals and Pfizer), offer greater selectivity and potency.³ Gilteritinib, a more selective FLT3 inhibitor, is approved for use in relapsed or refractory (R/R) AML with *FLT3* mutations and has demonstrated superior response rates to salvage chemotherapy.⁴ Crenolanib, still under investigation, holds promise due to its ability to inhibit both *FLT3* internal tandem duplication (ITD) and *FLT3* tyrosine kinase domain (TKD) mutations, providing a broader therapeutic scope.⁵ These agents play a crucial role in addressing *FLT3*-driven leukemogenesis and enhancing treatment outcomes for a high-risk group of patients with AML.

Quizartinib (Vanflyta; Daiichi Sankyo, Inc) is a new, potent tyrosine kinase inhibitor designed to target AML with *FLT3*-ITD mutations. Approved by the FDA in 2023, quizartinib represents a significant advancement in the treatment of *FLT3*-mutated AML, providing a new additional treatment option.⁶ As a selec-

tive inhibitor of the FLT3 receptor tyrosine kinase, quizartinib plays a critical role in disrupting the signaling pathways responsible for hematopoietic cell differentiation and proliferation.⁷ Quizartinib works by inhibiting FLT3 signaling, thereby reducing the proliferation and survival of leukemic blasts with *FLT3*-ITD mutations. This inhibition promotes apoptosis, which helps reduce disease burden. Its selectivity for FLT3 allows it to minimize off-target effects, making it an important option in the management of *FLT3*-mutated AML.⁷

QuANTUM-First Study

The QuANTUM-First trial (NCT02668653) was a randomized, double-blind, placebo-controlled phase 3 study that established quizartinib's efficacy in combination with standard chemotherapy in newly diagnosed patients with *FLT3*-ITD-positive AML. The study included 539 patients who were randomly assigned to receive either quizartinib or placebo along with standard induction chemotherapy (cytarabine and anthracycline).⁸

The trial demonstrated a significant improvement in median OS in the quizartinib group of 31.9 months compared with 15.1 months in the placebo group.⁸ The improvement in survival emphasized quizartinib's role in reducing the risk of relapse and prolonging life in patients with *FLT3*-ITD-positive AML. In addition, event-free survival also showed meaningful improvement, highlighting quizartinib's ability to enhance remission rates and delay disease progression.

Dosing and Administration

Quizartinib is available as 17.7-mg and 26.5-mg oral tablets.⁶ The dosing is as follows:

- Induction therapy: 35.4 mg orally once daily on days 8 to 21 of "7+3" (cytarabine [100 or 200 mg/m²/d] on days 1 to 7 plus daunorubicin [60 mg/m²/d] or idarubicin [12 mg/m²/d] on days 1-3) and on



days 8 to 21 or 6 to 19 of an optional second induction (“7+3” or “5+2” [5 days cytarabine plus 2 days daunorubicin or idarubicin])

- Consolidation therapy: 35.4 mg orally once daily on days 6 to 19 of high-dose cytarabine (1.5 to 3 g/m² every 12 hours on days 1, 3, and 5) for up to 4 cycles
- Maintenance therapy: 26.5 mg orally once daily on days 1 to 14, followed by 53 mg once daily, thereafter, for up to thirty-six 28-day cycles

Quizartinib is typically used in combination with a standard chemotherapy regimen during induction and consolidation, and as monotherapy during the maintenance phase following induction chemotherapy. Quizartinib can be taken with or without food at approximately the same time each day.⁶

Adverse Effects and Monitoring

Like other tyrosine kinase inhibitors, quizartinib is associated with a variety of adverse effects (AEs). Common hematologic toxicities include neutropenia, anemia, and thrombocytopenia. Other frequently reported AEs include peripheral edema, fatigue, fever, nausea, vomiting, and diarrhea.⁹

Quizartinib is known to cause QT prolongation, which can lead to serious cardiac events such as ventricular arrhythmias and torsades de pointes.⁶ Due to the potential for QT prolongation, it is critical for patients receiving quizartinib to undergo electrocardiogram (ECG) monitoring and serum electrolytes assessments, including potassium, magnesium, and calcium levels, before starting this medication. Strong CYP3A inhibitors, as well as other QT-prolonging drugs, should be avoided during therapy, as they can also potentiate the risk for QT prolongation.⁹

QT interval monitoring should be conducted frequently, with ECGs recommended at baseline, weekly during induction and consolidation therapy, weekly for at least the first month of maintenance, and periodically thereafter.⁶ If the corrected QT interval using the Fridericia formula (QTcF) exceeds 450 milliseconds, quizartinib should not be initiated. For a QTcF of 480 milliseconds or higher, the dose should be interrupted until the QTcF returns to below 450 milliseconds. If QTcF exceeds 500 milliseconds at any point, quizartinib should be permanently discontinued due to the high risk of severe arrhythmias.⁶ Additionally, electrolyte imbalances should be corrected, and the patient should be closely monitored for any signs of cardiac instability throughout the course of treatment.⁶

REMS Program


The Risk Evaluation and Mitigation Strategy (REMS) program for quizartinib, known as Vanflyta REMS, was established to address the serious risk of QT prolongation

and the potential for fatal arrhythmias such as torsades de pointes.¹⁰ Under this program, health care providers and institutions must comply with specific requirements before prescribing and dispensing quizartinib. Prescribers must be certified by enrolling in the REMS program, which involves completing training in the risks associated with quizartinib, particularly its QT prolongation risk, and how to appropriately monitor patients. Similarly, pharmacies must be certified to dispense quizartinib by enrolling in the REMS program, which ensures they are aware of the medication’s risks and the need for regular ECG monitoring and electrolyte management.¹⁰

