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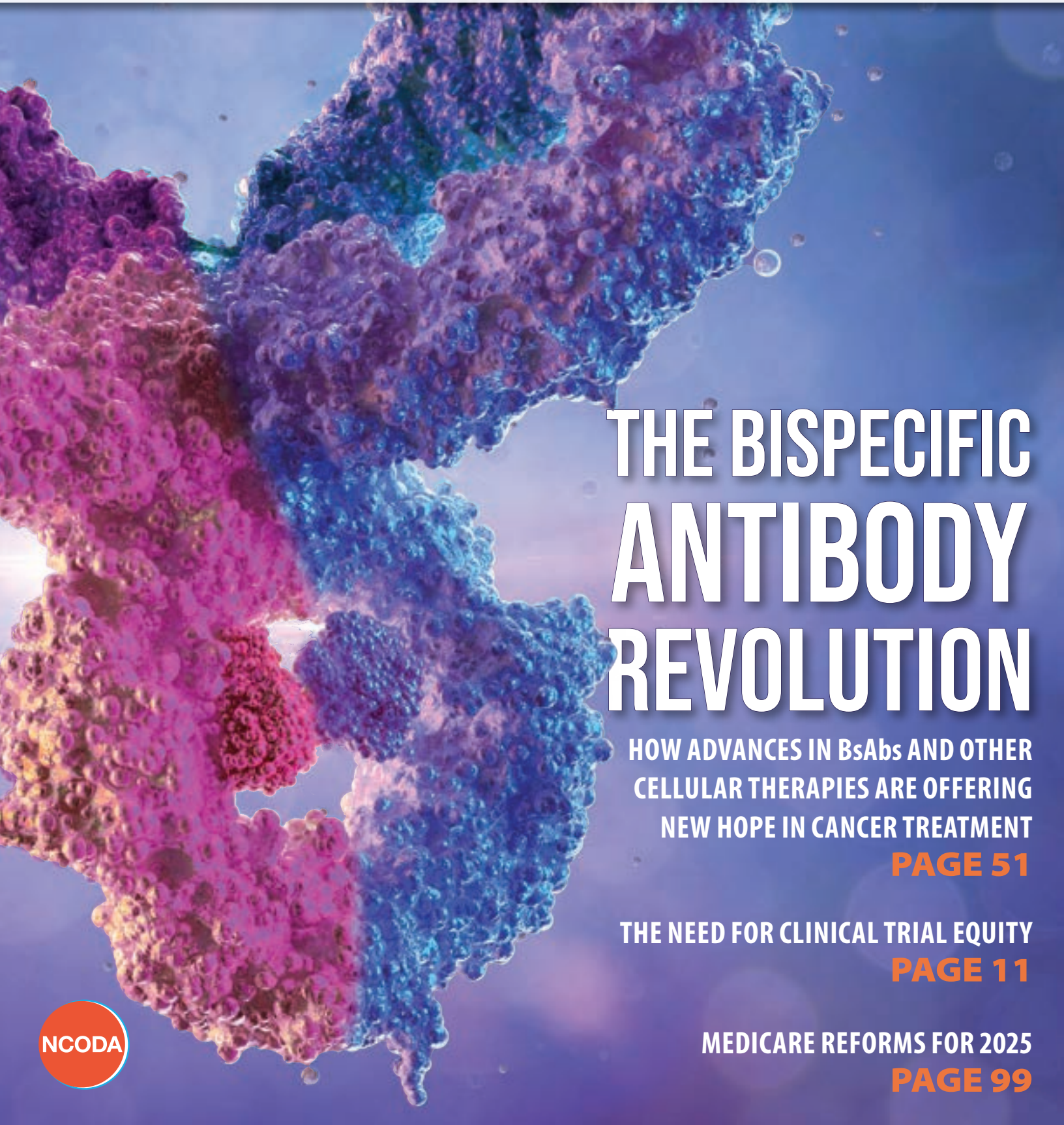

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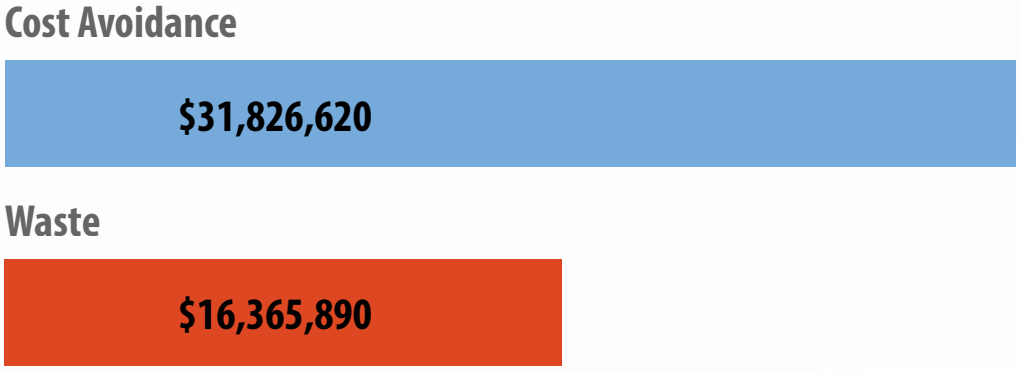

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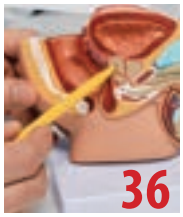

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ONCOLYTICS TODAY CONTINUES TO GROW, THANKS TO CONTRIBUTIONS FROM NCODA MEMBERS

Welcome to the Fall 2024 issue of ***Oncolytics Today***, one of the largest editions in our six-year history.

Like NCODA itself, which now boasts a membership of more than 11,000 members from 200+ different countries — an accelerated growth rate in the last year — ***Oncolytics Today*** also is expanding.

Randy Erickson

The magazine now has a readership of more than 30,000 healthcare professionals across the globe.

This impressive growth is primarily due to one factor: the active participation of NCODA members contributing information to or accessing information from the publication or one of our many other resources: Positive Quality Interventions, PQIs in Action, Oral Chemotherapy Education sheets, Intravenous Cancer Treatment Education sheets, the Oncology State Legislation Tracking Tool, oncology webinars and PQI Podcasts.