Patients must receive counseling on the risk of QT prolongation, including the importance of attending scheduled ECG appointments and adhering to electrolyte monitoring. The REMS program also requires that patients are provided with a medication guide, outlining the risk of QT prolongation and signs of arrhythmias they should monitor for, such as dizziness or palpitations. Regular reporting and documentation of QTcF intervals are required, and any instances of QTcF prolongation beyond the safety thresholds must be addressed per the REMS guidelines, including dose modifications or discontinuation, if necessary.¹⁰

Place in NCCN Guidelines

According to the National Comprehensive Cancer Network (NCCN) guidelines for AML, quizartinib is recommended as a standard treatment option for patients with newly diagnosed FLT3-ITD–positive AML, in combination with chemotherapy. Quizartinib is classified as a category 1 recommendation for these patients in the context of induction therapy, underscoring its strong evidence of efficacy based on randomized clinical trials. It is also recommended for use during consolidation therapy following induction and consolidation phases.¹¹

Compared with other FLT3 inhibitors, quizartinib has demonstrated significant efficacy, particularly for FLT3-ITD mutations, and its approval provides an alternative to drugs such as midostaurin and gilteritinib. Although midostaurin is also recommended in the first-line setting for FLT3-mutated AML, its role primarily focuses on broader FLT3 mutations, including both ITD and TKD types. Quizartinib, on the other hand, has more selectivity for FLT3-ITD and has shown superior potency in this subgroup. Additionally, gilteritinib, which is recommended primarily for R/R FLT3-mutated AML, offers another therapeutic option but is generally used after the failure of first-line therapies. The incorporation of quizartinib into the NCCN guidelines reflects its pivotal role in improving survival outcomes for FLT3-ITD–positive patients and solidifies its place among FLT3-targeted therapies as a first-line treatment option in AML. 

New Therapy for Chronic Graft-Vs-Host Disease: Axatilimab

Axatilimab is a colony-stimulating factor-1 receptor-blocking monoclonal antibody indicated after 2 lines of systemic therapy.

Grashma Vadakkel, PharmD, BCOP; Melinda Cook, PharmD, BCOP; Kristian Casem, PharmD, BCOP; and Stephen Eng, PharmD, BCOP

ABOUT THE AUTHORS

Grashma Vadakkel, PharmD, BCOP, is a bone marrow transplant clinical pharmacy specialist at Memorial Sloan Kettering Cancer Center in New York, New York.

Melinda Cook, PharmD, BCOP, is a bone marrow transplant clinical pharmacy specialist at Memorial Sloan Kettering Cancer Center in New York, New York.

Kristian Casem, PharmD, BCOP, is a bone marrow transplant clinical pharmacy specialist at Memorial Sloan Kettering Cancer Center in New York, New York.

Stephen Eng, PharmD, BCOP, is a bone marrow transplant clinical pharmacy specialist at Memorial Sloan Kettering Cancer Center in New York, New York.

ABSTRACT

Chronic graft-vs-host disease (cGVHD) is a late and serious complication of allogeneic hematopoietic stem cell transplant. Although first-line cGVHD therapy consists of corticosteroids, about half of patients will experience steroid-dependent or steroid-refractory disease, necessitating further treatment. The FDA recently approved axatilimab (Niktimvo; Incyte Corporation), a humanized IgG4 monoclonal antibody that inhibits colony-stimulating factor-1 receptor, based on positive results from the AGAVE-201 trial (NCT04710576), which showed a 50% to 74% overall response rate and acceptable tolerability. This review will examine key concepts and takeaways from the AGAVE-201 trial and discuss treatment considerations for patients with steroid-dependent and steroid-refractory cGVHD.

disease and will require additional lines of therapy.³ Until recent FDA approvals, therapy for these patients typically relied on provider experience due to limited data. Recent discoveries in cGVHD pathogenesis have resulted in novel therapeutic options for patients with steroid-dependent and steroid-refractory cGVHD. Currently, there are 4 FDA-approved agents for the treatment of steroid-dependent and steroid-refractory cGVHD, with axatilimab (Niktimvo; Incyte Corporation) most recently approved in August 2024.⁴⁻⁷

Axatilimab is a humanized IgG4 monoclonal antibody that inhibits colony-stimulating factor-1 receptor (CSF1R) signaling, blocking the differentiation of CSF1R-expressing monocytes and macrophages. The reduction of circulating pathologic proinflammatory monocytes and macrophages disrupts the transforming growth factor- β -mediated development of fibrosis, thereby reducing the rate of, and in some cases reversing, fibrotic changes associated with cGVHD.^{2,4}

AGAVE-201 Trial

Axatilimab was approved based on the results of the AGAVE-201 trial (NCT04710576). This was a phase 2, international, randomized study that evaluated axatilimab in patients with recurrent or refractory cGVHD. Patients were included if they had active signs or symptoms of cGVHD according to the 2014 National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD. Patients were also included if they were previously treated with 2 or more lines of systemic therapy and were aged 2 years or older. Systemic corticosteroids, calcineurin inhibitors, and mechanistic target of rapamycin inhibitors were permitted during the trial; however, other concomitant systemic therapies for

Chronic graft-vs-host disease (cGVHD) is a late complication of allogeneic hematopoietic stem cell transplantation that can occur months to years post transplant and is associated with significant morbidity and mortality.¹ The disease develops through a multistep, complex process that includes early inflammation and tissue injury, chronic inflammation and aberrant tissue repair, and fibrosis. It can affect any organ system in the body, exhibiting clinical features similar to systemic sclerosis and interstitial lung disease.^{2,3} Although cGVHD has been described since the late 1970s, corticosteroids have remained the first-line treatment. Unfortunately, about half of patients with cGVHD will experience steroid-dependent or steroid-refractory

cGVHD were required to be discontinued. Patients were excluded if they had relapse of malignancy, posttransplant lymphoproliferative disorder, history of chronic pancreatitis, history of myositis, or uncontrolled infection.²

Patients were randomized to 3 dosing groups according to the severity of cGVHD and previous use of an FDA-approved therapy. These dosing groups included 0.3 mg/kg every 2 weeks (0.3-mg dose group), 1 mg/kg every 2 weeks (1-mg dose group), or 3 mg/kg every 2 weeks (3-mg dose group). Axatilimab therapy continued until disease progression, unacceptable toxicity, or no disease response within 9 months of starting therapy. The primary objective of this study was overall response, which was defined as complete or partial response. The most notable secondary end point was the reduction of symptoms using the modified Lee Symptom Scale.

Results

At the time of analysis, 241 patients were enrolled among the 3 groups: 0.3-mg group (n = 80), 1-mg group (n = 81), and 3-mg group (n = 80). Baseline characteristics were similar across the 3 groups, with most patients experiencing severe cGVHD affecting 3 or 4 organs. The most commonly involved organs were the eyes, lungs, skin, and joints/fascia. Patients had a median of 4 prior lines of therapy, including at least 1 FDA-approved agent (mainly ruxolitinib [Jakafi; Incyte Corporation]), and most were receiving concomitant systemic corticosteroids.²

Axatilimab showed an impressive overall response in 50% of patients (95% CI, 39%-61%) in the 0.3-mg group, 67% of patients (95% CI, 55%-77%) in the 1-mg group, and 74% of patients (95% CI, 63%-83%) in the 3-mg group. A clinically significant reduction in symptoms (defined as a decrease of more than 5 points on the modified Lee Symptom Scale) was reported in 60% of patients in the 0.3-mg group, 69% of patients in the 1-mg group, and 41% of patients in the 3-mg group within the first 6 cycles of therapy. The median time to reduction of symptoms was 1.7 months (0.3-8.6 range), 1.1 months (1-9.3 range), and 1.1 months (0.9-8.0 range), respectively. For organ system response, specifically in the 0.3-mg dose group, notable complete responses were observed in the lower gastrointestinal (GI) tract (90%), upper GI tract (82%), esophagus (65%), and mouth (42%).

Safety and Tolerability

The trial notes that axatilimab was very well tolerated. The most common adverse effects (AEs) included transient laboratory abnormalities not associated with end organ damage. However, there were a few AEs worth noting. Of the 241 patients enrolled in the study, 1 patient in the 3-mg group experienced a grade 3 elevation of creatine kinase that was associated with grade 2 myositis and grade 3 myocardial infarction. Infusion-related reactions were observed in 8%, 5%, and 1% of patients in the 0.3-mg, 1-mg, and 3-mg groups, respectively. Infections

were common in 73%, 73%, and 70%, respectively. These infections included COVID-19 (occurring in approximately 20% of patients), cytomegalovirus, Epstein-Barr virus, and invasive fungal infection. AEs that led to dose interruption were observed in 39%, 41%, and 32% of patients in the respective groups. Discontinuation rates were 6% in the 0.3-mg group, 22% in the 1-mg group, and 18% in the 3-mg group. Periorbital edema was also observed.²

Discussion

The results of the AGAVE-201 study supported the FDA approval of axatilimab monotherapy in patients who have received at least 2 lines of systemic therapy with recurrent or refractory cGVHD.⁴ Axatilimab showed impressive efficacy, with overall response rates occurring in 50% to 74% of patients in a population that consisted of primarily severe cGVHD. Improvement was observed in patients with inflammatory and fibrotic GVHD, and patients reported clinically meaningful improvements in quality of life. In patients with skin cGVHD, not only was symptom control noted, but some patients reported resolution of skin sclerosis after starting treatment. Axatilimab was well tolerated, with toxicities associated with CSF1R signaling including transient elevations of enzyme levels and periorbital edema.^{2,4} Although high infection rates were noted, these rates are similar to what is expected with other FDA-approved cGVHD therapies.¹ Patients should be monitored and provided with infection prophylaxis as appropriate.