Over 40 authors contributed to the more than two dozen articles that make up the Fall 2024 issue of ***Oncolytics Today***, including healthcare professionals from Croatia and Greece as well as the United States.

Starting on **Page 51**, this issue focuses on **Emerging Therapies**, specifically new T cell-engaging bispecific antibodies (BsAbs), which have seen a rapid evolution since blinatumomab, the U.S. Food and Drug Administration's (FDA's) first BsAb approval, in 2014. In the past three years, the FDA has approved eight new drugs for the treatment of r/r follicular lymphoma, r/r diffuse large B-cell lymphoma, r/r multiple myeloma, second-line and beyond extensive stage small cell lung cancer (SCLC), and advanced uveal melanoma.

Lotanna Ezeofor, PharmDc, and **Kelly Brunk**, PharmD, BCOP, provide an overview of all nine drugs — including tear-out charts listing their administration — beginning on **Page 52**.

While BsAbs have shown promising results, that efficacy can come at a price. BsAbs can result in significant adverse effects, such as Cytokine Release Syndrome and neurotoxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome.

Sarah Rockwell, PharmD, BCOP, looks at this challenge and offers strategies for launching BsAbs treatment in the community setting on **Page 64**.

Tarlatamab, one of the most recently approved BsAbs, is a bispecific T cell-engager with a novel mechanism of action for the treatment of adults with extensive stage SCLC. This therapy is the first of its kind for a major solid tumor.

Edgardo Mendoza, PharmD, summarizes the drug and its use on **Page 69**.

Another recent approval is lifileucel, which uses tumor-infiltrating lymphocytes, or TILs, to treat melanoma. TIL therapy is similar to chimeric antigen receptor T-cell (CAR-T) therapy, except that cells are harvested from the patient's tumor rather than their blood.

Katelyn Yamartino, PharmD, reviews this new drug on **Page 72**.

Antibody-drug conjugates (ADCs) offer another promising development in cellular therapy.

One such ADC is sacituzumab govitecan-hziy, which already has proven effective in the treatment of triple-negative breast cancer. A recent second-phase clinical trial has shown the drug to also be effective in treating breast cancer brain metastases as well as primary brain tumors.

Andrew Brenner, MD, PhD, the trial's director, discusses the study and its results on **Page 76**.

Finally, we take a look at CAR-T therapy and the challenges of the complex health issues that can occur both before and after the patient receives their treatment.

Maggie Nelson, PharmD, BCOP, outlines monitoring and treatment protocols for adaptive immunity issues and delayed toxicities experienced by CAR-T patients on **Page 79**.

In addition to the new cellular therapies, we also have a wide variety of articles focusing on:

- Specific diseases and treatments;
- Oncology issues including clinical trial equity, financial toxicity and the effect of pharmacy benefit managers on prescription drug pricing;
- Community practice management and administration; and
- NCODA resources and initiatives.

As always, we hope you will find this issue of ***Oncolytics Today*** insightful as well as inspirational.

Randy Erickson, RN, BSN, MBA
NCODA Executive Council Chair

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HARNESSING AI AND PRESCREENING HUBS IN ONCOLOGY:

TECHNOLOGY CONVERGENCE SPURS A PARADIGM SHIFT TOWARD PRECISION MEDICINE AT SCALE

By Arturo Loaiza-Bonilla, MD, MSEd, FACP

As oncology embraces the age of precision medicine, artificial intelligence (AI) and advanced screening methodologies are driving significant shifts in drug discovery and clinical trial design.

Master prescreening protocols and AI-powered tools like DrugGPT are now central to optimizing patient identification and ensuring equitable access to cutting-edge treatments.

The convergence of these technologies is streamlining the entire clinical trial process — from drug development to patient recruitment — marking a new era in oncology. This article explores how AI is revolutionizing oncology, the critical role of prescreening hubs, and why collaboration across the research ecosystem is essential for scalable solutions.

AI'S ROLE IN DRUG DISCOVERY & CLINICAL TRIAL MATCHING

Traditional drug discovery has always been a resource-intensive endeavor, often requiring years of research and massive financial investments.

Despite these efforts, late-stage trial failures remain common due to unforeseen toxicities or poor efficacy. AI is fundamentally altering this paradigm by rapidly analyzing extensive datasets to predict the success of drug candidates and optimize trial designs.

Arturo Loaiza-Bonilla
(AI rendering)

Machine learning models now have the capacity to synthesize genomic, proteomic and clinical data to pinpoint novel therapeutic targets. The real value of AI in this context lies in its predictive capabilities — identifying potential toxicities early in the development process and optimizing treatment protocols for specific patient populations. This process not only accelerates drug development but also reduces trial costs and improves patient outcomes.

In clinical trials, AI is increasingly being integrated into matching algorithms that identify eligible patients based on molecular and genetic profiles.

For example, at Massive Bio, our AI-enabled platform leverages next-generation sequencing (NGS) data and real-world patient records to double the potential pool of trial participants. This approach addresses one of oncology's most persistent challenges: enrolling patients with complex, multifactorial eligibility criteria.

By automating patient-trial matching, AI not only expedites the process but also reduces the risk of human error, ensuring that the right patients are connected to the right trials.

MASTER PRESCREENING PROTOCOLS: A NEW STANDARD IN PRECISION ONCOLOGY

Master prescreening protocols represent the next generation of clinical trial design, focusing on molecularly guided patient selection. These protocols integrate AI and comprehensive genomic testing to match patients with the most appropriate trials quickly and efficiently.

Traditionally, trial enrollment involved a laborious and manual screening process, often resulting in delays and missed opportunities for eligible patients.

Master prescreening protocols streamline this process by centralizing patient data and leveraging AI algorithms to automatically evaluate trial eligibility.

A key advantage of these protocols is scalability. In a study presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting, our platform was shown to increase patient eligibility for trials by twofold while reducing the time required for manual screening by up to 19,500 hours for a cohort of 5,600 patients across 23 trials.[1]

This efficiency not only accelerates trial enrollment but also democratizes access by identifying eligible patients who may otherwise have been overlooked due to logistical challenges or geographical limitations.

DECENTRALIZED CLINICAL TRIALS AND PRESCREENING HUBS

The shift toward decentralized clinical trials is

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HARNESSING AI

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enabling greater patient access, particularly in underserved and remote populations.

The COVID-19 pandemic underscored the need for flexible, patient-centric trial models, driving the adoption of decentralized methodologies that leverage telemedicine, remote monitoring, and local testing. AI-driven prescreening hubs are a natural extension of this model, offering a centralized resource for patient identification and trial matching.[2]

These hubs serve as command centers that monitor patient progress in real-time, ensuring that trial options are continually updated as new data emerges.

For instance, AI systems can track changes in patient biomarkers, disease progression and trial availability, automatically alerting clinicians when new opportunities arise.

Such systems are analogous to the recommendation engines used in e-commerce, but in this context, they direct patients to lifesaving treatments rather than consumer goods.

The integration of AI tools like DrugGPT[3] into these hubs further enhances precision in trial matching. DrugGPT, developed at the University of Oxford, uses machine learning to predict patient responses to different therapies, optimizing treatment plans and improving trial outcomes. By incorporating DrugGPT into prescreening protocols, we can refine patient selection and ensure that those enrolled are the most likely to benefit from the therapy being tested.

AI'S ROLE IN PATIENT RECRUITMENT

In a recent discussion on the ASCO Daily News Podcast,[4] the potential of AI to transform patient recruitment was highlighted. Current patient-trial matching systems are labor-intensive, with each screening requiring an average of 25 minutes per trial per patient. This inefficiency not only delays enrollment but also limits the number of trials that can be considered.

AI systems, by contrast, can perform multitrial matching in seconds, significantly expanding the pool of eligible patients.

This also underscored the importance of integrating NGS data into electronic medical records to improve the efficiency of AI-driven trial matching. The advent of the 21st Century Cures Act has reduced information blocking, enabling more seamless access to patient data. As these dataflows become more standardized, the accuracy and speed of AI algorithms will only improve, further optimizing the trial matching process.

OVERCOMING THE LAST-MILE CHALLENGE IN CLINICAL TRIALS

Even after identifying eligible patients, converting interest into actual trial participation remains a significant challenge. This "last-mile" problem involves the logistical and psychological barriers that prevent patients from enrolling, even when a trial option is presented. Prescreening hubs, combined with AI-driven command centers, offer a solution by guiding patients through every step of the enrollment process — from initial interest to signing the consent form.

One key insight from the ASCO discussion is that many patients require continuous support from diagnosis through trial enrollment. AI tools can help by tracking patient progress and reengaging them at critical moments when a new trial becomes relevant.

This dynamic approach ensures that patients receive timely information about their options, thereby increasing trial participation rates and optimizing care pathways.

THE PATH FORWARD: COLLABORATION AND INNOVATION

The future of oncology lies in the seamless integration of AI, prescreening hubs, and decentralized trials.

To fully realize this vision, collaboration across the research ecosystem is essential. Pharma companies, regulatory bodies, and technology providers must work together to create unified standards that allow AI-driven solutions to scale effectively.

As tools like DrugGPT become more sophisticated, they will increasingly serve as the backbone of precision oncology, guiding both clinical decisions and trial designs.

At Massive Bio, our work with the Precision Cancer Consortium and collaborations with institutions like CancerX exemplify the potential of these collaborative efforts. By breaking down silos and focusing on shared goals, we can build a more inclusive, efficient, and patient-centered oncology ecosystem.

CONCLUSION

The convergence of AI, master prescreening protocols and decentralized trial models marks a significant leap forward in precision oncology. These innovations are not only enhancing drug discovery but also making clinical trials more accessible, equitable and efficient. By harnessing the power of AI, we can ensure that every patient has access to personalized treatment options at the right time, regardless of where they are in their cancer journey.

As we continue to refine these technologies and integrate them into everyday practice, the ultimate goal remains clear: to deliver better outcomes for all patients, faster and at a greater scale than ever before.

▲ **Arturo Loaiza-Bonilla**, MD, MSEd, FACP, is Co-Founder and Chief Medical Officer, of Massive Bio in New York, New York.

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NCODA'S POSITIVE QUALITY INTERVENTION IN ACTION

WE MUST DO MORE TO EXPAND CANCER CLINICAL TRIALS AND IMPROVE EQUITY

By Suzanne M. Miller, PhD

In the world of oncology, clinical trials are essential to advancing medical knowledge and improving patient care.

Clinical trials help move oncology discoveries from concept into life-changing cancer treatments. In addition to advancing science, they often give patients access to promising new treatment approaches.

Suzanne Miller

Yet only about 5% of patients with cancer participate in clinical trials and even fewer are from minority communities.[1] This has implications for the speed we can test new treatments; for equitable access to novel therapies and for understanding how well drugs work in diverse patient populations.

We need to expand participation in clinical trials to offer better options for current patients and to improve outcomes and reduce side effects for patients in the future.

I've devoted my career to understanding decision-making among cancer patients, including research into barriers to cancer clinical trials. I see how clinical trials too often are disconnected from the system that provides cancer treatment. Widespread misconceptions about clinical trials needlessly frighten patients. And, yes, there are real-world barriers such as time, travel and cost.

My research found patients worry about the costs of clinical trials. Most clinical trials compensate patients, but we need to do more.[2]

In addition to my role as a professor and researcher, I sit on the board of the HealthWell Foundation, an independent, nonprofit organization that assists patients with copayments, premiums, deductibles and out-of-pocket expenses.

I worked with the HealthWell Foundation as the organization recently announced its sponsorship of the Family

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EQUITY

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Reach's Clinical Trial Access Fund, which provides financial support to oncology patients enrolled in an oncology clinical trial. The fund provides financial assistance for food, transportation, housing and utilities for patients — and is part of the HealthWell Foundation's participation in the Cancer Moonshot Initiative, coordinated by the White House.

The HealthWell Foundation's efforts are a small step forward. I believe everyone who works with cancer patients — in hospitals, pharmaceutical companies, patient advocacy groups and charitable programs — must do more to increase participation in clinical trials and potentially lifesaving cancer treatments.