Axatilimab's clinical applicability in the real-world setting is supported by the trial population, which included a majority of patients who had been previously treated with ruxolitinib.² However, the use of axatilimab in combination with the other current FDA-approved agents and their optimal sequencing remains to be determined. The other current FDA-approved agents for the treatment of steroid-dependent or steroid-refractory cGVHD include ibrutinib (Imbruvica; Janssen Biotech, Inc and Pharmacyclics LLC) after 1 or more lines of systemic therapy, ruxolitinib after 1 or 2 lines of systemic therapy, and belumosudil (Rezurock; Kadmon Pharmaceuticals, LLC) after 2 or more lines of systemic therapy (Table^{2,4-10}).⁵⁻⁷ Current literature recommends sequencing not only by FDA labeling, but by using patient-specific factors, such as GVHD characteristics, costs, provider experience, and AEs. Median time to response may also be considered.³ As therapies for the treatment of cGVHD may take weeks to months before patients experience symptom improvement, it is important to provide organ-specific supportive care modalities and referrals to specialty services (ie, nutrition, dermatology, ophthalmology, etc) for further symptom management. Patients should also be provided with adequate anti-infective prophylaxis, as they experience immunosuppression from the therapies used to treat cGVHD and from cGVHD itself.³

TABLE. Current FDA-Approved Therapies for cGVHD^{2,4-10}

Drug name (brand)	Approval year	FDA indication	Median time to response	Dosing (adult) ^a	Notable AEs
Ibrutinib ^{7,8} (Imbruvica; Janssen Biotech, Inc and Pharmacyclics LLC)	2017	After ≥1 line of systemic therapy	12 weeks	420 mg orally once daily	Fatigue, diarrhea, thrombocytopenia, bruising
Ruxolitinib ^{6,10} (Jakafi; Incyte Corporation)	2021	After 1-2 lines of systemic therapy	3 weeks	10 mg orally twice daily	Anemia, thrombocytopenia, neutropenia, infection
Belumosudil ^{5,9} (Rezurock; Kadmon Pharmaceuticals, LLC)	2021	After ≥2 lines of systemic therapy	5 weeks	200 mg orally once daily	Fatigue, diarrhea, nausea, cough
Axatilimab ^{2,4} (Niktimvo; Incyte Corporation)	2024	After ≥2 lines of systemic therapy	0.3-mg group: 1.7 months (range, 0.3-8.6)	0.3 mg/kg IV every 3 weeks (maximum dose of 35 mg)	Infection, periorbital edema, elevated lab abnormalities (eg, CPK, AST/ALT, lipase/amylase, GGT)

AEs, adverse effects; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma-glutamyl transpeptidase; IV, intravenous. ^aSignificant drug interactions exist. Please refer to agent-specific monograph for individual dosing.

Conclusion

Axatilimab provides a novel mechanism and efficacious next line of therapy in patients with severe cGVHD symptoms who have been treated with at least 2 lines of systemic therapy. More research is needed to determine sequencing and the potential use of axatilimab in earlier lines of therapy. Ongoing studies (eg, NCT06388564, NCT06132256, NCT03604692) are exploring axatilimab in combination with other therapies for cGVHD, using axatilimab in earlier lines of therapy for cGVHD, and examining the use of axatilimab in other fibrotic diseases.¹²⁻¹⁴

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Lisocabtagene Maraleucel Expands the Therapeutic Landscape for Relapsed/Refractory Non-Hodgkin Lymphoma

This CAR T-cell therapy has revolutionized the management of high-risk and relapsed or refractory disease.

Eve Hughes, PharmD; and Jordan Scott, PharmD

ABOUT THE AUTHORS

Eve Hughes, PharmD, is a PGY-2 oncology pharmacy resident at Roswell Park Comprehensive Cancer Center in Buffalo, New York.

Jordan Scott, PharmD, is a clinical pharmacy specialist at Roswell Park Comprehensive Cancer Center in Buffalo, New York.

Treatment of non-Hodgkin lymphoma (NHL) has historically been centered around the administration of chemotherapy. In the relapse setting, autologous stem cell transplantation (ASCT) is a mainstay of treatment. However, with the introduction of cellular therapies such as bispecific antibodies and chimeric antigen receptor (CAR) T-cell therapy, the treatment landscape for NHL has changed. Given that more than 120 types of NHL exist, with a wide variance in morphologic, immunophenotypic, genetic, and clinical features, it is often difficult to find a single cellular product with efficacy across subtypes. Lisocabtagene maraleucel (liso-cel, Breyanzi; Juno Therapeutics, Inc) has begun to bridge this gap, as this product has revolutionized the management of high-risk and relapsed/refractory (R/R) NHL, gaining FDA approvals in large B-cell lymphoma (LBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). In this therapeutic spotlight, we will review the new indications for liso-cel and how this CAR T-cell therapy varies in its efficacy and toxicity profile.

Although all FDA-approved CAR T-cell products target CD19, slight variances in the binding domain led to differences in the efficacy and toxicity profiles. Liso-cel comes as a 1:1 ratio of CD8 and CD4 CAR T cells. Despite lacking the CD8 hinge and transmembrane region seen in other products, liso-cel utilizes an immunoglobulin G4 hinge region and CD28 transmembrane domain, which play a role in the CAR T-cell activation and proliferation.