Clinical trial participants should reflect the people most likely to need the treatments being tested. Equity creates more reliable research. We need to counter profoundly low representation of minority patients.

More than 13% of patients with cancer are Black, but participation among Black patients in clinical trials is only about 4% to 6%.[3]

Another current deficiency surrounding access to clinical trial participation is the lack of data on Hispanic and Asian populations. An essential component of improving how we convey information about clinical trials is to collect data that includes beliefs and barriers of these populations.

Our research found higher rates of medical mistrust among Black patients and less knowledge about clinical trials compared to White patients. Yet we also found that when clinical trials were offered and targeted education was provided, willingness to participate in clinical trials did not vary by race.[4] Education and willingness to engage patients from different backgrounds is key to addressing health disparities and improving equity.

What do we need to do? We cannot just hand cancer patients a piece of paper where they can check "Yes" or "No" to the possibility of a clinical trial and end the conversation right there. We need to listen and address patient concerns A clear and accurate response that addressing language barriers when present can increase participation.

If we want better cancer treatments for tomorrow, we must help patients understand the value of clinical trials, not just for scientific advances, but also for their own health. We must rethink how we talk to patients about clinical trials — as well as provide practical solutions that recognize the real-world challenges they face.

Patients too often think that if they join a clinical trial, they may not get treated at all. Patients should understand that every patient in a clinical trial gets at least the best current standard treatment and will be randomly assigned to an additional or alternative experimental treatment.[5]

All trials are carefully evaluated by independent committees to be sure that the best possible care is provided to all participants. All trials involve detailed attention to patients' symptoms and the status of their cancer. In a clinical trial, there will be physicians and nurses monitoring you carefully and regularly.

I believe that clinical trials offer the best possible care — regardless of whether a patient is in the control group and receives the standard of care or experimental therapy.

If we want better cancer treatments for tomorrow, we must help patients understand the value of clinical trials, not just for scientific advances, but also for their own health. We must rethink how we talk to patients about clinical trials — as well as provide practical solutions that recognize the real-world challenges they face.

▲ **Suzanne M. Miller**, PhD, is a member of the HealthWell Foundation Board of Directors. She also is a is a professor in the Cancer Prevention and Control Program at Fox Chase Cancer Center/Temple University Health System in Philadelphia.

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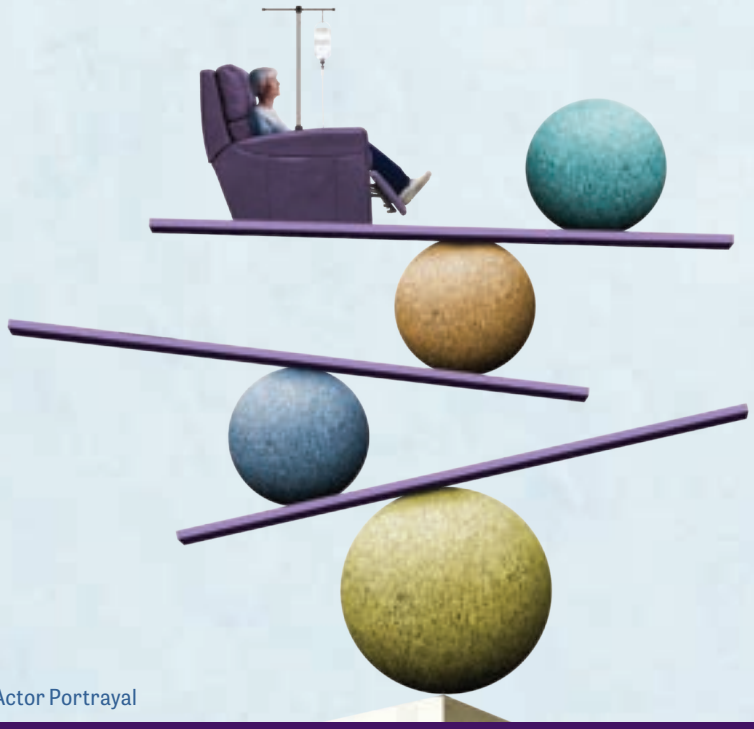

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azurity pharmaceuticals

PHARMACY BENEFIT MANAGERS UNDER FIRE: A SUMMARY OF CONGRESSIONAL HEARINGS

The U.S. House Committee on Oversight and Accountability held a high-profile hearing on July 23, bringing intense scrutiny to the role of Pharmacy Benefit Managers (PBMs) in the American healthcare system. This hearing followed a Senate Finance Committee meeting on May 1, which similarly focused on PBMs and their impact on prescription drug pricing.

Across both chambers of Congress, lawmakers expressed bipartisan concern over the practices of these powerful middlemen, who manage prescription drug benefits on behalf of health insurers.

THE ROLE AND INFLUENCE OF PBMS

PBMs are critical players in the U.S. healthcare system, influencing the cost and accessibility of prescription drugs for millions of Americans. PBMs negotiate with drug manufacturers on behalf of insurers to determine which drugs are covered under various health plans and at what cost. They also negotiate rebates and discounts with manufacturers, which are ultimately supposed to lower the cost of drugs for consumers.

However, the role of PBMs has come under increasing scrutiny as drug prices in the U.S. have soared. Critics argue that PBMs contribute to higher drug prices by prioritizing their profits over patients' health. They point to the lack of transparency in PBM operations, the complexity of rebate structures, and allegations of anticompetitive practices as key areas of concern.

HOUSE OVERSIGHT COMMITTEE HEARING

The House Committee on Oversight and Accountability, chaired by Rep. James Comer (R-KY), conducted a tense hearing with the CEOs of the three largest PBMs — CVS Health, Express Scripts, and Optum Rx — testifying before the committee. The hearing focused on the role of PBMs in driving up prescription drug costs, the lack of transparency in their business practices and allegations of anticompetitive behavior.

Rep. Comer opened the hearing with a pointed critique of PBMs, accusing them of exploiting their position in the healthcare market to increase their profits at the expense of patients' health. "PBMs have grown too powerful, and they are hurting American families who struggle to afford their medications," Comer said. "We are here to get answers and to hold these companies accountable."