R/R Large B-Cell Lymphoma

The original approval in R/R LBCL came as a result of data from the TRANSCEND NHL 001 study (NCT02631044) in 2021.^{1,2}

In efforts to expand the scope of CAR T-cell use, investigators compared liso-cel with ASCT in the early R/R setting (less than 12 months post completion of first-line chemotherapy) in the TRANSFORM trial (NCT03575351).³ The trial's primary end point was event-free survival, and liso-cel demonstrated significant improvement among patients at 10.1 months (95% CI, 6.1-not reached) vs 2.3 months (2.2-4.3) among those in the ASCT arm.² Notably, patients who are at a high risk of early relapse following frontline chemotherapy are often considered to have chemorefractory disease and do not respond as well to transplant as those who have durable responses from first-line chemotherapy. Despite this trend, the TRANSFORM data proved that liso-cel could provide benefit to patients with LBCL who experienced relapse less than 12 months following the completion of first-line treatment.¹⁻³

R/R Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Indolent NHLs have historically been difficult to treat despite being much more prevalent. A prime example is CLL/SLL, as new cases occur at a rate of 4.5 per 100,000 men and women per year. Studies have shown that new targeted therapies including Bruton tyrosine kinase (BTK) and B-cell lymphoma-2 (BCL2) inhibitors have demonstrated significant efficacy. However, patients with R/R CLL/SLL who experience progression after receiving BTK and BCL2 inhibitors often have few treatment options and poorer outcomes. Real-world evidence has demonstrated that as these treatment options are exhausted, CLL no longer behaves as an indolent or chronic disease, indicating an unmet



TABLE. Frequency, Onset, and Duration of CRS and NEs in Liso-Cell¹⁻⁶

Indication	CRS			ICANS		
	Any grade frequency, % (grade 3)	Median onset, days (range)	Median duration, days (range)	Any grade frequency, % (grade 3)	Median onset, days (range)	Median duration, days (range)
LBCL	45 (1.3)	5 (1-15)	5 (1-17)	35 (12)	8 (1-46)	12 (1-87)
CLL/SLL	83 (9)	4 (1-18)	6 (2-37)	46 (20)	7 (1-21)	7 (1-83)
FL	58 (1)	6 (1-17)	3 (1-10)	15 (2)	8.5 (4-16)	3.5 (1-7)
MCL	62 (1)	4 (1-10)	4 (1-14)	33 (10)	8 (1-25)	5 (1-45)

CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; FL, follicular lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; MCL, mantle cell lymphoma; NEs, neurotoxic events; SLL, small lymphocytic lymphoma.

need. In March 2024, liso-cel received the first CAR T-cell therapy approval for the treatment of adult patients with R/R CLL/SLL who have received at least 2 lines of therapy, including a BTK inhibitor and a BCL2 inhibitor, following data from the TRANSCEND CLL 004 study (NCT03331198).⁴

TRANSCEND CLL 004 is a phase 1/2 open-label multicenter study that enrolled 139 patients, 117 of whom received liso-cel infusion at 2 different dose levels. The primary end point was complete response or remission, and the rate was 18% at a median follow-up of just under 20 months. These responses were also durable, with a median duration of response (DOR) of 35.3 months overall; this was not reached prior to data publication in those who achieved a complete response. Because a single infusion of liso-cel was shown to induce a complete response or remission in patients with R/R CLL or SLL while maintaining a manageable adverse effect profile, liso-cel received its indication for this subset of patients.⁴

R/R Follicular Lymphoma

Soon after its approval in CLL/SLL, liso-cel gained one of its most recent indications in another indolent lymphoma. In May 2024, the FDA approved the agent for adults with R/R FL who have also received 2 or more lines of prior therapy. This approval was supported by the results of the multicenter, open-label phase 2 TRANSCEND FL study (NCT04245839). CAR T therapy is an option for R/R FL after 2 or more lines of prior systemic therapy; previously, there was no consensus on the optimal timing in the disease course, as no data existed on the second-line treatment of patients with high-risk features. Investigators evaluated liso-cel in TRANSCEND FL in the second-line setting for patients who had disease progression within 24 months after treatment with an anti-CD20 antibody and alkylator less than 6 months following diagnosis. In the second line, the FL ORR was 96%, and all responders achieved a complete response. The DOR rate was 77.1% at 18 months. Following the response

rates and DOR seen in this study, liso-cel gained this indication under an accelerated approval.⁵

R/R Mantle Cell Lymphoma

For patients with MCL, consolidative ASCT is often administered in the first-line setting. Without ASCT, patients are left with few options for treatment. However, newer combination therapies are moving salvage treatment options to the front line.

In a small cohort in the TRANSCEND NHL 001 trial, investigators assessed liso-cel for patients with R/R MCL, the results of which supported FDA approval for this indication in May 2024. This study included 104 patients (88 of whom received the CAR T-cell infusion) with R/R MCL. These patients were required to have disease that was refractory to at least 2 prior lines of therapy, including but not limited to BTK inhibitors, alkylating agents, and CD20-targeted agents. The median DOR was 15.7 months (95% CI, 6.2 to 24.0), and PFS was 15.3 months (95% CI, 6.6 to 24.9), making liso-cel the first commercial CAR T-cell product to show benefit in MCL. It is important to note that 23% of patients were TP53 positive, 31% had blastoid morphology, and only 30% had received prior ASCT, indicating that patients included in this cohort are likely those with less aggressive disease who respond well to other treatment options.⁶


Adverse Effect Profile

Although the avoidance of traditional chemotherapy toxicities presents advantages, the use of cellular therapies such as CAR T cell introduces novel complications, such as cytokine release syndrome (CRS) and neurotoxic events (NEs), that can be challenging to manage. Understanding these toxicities' frequency, onset, and duration is essential in early and appropriate management (Table¹⁻⁶). Compared with other CAR T-cell therapies, liso-cel generally presents with a later onset of CRS and NEs. In clinical practice, this facilitates the ability to discharge patients for outpatient monitoring much earlier on, as

Liso-cel cellular toxicities also present with a shorter duration and decreased frequency of grade 3 or higher toxicities, making this product a potential option for patients who may not tolerate intensive treatment in the R/R setting.

the expected onset of toxicity occurs between 5 and 8 days following cell infusion. Liso-cel cellular toxicities also present with a shorter duration and decreased frequency of grade 3 or higher toxicities, making this product a potential option for patients who may not tolerate intensive treatment in the R/R setting. Despite the rates of CRS and NEs seen in these trials, monitoring is recommended for at least 7 days following infusion, and this therapy is available only through a restricted Risk Evaluation and Mitigation Strategy program.