During the hearing, both Republican and Democratic members of the committee grilled the PBM executives about their business practices. Lawmakers questioned the executives on the opacity of rebate structures, the exclusion of lower-cost drugs from formularies and the impact of PBM practices on independent pharmacies.

The PBM executives defended their companies, arguing that they play a vital role in controlling drug costs and ensuring access to medications. They also pointed to the complexity of the pharmaceutical supply chain and the role and the role that drug manufacturers have in setting high medication prices.

SENATE FINANCE COMMITTEE HEARING

Earlier in the year, on May 1, the Senate Finance Committee, chaired by Sen. Ron Wyden (D-OR), held a similar hearing focused on PBMs. The Senate hearing aimed to examine the impact of PBM practices on drug pricing and access to medications, particularly for Medicare beneficiaries.

In his opening remarks, Sen. Wyden expressed concern about the growing influence of PBMs in the healthcare system. "PBMs were created to help manage drug costs, but the evidence suggests that they are now part of the problem rather than the solution," Wyden said. "It's time for Congress to take a hard look at the role PBMs play in our healthcare system."

The Senate hearing featured testimony

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LAWMAKERS EXPRESS THEIR DISSATISFACTION WITH PBMs

Rep. James Comer (R-KY), House Oversight Committee Chair: "PBMs have grown too powerful, and they are hurting American families who struggle to afford their medications."

Rep. Katie Porter (D-CA): "PBMs have created a system that is deliberately confusing. It's time to bring transparency to this industry and put patients first."

Rep. Nancy Mace (R-SC): "Independent pharmacies are being crushed by PBMs. We need to level the playing field and ensure that these small businesses can continue to serve their communities."

Rep. Jamie Raskin (D-MD): "It is unacceptable for profits to come at the expense of patients getting the basic medicine they need to lead their full and healthy lives."

Sen. Ron Wyden (D-OR), Senate Finance Committee Chair: "PBMs were created to help manage drug costs, but the evidence suggests that they are now part of the problem rather than the solution."

Sen. Chuck Grassley (R-IA): "The lack of transparency in the PBM industry is staggering. Patients and taxpayers deserve to know where their money is going and why drug prices keep going up."

Sen. Tammy Baldwin (D-WI): "For too long, PBMs have operated in the shadows, driving up costs for patients and undermining our healthcare system."

Sen. John Cornyn (R-TX): "We want to make sure that PBMs are serving their intended purpose — helping to control drug costs — not taking advantage of their position to increase their profits."

PBMs

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from healthcare experts, independent pharmacy owners and patient advocates, who painted a picture of a system where PBMs wield enormous power with little accountability. Witnesses described how PBM practices, such as formulary exclusions and clawbacks, have driven up costs for patients and squeezed independent pharmacies out of business.

One of the key issues discussed during the hearing was the so-called "rebate trap," where PBMs receive significant rebates from drug manufacturers but do not pass those savings on to consumers. Instead, critics argue, PBMs pocket the rebates, leading to higher out-of-pocket costs for patients.

Sen. Chuck Grassley (R-IA), a longtime critic of PBMs, echoed these concerns during the hearing. "The lack of transparency in the PBM industry is staggering," Grassley said. "Patients and taxpayers deserve to know where their money is going and why drug prices keep going up."

BIPARTISAN CONCERNS

Both hearings underscored the bipartisan nature of concerns about PBMs. Lawmakers from both parties expressed frustration with the lack of transparency in the PBM industry and the impact of PBM practices on drug prices.

Rep. Katie Porter (D-CA) criticized PBMs for their complex and opaque pricing structures, which she argued make it difficult for patients and policymakers to understand the true cost of prescription drugs. "PBMs have created a system that is deliberately confusing," Porter said during the House hearing. "It's time to bring transparency to this industry and put patients first."

On the Republican side, Rep. Nancy Mace (R-SC) highlighted the impact of PBM practices on independent pharmacies, many of which have struggled to stay in business due to what they describe as unfair reimbursement rates and fees imposed by PBMs. "Independent pharmacies are being crushed by PBMs," Mace said. "We need to level the playing field and ensure that these small businesses can continue to serve their communities."

In the Senate, Sen. Tammy Baldwin (D-WI) and Sen. John Cornyn (R-TX) have introduced bipartisan legislation aimed at increasing transparency in the PBM industry. The proposed bill, the "Pharmacy Benefit Manager Transparency Act," would require PBMs to disclose their rebate agreements with drug manufacturers, as well as the fees they charge pharmacies. The bill would also prohibit certain PBM practices such as spread pricing, where PBMs charge health plans more for a drug than they reimburse pharmacies and pocket the difference.

Sen. Baldwin argued that the legislation is necessary to rein in PBMs and protect patients. "For too long, PBMs have operated in the shadows, driving up costs for patients and undermining our healthcare system," Baldwin said. "This bill will shine a light on their practices and ensure that patients get the savings they deserve."

Sen. Cornyn emphasized that the bill is not about punishing PBMs but about creating an impartial system for all stakeholders. "We want to make sure that PBMs are serving their intended purpose — helping to control drug costs — not taking advantage of their position to increase their profits," Cornyn said.

THE ROAD AHEAD

As Congress continues to investigate the role of PBMs in the healthcare system, it remains to be seen what impact these hearings will have on legislation and regulation. Both the House and Senate have signaled a willingness to pursue reforms, but the complexity of the PBM industry and the powerful parties at stake suggest that achieving meaningful change will be challenging.

In the meantime, PBMs are likely to face continued vigilence from lawmakers, regulators and the public. The hearings have brought new attention to the role of PBMs in driving up drug costs, and there is growing momentum for reform.

As Comer stated during the House hearing, "The American people deserve answers, and they deserve action. We will not rest until we have held these companies accountable and ensured that our healthcare system works for everyone, not just the powerful few."

COMER ACCUSES LEADERS OF THREE LARGEST PHARMACY BENEFIT MANAGERS OF LYING

During the July 23 hearing, House Oversight Committee chair **James Comer (R-KY)** accused leaders of the three largest PBMs — CVS Health, Express Scripts, and Optum Rx — of providing misleading information to Congress in previous testimonies. Comer threatened them with fines or jail time if they did not correct their statements.

"We have reason to believe that you have not been forthcoming with this committee," Comer said. "We are prepared to take appropriate action if we find that you have misled Congress."

Comer gave the companies' leaders until Sept. 11 to revise their testimony. As of mid-September, however, all three had reportedly declined to change any testimony. Nor had Comer responded to their refusal.

PBM executives initially denied the allegations during the hearing, insisting that they had been truthful in their previous testimonies.

Comer's accusation has added to the growing pressure on PBMs to increase transparency and accountability in their operations.

▲ **EDITOR'S NOTE:** This content has been created by an AI language model and is intended to provide general information. While we strive to deliver accurate and reliable content, it may not always reflect the latest developments or expert opinions.

Copay Accumulators

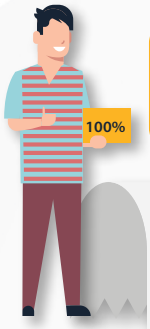
what to know & what's the difference?

Without accumulator programs

Patients with certain types of insurance can use manufacturer coupon cards to cover copays

Your Deductible

The patient's manufacturer coupon card helps to meet their deductible requirement



Once the deductible has been met, insurance will begin providing maximum coverage

RECEIPT

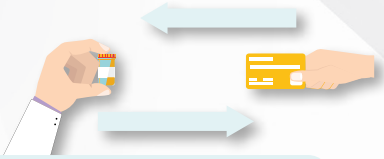
Prescription Drug Cost	$2,000.00
Manufacturer Coupon Value	-$1,995.00
Your Total at the Counter	$5.00

$2,000.00
Annual Deductible

$0.00
Remaining Deductible After Coupon*

*$2,000.00 = $5.00 paid by patient
$1,995.00 coupon

With accumulator programs



Patients can still use their coupon cards but ...

Your Deductible

With the accumulator program, the amount paid by your coupon card would no longer count towards helping to meet your deductible

You as the patient will still need to pay all the money left over to reach your deductible

RECEIPT

Prescription Drug Cost	$2,000.00
Manufacturer Coupon Value	-$1,995.00
Your Total at the Counter	$5.00

$2,000.00
Annual Deductible

$1,995.00
Remaining Deductible After Coupon*

*Only $5.00 counts toward the patient's deductible and health insurers keep the $1,995.00 coupon!

VS.

An example of what happens at the pharmacy counter

NCODA

Scan QR Code To View What States Have Active Legislation Or Enacted Laws Regarding Copay Accumulators

RISING CANCER COSTS

WE HAVE AN OPPORTUNITY TO ADVOCATE FOR PATIENTS SUFFERING FROM FINANCIAL TOXICITY & INSECURITY

By Hardeep Phull, MD, & Natasha Olson, PharmD

An article in the *Wall Street Journal* really hit home for many of us who provide cancer care.

The aptly titled "Cancer is Capsizing Americans' Finances" tells the story of Gwendolyn Jackson, who, in addition to being a newly diagnosed cervical cancer patient, is facing higher drug prices, rising out-of-pocket costs and reduced income.

The financial stress created an additional burden of emotions beyond her cancer diagnosis, resulting in an immense economic strain on her family, who nearly lost everything they owned.[1]

Sadly, stories like Jackson's are becoming more common. Indeed, we in oncology often talk to patients about treatment risks and toxicity of the therapy they are about to embark on. However, in the last few years, many practices have started to devote just as much time discussing financial toxicity.

Hardeep Phull

Natasha Olson

This is a topic that is often ignored and even stigmatized, to the point that some patients even feel embarrassed to bring it up with their doctors. Patients in need of financial assistance and resources often are already overwhelmed, vulnerable and scared from their cancer diagnosis. Therefore, it is essential to broach this topic with empathy and compassion.

Unfortunately, even given the option of funding resources and proactive care teams, many patients and their families accept financial toxicity and its surrounding stigma as the norm, not realizing that deciding between health and having a roof over their heads or food on the table should not be a given.

Here are the grim facts:[2]

CONTINUED ON NEXT PAGE

SELECT LIST OF AVAILABLE RESOURCES FOR CANCER PATIENTS AND FAMILIES

RESOURCE	WEBSITE	DESCRIPTION
American Cancer Society (ACS)	www.cancer.org	This website helps identify programs and resources to assist patients with cancer-related expenses, including housing, caregiver expenses, transportation, food costs, dental care and temporary assistance. It also has resources for Supplemental Security Income and Social Security Disability Insurance.
Cancer Care	www.cancercare.org	This organization lists numerous resources, including government funding, pharmaceutical assistance programs, community organizations, nonprofits and national cancer organizations. Cancer Care's "Helping Hand" resource offers a searchable database for regional assistance.
Conquer Magazine	www.conquer-magazine.com	*Conquer* is an online community for people affected by cancer, offering resources including articles on the latest therapies, cancer support guides and support groups. It also identifies foundations and nonprofit organizations providing financial assistance by cancer type.
Direct Manufacturer Assistance Programs	Search by the name of the cancer medicine to find the manufacturer.	Many drug manufacturers, from AstraZeneca to Pfizer, offer financial assistance and co-pay assistance options for cancer-related medications, regardless of insurance.
HealthWell Foundation	www.healthwellfoundation.org	The HealthWell Foundation is a leading independent non-profit dedicated to improving access to healthcare for America's underinsured. When health insurance is not enough, they fill the gap by assisting with copays, premiums, deductibles and out-of-pocket expenses.
Leukemia & Lymphoma Society (LLS)	www.lls.org	For patients with leukemia or lymphoma, LLS provides co-pay assistance for medical expenses and insurance premiums, along with resources for transportation assistance, caregiver support and patient support groups.
NCODA Financial Assistance Tool	www.ncoda.org/financial-assistance	NCODA's very own financial assistance tool provides up-to-date and comprehensive financial resource information about dozens of chemotherapy and cancer care treatment options.
NCODA Treatment Support Kits	www.ncoda.org/treatment-support-kits	NCODA provides Treatment Support Kits (TSKs) containing educational information and complimentary supportive care medicines and products to help manage common adverse events, saving patients money and time.
PAN Foundation	www.panfoundation.org	The PAN Foundation is one of the nation's largest charitable organizations, providing financial assistance that helps people afford their prescription medications. They serve as a critical safety net for people who are living with chronic and rare diseases and who, despite their insurance coverage, need more help.