Conclusion

Overall, liso-cel is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of a broad range of R/R B-cell malignancies, including LBCL, CLL/SLL, FL, and MCL. The efficacy is supported by clinical trial data showing high response rates and durable remissions in these historically difficult-to-treat disease states. The expanded indications of CAR T therapy have transformed the treatment landscape of R/R B-cell malignancies, providing a novel therapy for patients who have exhausted multiple lines of traditional subsequent therapies. Despite expanded access to these treatments, it remains vital to provide appropriate toxicity monitoring and management based on expected frequency and onset. Future research and clinical trials will be crucial as CAR T-cell therapies continue to be optimized, addressing further unmet needs for patients with lymphoma. 

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Advancing Care for Metastatic Breast Cancer: Oncology Pharmacists Tackle Innovation, Biomarkers, and Operational Hurdles

New drugs and collaborative care may be key to overcoming trial closures, weak guidelines, and inefficiencies.

Alana Hippensteele, Lead Editor

During a *Pharmacy Times* Clinical Forum held in Dallas, Texas, a panel of oncology pharmacists discussed challenges and recent advancements in *ESR1*-mutated metastatic breast cancer (MBC) management, biomarker testing, and operational hurdles. During the discussion, panelist Virali Patel, PharmD, MBA, a pharmacy manager at Texas Oncology, noted that there has been a scarcity of innovative therapies for advanced-stage cancers compared with earlier stages, leaving a gap in options for metastatic disease. According to Patel, current clinical research efforts are seemingly concentrating more on fine-tuning adjuvant therapies or optimizing existing regimens.

“I feel like there are a lot of early-stage [therapies] and I don’t see that much in the metastatic or the advanced setting,” Patel said. “I feel like everything that started in metastatic—and this is common for a lot of metastatic [disease regimens]—they just move up front. I’ve heard a lot about early-stage [disease], but I don’t really know if there’s anything new and great to expect for advanced [disease].”

According to panel moderator Rose DiMarco, PharmD, BCPS, BCOP, clinical trials in MBC have encountered obstacles, such as trial closures due to toxicity, leaving limited options for innovation in this space. However, phase 1 programs and basket trials continue to explore new possibilities.

“Other diseases are definitely having a moment, I think. For [breast cancer], we do have lots of trials [in early-stage disease], and lots of tweaking [of existing therapies], like in the adjuvant setting, chemotherapies, and doing different things there, but not a lot of movement,” said DiMarco, an oncology pharmacy manager at Sidney Kimmel Cancer Center, Jefferson Health, in Philadelphia, Pennsylvania. “We have a big phase 1 program, so we’ve got some of those, but not really anything specifically for MBC—but a lot of basket trials, and stuff like that.”

Biomarker Testing

Another significant theme was the variability in approaches to biomarker testing across institutions. Biomarker testing at progression was emphasized by panelists as critical, given the dynamic nature of MBC,

as tumor biology can evolve quickly. However, although biomarker testing at progression is commonly physician-driven, a lack of standardized procedures for biomarker testing complicates processes, which can require additional support from pharmacists. The emergence of precision medicine teams has helped streamline certain aspects of the biomarker testing process, such as test facilitation and therapy guidance, but these practices vary widely among sites, according to the panelists.

The panelists also noted that electronic medical records (EMRs) present an untapped potential for optimizing biomarker testing. Current systems often rely on clinical review teams to identify gaps in testing through chart reviews and manual prompts. Although artificial intelligence (AI) could enhance these systems by recognizing patterns and suggesting tests, barriers, such as alert fatigue and limited system interoperability, can hinder implementation. For this reason, integrating AI into EMRs will require thoughtful design to avoid overloading health care providers with notifications.

The panelists also noted that guidelines, such as those from the National Comprehensive Cancer Network (NCCN), are crucial to help standardize biomarker testing recommendations for breast cancer, but they currently lack robust guidance from NCCN and others, especially in comparison with current lung cancer guidelines. Enhancing these resources and integrating better EMR functionalities potentially could drive more consistent biomarker testing, according to the panelists. Additionally, fostering interconnectivity among diverse EMR platforms could streamline care for patients transitioning between health systems, reducing information gaps and delays in treatment.

Participants also highlighted operational inefficiencies, particularly in EMR systems, which struggle to integrate seamlessly with testing platforms. Standardizing reporting formats from various testing companies and improving EMR interoperability were cited as crucial advancements needed to simplify workflows and reduce manual data entry errors. The reliance on third-party systems for payer-directed testing further adds complexity, often necessitating manual reconciliation of information if mistakes occur, the panelists explained.

“Physicians can misread test results and accidentally put in mutation positive [when it wasn’t],” said Astrid Slaughter, PhD, RPh, a pharmacy manager at Texas Oncology Round Rock. “So we compare all the data [to confirm accuracy], and sometimes we’ll notice an error and say, ‘Hang on—this patient didn’t have an *AKT* mutation, but you marked it positive.’ It still takes a lot of manual reconciliation of information right now.”