FINANCIAL TOXICITY

CONTINUED FROM PREVIOUS PAGE

▲ One in 12 adults in the U.S. has medical debt ($220 billion total).

▲ Three million Americans owe more than $10,000 in medical debt.

▲ Medical debt is more common for those with low/middle income, no health insurance and poor health/disabilities.

▲ To compensate, 70% cut spending on essentials including food and clothing, 60% use up their savings or retirement, 40% take on extra jobs, 37% borrow money from friends/family, 33% increase credit card usage and 20% change living situations.

▲ Many patients risk bankruptcy, foreclosure and homelessness.

PATIENT RIGHTS

Unfortunately, many cancer patients do not know or have access to financial advisors or resources to understand their rights and other key concepts, including the right to:

▲ Review bills in an accurate/timely manner;

▲ Negotiate lower prices;

▲ Seek fair repayment plans;

▲ Prioritize and consolidate debt; and

▲ Receive unbiased help.

Financial toxicity is a vicious cycle. Individuals burdened with debt are more likely to skip or delay care. Many face perpetual, worsening debt over time by

CONTINUED ON NEXT PAGE

FINANCIAL TOXICITY

CONTINUED FROM PREVIOUS PAGE

compounding unfavorable loans, accumulating credit card interest and seeking paycheck advances.

Such poor financial alternatives can create a generational cycle that is hard to contain, leading to broken families, ruined careers and lost opportunities.

The mental health impact is equally severe: 60% develop disorders, including substance abuse or addiction, while 42% suffer damage to their self-worth.

Though not directly about cancer, "Ordinary Angels," the 2024 film starring Hilary Swank, paints a realistic picture of the grim reality of financial toxicity in healthcare.[3] Set in Louisville in the 1990s, it tells the story of Sharon Stevens, a struggling alcoholic and hairdresser who finds purpose in helping a widower raise money to pay his daughter's medical bills.

Diagnosed with biliary atresia, the girl requires a liver transplant. Due to her father's lack of health insurance, the family racks up hundreds of thousands of dollars in medical bills. The debt eventually is paid off through Stevens' tireless efforts and advocacy.

Though it is a feel-good movie about the power of community and the human spirit, the underlying theme is nonetheless very disheartening.

Indeed, the truth is that very few patients have the fortune of a relentless advocate/miracle worker like Stevens, much less the knowledge or resources to have a fighting chance.

Therefore, we must empower all people to have a chance to regain their health and dignity, by fixing gaps in care and health-related costs.

We must meaningfully address financial toxicity and insecurity by identifying resources and assistance programs for every cancer patient.

Essentially, our collective goal should be striving to make the stories and statistics like the ones in the *Wall Street Journal* article and "Ordinary Angels" obsolete for patients in the future.

▲ **Hardeep Phull**, MD, is the Director of Medical Oncology at Palomar Health in Escondido, California. **Natasha Olson**, PharmD, is Senior Manager of Content Development & Strategy at NCODA in Spokane, Washington.

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1. "Cancer Is Capsizing Americans' Finances. 'I Was Losing Everything.'" The Wall Street Journal, 28 May 2024, www.wsj.com/health/healthcare/cancer-cost-patient-debt-dd7c540c.

2. "Peterson-Kaiser Health System Tracker." Peterson-Kaiser Health System Tracker, www.healthsystemtracker.org.

3. "User Submitted Review of 'Ordinary Angels.'" IMDb, 2024, www.imdb.com/review/rw9657698.

PADCEV® + pembrolizumab in 1L la/mUC

START STRONGER. LIVE LONGER.

BOXED WARNING: SERIOUS SKIN REACTIONS

- **PADCEV can cause severe and fatal cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which occurred predominantly during the first cycle of treatment, but may occur later.**
- **Closely monitor patients for skin reactions.**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.**

INDICATION

PADCEV, in combination with pembrolizumab, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Skin reactions Severe cutaneous adverse reactions, including fatal cases of SJS or TEN occurred in patients treated with PADCEV. SJS and TEN occurred predominantly during the first cycle of treatment but may occur later. Skin reactions occurred in 70% (all grades) of the 564 patients treated with PADCEV in combination with pembrolizumab in clinical trials. When PADCEV was given in combination with pembrolizumab, the incidence of skin reactions, including severe events, occurred at a higher rate compared to PADCEV as a single agent. The majority of the skin reactions that occurred with combination therapy included maculo-papular rash, macular rash and papular rash. Grade 3-4 skin reactions occurred in 17% of patients (Grade 3: 16%, Grade 4: 1%), including maculo-papular rash, bullous dermatitis, dermatitis, exfoliative dermatitis, pemphigoid, rash, erythematous rash, macular rash, and papular rash. A fatal reaction of bullous dermatitis occurred in one patient (0.2%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Skin reactions led to discontinuation of PADCEV in 6% of patients.

Skin reactions occurred in 58% (all grades) of the 720 patients treated with PADCEV as a single agent in clinical trials. Twenty-three percent (23%) of patients had maculo-papular rash and 34% had pruritus. Grade 3-4 skin reactions occurred in 14% of patients, including maculo-papular rash, erythematous rash, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. The median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 8 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=75), 24% of patients restarting at the same dose and 24% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 3.1% of patients.

Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated. For persistent or recurrent Grade 2 skin reactions, consider withholding PADCEV until Grade ≤1. Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for Grade 3 skin reactions. Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV. Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials. In clinical trials of PADCEV as a single agent, 17% of the 720 patients treated with PADCEV developed hyperglycemia of any grade; 7% of patients developed Grade 3-4 hyperglycemia (Grade 3: 6.5%, Grade 4: 0.6%). Fatal events of hyperglycemia and DKA occurred in one patient each (0.1%). The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. The median time to onset of hyperglycemia was 0.5 months (range: 0 to 20 months). Hyperglycemia led to discontinuation of PADCEV in 0.7% of patients. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. Of the patients who initiated insulin therapy for treatment of hyperglycemia, 66% (23/35) discontinued insulin at the time of last evaluation. Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. If blood glucose is elevated (>250 mg/dL), withhold PADCEV.