Liquid vs Tissue Biopsy

During a discussion on liquid vs tissue biopsy considerations, the panelists emphasized that payers’ policies on reimbursement significantly influence testing practices. Additionally, they noted that lobbying for changes to these practices has proved challenging. In clinical scenarios looking at detecting *ESR1* mutations, liquid biopsies are generally prioritized due to their ease of administration and patient acceptability. Liquid biopsies are particularly useful during disease progression or when traditional tissue sampling is difficult.

However, tissue biopsies remain indispensable when liquid biopsies fail to detect actionable mutations or when clinical symptoms suggest discrepancies.

“If the patient is willing to get a fresh biopsy, I think we’re always going to try to do that. I usually don’t go back and look at previous results unless we have a new indication, and we’re trying to see if patients qualify for it,” DiMarco said. “I don’t know if that’s something that will continue as things get approved, but over the past couple of years with so many new approvals, I’ve just been like, ‘Oh my goodness, we have a new drug, let’s see who can be treated on this right now,’ so that’s been our go-to because it does take time to get fresh tissue.”

Emerging Challenges and Practices in Oncology Pharmacy

With significant challenges present in sequencing therapies, interpreting clinical data, and addressing patient-specific needs, the group emphasized the importance of baseline metabolic assessments, such as hemoglobin A_{1c}, before initiating certain treatments. For example, alpelisib (Piqray; Novartis) can exacerbate hyperglycemia, so panelists noted that metformin is commonly prescribed prophylactically for

patients with a body mass index over 25 or elevated HbA_{1c}. Dosing begins conservatively at 500 mg daily, increasing as tolerated, with endocrinology referrals when necessary.

“Metformin 500 to start once a day, and you could go up to 1000 twice a day. After that, they go to endocrinology,” said Rochelle Horadam, RPh, BCOP, a breast medical oncology pharmacist at UT Southwestern Medical Center in Dallas. “Then it’s out of my scope [because] I don’t know those drugs well enough to make those decisions.”

DiMarco noted that she will also work with colleagues in endocrinology at her institution to support treatment with alpelisib.

“Because I had such an awful time with alpelisib for several patients, I have a friend in endocrinology, and he is really interested in this pathway,” DiMarco said. “I was doing calls every other day [to patients], asking, ‘What did you eat today?’ and things like that, and it was just crazy, because we have a full-day breast [cancer] clinic, and I’m seeing 20 to 30 patients a day, but I have to call patients every day and ask what they’re eating because I just could not get their sugars under control. [I reached out to] endocrinology, and he has this rotating list of fellows who are really interested in this.”

Panelists also highlighted increasing insurance pushback as a challenge, particularly in relation to insurance requiring step-therapy protocols that do not align with best clinical practices. These pushbacks can restrict the timely adoption of new therapeutic indications, forcing pharmacists to navigate prior authorization processes.

Additionally, the panelists noted challenges relating to the complexity of administering multidrug regimens, particularly when managing adverse effects (AEs). Cyclin-dependent kinase (CDK) 4/6 inhibitors such as palbociclib (Ibrance; Pfizer Inc) are often chosen for their favorable tolerability profile compared with abemaciclib (Verzenio; Eli Lilly and Company), despite concerns about potentially sacrificing efficacy. AEs such as diarrhea, stomatitis, and QT prolongation pose significant management challenges, further complicated by limited real-world data.

“Palbociclib is the softer option. Maybe it is the best option, [and] in my experience patients tend to be on ribociclib and abemaciclib longer, so I am worried that we’re compromising some efficacy because of how toxic abemaciclib is on its own, but

continued on page 64

continued from page 59

it's still so early," DiMarco said. "[Palbociclib] is still really young [as a therapy on the market], and I don't have a ton of experience with it."

DiMarco noted that clinical trials are investigating palbociclib as a combination therapy due to its toxicity profile, but Horadam expressed concern.

"I wonder if they picked palbociclib because it's such a well-tolerated drug that most patients do well with, and abemaciclib has some really vicious AEs, especially the stomatitis associated with that drug," Horadam said. "So maybe they pick palbociclib because it is pretty well tolerated compared [with] abemaciclib, with its AEs like diarrhea and QT prolongation. I honestly don't know why they chose that drug, [though], and time will tell how effective it is."

Real-World Data

The panel underscored the importance of integrating real-world evidence into drug development and regulatory processes. According to the panelists, drug design should prioritize patient adherence and feasibility, particularly for complex regimens involving oral and intravenous therapies. Moreover, the panelists advocated for greater regulatory oversight to ensure confirmatory phase 3 trials align with phase 2 approvals, safeguarding patient access without compromising safety or efficacy.

A recurring theme was also frustration with current clinical trial designs, which often lack comprehensive pharmacokinetic and dosing data. The panelists expressed concerns over the limited applicability of trial results to real-world patient populations, such as those with organ dysfunction or comorbidities. The absence of such data hampers evidence-based decision-making and necessitates reliance on anecdotal reports or smaller studies, according to the panelists.

The panelists also noted a lack of robust sequencing data for newer therapies, such as *ESR1* inhibitors and *PIK3CA*-targeted agents. Although clinical intuition plays a role, there is no established best practice for prioritizing these therapies, according to the panelists. They noted that pharmacists often rely on physician preferences, patient characteristics, and genomic reports for these newer therapies. For example, allele frequency from next-generation sequencing results might influence

therapeutic decisions. Additionally, the duration of prior responses to CDK4/6 inhibitors, such as abemaciclib, can guide the choice of subsequent agents such as elacestrant (Orserdu; Stemline Therapeutics, Inc).

Emerging Therapies

Emerging approaches, including proteolysis-targeting chimeras (PROTACs) and sarcoendoplasmic reticulum calcium ATPase (*SERCA*)-targeting therapies, present exciting pathways for refining endocrine resistance strategies. Additionally, biomarker-driven therapies are gaining traction, with FGFR inhibitors being a notable area of interest, despite toxicity challenges such as nail damage observed with drugs such as erdafitinib (Balversa; Janssen Biotech, Inc). Broad adoption of biomarker testing, such as RNA assays for mutations and fusions, is pivotal in identifying candidates for targeted therapies, though the panelists noted that some tests report lower identification rates for *ESR1* or *PIK3CA* mutations compared with manufacturer claims.

The oral selective estrogen receptor degrader elacestrant, though relatively new, shows promise, with manageable adherence due to its simple regimen, according to the panelists. However, its use in later treatment lines for *ESR1*-mutated cancers may limit observable outcomes. Notably, the panelists all agreed that earlier intervention could provide better treatment outcomes with elacestrant, based on their clinical experience in practice, underscoring the need for additional postmarketing data to understand long-term implications, such as hyperlipidemia and cardiovascular risks.

"For *ESR1* [MBC], you could do elacestrant first, but I don't think we have sequencing data yet. I don't know if there's any best practice out there. I think it's just 'go with your soul' here," DiMarco said. "It's not like *BRCA* data, where we know that the earlier you treat with a PARP inhibitor, usually things go better than later lines of therapy. We just don't have that data right now."

For example, in the EMERALD trial (NCT03778931), investigators evaluated elacestrant as a therapy for patients with advanced breast cancer with *ESR1* mutations, especially following progression on CDK4/6 inhibitors. Approximately 50% of trial participants had detectable *ESR1*

mutations, and many had undergone multiple endocrine therapies. The standard of care comparison was monotherapy with another endocrine agent, raising questions about whether chemotherapy, such as capecitabine (Xeloda; Genentech, Inc), might have been a more robust comparator during that period.

Despite the trial showing a clear mechanism of action and benefits for *ESR1* mutation–positive disease, its design faced critique for lacking investigative rigor. Clinicians noted the challenges of sequencing elacestrant with other agents such as PIK3CA inhibitors and its limited efficacy as a monotherapy. However, combinations with CDK4/6 inhibitors or novel agents such as alpelisib and everolimus (Afinitor; Novartis), are also being explored in clinical trials, potentially enhancing its clinical utility and offering alternatives to fulvestrant (Faslodex; AstraZeneca), a drug patients often dislike because of its painful administration.

According to the panelists, real-world application of elacestrant, which is often off-label, further supports a preference for combinatory use with agents such as abemaciclib or capecitabine over monotherapy. Ongoing trials and the development of synergistic combinations are anticipated to refine its role in treatment paradigms.

“In the pipeline there are a lot of trials out there looking at elacestrant in combination with other therapies, which I’m actually really excited about, because there is one looking at elacestrant in combination with alpelisib,” DiMarco said. “I think that could be really interesting, especially if the efficacy is as good as what we think it could be, and it may be better than fulvestrant, which our patients absolutely hate; no matter what you do, they just hate that injection. So anything to get rid of that would be great, in my opinion.”

The panelists noted that therapy with capivasertib (Truqap; AstraZeneca), an AKT protein kinase inhibitor, brings its own set of challenges, including severe rashes that can be debilitating without proper prophylaxis. Clinicians have adopted strategies such as having patients start antihistamines (eg,

loratadine) a week before treatment to reduce the incidence of severe dermatologic reactions.

For the PI3K inhibitor alpelisib, which is often complicated by severe hyperglycemia, oncology teams face the dual challenge of addressing cancer while mitigating metabolic AEs. When treating with PI3K inhibitors generally, the panelists noted that communication between inpatient pharmacists and other health care professionals in the hospital is crucial for safely managing hyperglycemia. In severe cases, discontinuation of these agents does provide a rapid reversal of this AE, allowing for a safety net during treatment.

DiMarco noted that she has also looked into emerging therapies such as PROTACs, SERCAs, and selective estrogen receptor modulators.

“The PROTACs are basically an enzyme degrader. So, it’s similar, I think, to fulvestrant, but maybe a little more refined. A SERCA has something to do with calcium signaling and ATPase. It is a really interesting pathway... and I highly recommend you look into it, if you’re into biology,” DiMarco said. “But I think we’re going to see this [combination therapy] and [investigation into] novel biomarker targets—I’m super excited about FGFR. I feel like we’ve been hearing about FGFR for the past 10 years, and there has been no movement, but I think we’re finally getting close to actually seeing an FGFR inhibitor hit the market, not just in breast cancer either, so I’m really excited for that.”

Future Outlook

Despite notable challenges, the panelists expressed optimism about the growing arsenal of oncology drugs. They called for collaborative efforts among pharmaceutical companies, regulatory agencies, and health care providers to enhance trial designs, improve access, and refine treatment strategies. The discussion also underscored the critical role oncology pharmacists play when navigating the complexities of cancer care, balancing clinical evidence with patient-centered approaches, and advocating for systemwide improvements. 🌐