Pneumonitis/Interstitial Lung Disease (ILD) Severe, life-threatening or fatal pneumonitis/ILD occurred in patients treated with PADCEV. When PADCEV was given in combination with pembrolizumab, 10% of the 564 patients treated with combination therapy had pneumonitis/ILD of any grade and 4% had Grade 3-4. A fatal event of pneumonitis/ILD occurred in two patients (0.4%). The incidence of pneumonitis/ILD, including severe events, occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as a single agent. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26 months).

In clinical trials of PADCEV as a single agent, 3% of the 720 patients treated with PADCEV had pneumonitis/ILD of any grade and 0.8% had Grade 3-4. The median time to onset of any grade pneumonitis/ILD was 2.9 months (range: 0.6 to 6 months).

Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations. Withhold PADCEV for patients who develop Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis/ILD.

Peripheral neuropathy (PN) When PADCEV was given in combination with pembrolizumab, 67% of the 564 patients treated with combination therapy had PN of any grade, 36% had Grade 2 neuropathy, and 7% had Grade 3 neuropathy. The incidence of PN occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as a single agent. The median time to onset of Grade ≥2 PN was 6 months (range: 0.3 to 25 months).

PN occurred in 53% of the 720 patients treated with PADCEV as a single agent in clinical trials including 38% with sensory neuropathy, 8% with muscular weakness and 7% with motor neuropathy. Thirty percent of patients experienced Grade 2 reactions and 5% experienced Grade 3-4 reactions. PN occurred in patients treated with PADCEV with or without preexisting PN. The median time to onset of Grade ≥2 PN was 4.9 months (range: 0.1 to 20 months). Neuropathy led to treatment discontinuation in 6% of patients.

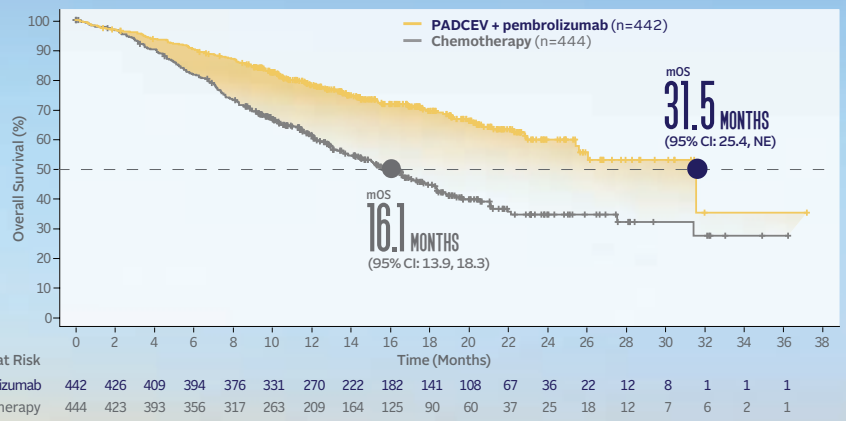
Monitor patients for symptoms of new or worsening PN and consider dose interruption or dose reduction of PADCEV when PN occurs. Permanently discontinue PADCEV in patients who develop Grade ≥3 PN.

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV as a single agent in clinical trials in which ophthalmologic exams were scheduled. The majority of these events involved the cornea and included events associated with dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy. Dry eye symptoms occurred in 30% of patients, and blurred vision occurred in 10% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.7 months (range: 0 to 30.6 months). Monitor patients for ocular disorders.

A STANDARD OF CARE ACROSS 1L la/mUC[1-4]

PADCEV + PEMBROLIZUMAB NEARLY DOUBLED mOS AND mPFS VS PLATINUM-BASED CHEMOTHERAPY[1]*

SUPERIOR OS VS CHEMOTHERAPY
(HR=0.47; 95% CI: 0.38, 0.58; *P*<0.0001)



Number at Risk																		
PADCEV + pembrolizumab	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

- **mPFS 12.5 months (95% CI: 10.4, 16.6) vs 6.3 months (95% CI: 6.2, 6.5)** (HR=0.45; 95% CI: 0.38, 0.54; *P*<0.0001)[1]

*EV-302 is a phase 3, randomized, open-label trial of previously untreated la/mUC patients evaluating PADCEV + pembrolizumab (n=442) vs platinum-based chemotherapy (gemcitabine with cisplatin or carboplatin; n=444). Dual primary endpoints were OS and PFS by BICR per RECIST v1.1. Additional endpoints included ORR by BICR per RECIST v1.1; **68% ORR (95% CI: 63.1, 72.1) with PADCEV + pembrolizumab vs 44% ORR (95% CI: 39.7, 49.2) with chemotherapy (*P*<0.0001).**[1,4]

Patients were randomized 1:1 to receive either PADCEV 1.25 mg/kg via IV infusion on days 1 and 8 of every 21-day cycle in combination with pembrolizumab 200 mg IV on day 1 of every 21-day cycle or gemcitabine 1000 mg/m^2 on days 1 and 8 in combination with either cisplatin 70 mg/m^2 or carboplatin AUC 4.5 or 5 on day 1 of every 21-day cycle. Treatment continued until clinical progression, disease progression per BICR, unacceptable toxicity, or completion of maximum cycles.[1,4]

Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

Infusion site extravasation Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 720 patients treated with PADCEV as a single agent in clinical trials, 1% of patients experienced skin and soft tissue reactions, including 0.3% who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

Embryo-fetal toxicity PADCEV can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during PADCEV treatment and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

ADVERSE REACTIONS

Most common adverse reactions, including laboratory abnormalities (≥20%) (PADCEV in combination with pembrolizumab) Increased aspartate aminotransferase (AST), increased creatinine, rash, increased glucose, PN, increased lipase, decreased lymphocytes, increased alanine aminotransferase (ALT), decreased hemoglobin, fatigue, decreased sodium, decreased phosphate, decreased albumin, pruritus, diarrhea, alopecia, decreased weight, decreased appetite, increased urate, decreased neutrophils, decreased potassium, dry eye, nausea, constipation, increased potassium, dysgeusia, urinary tract infection and decreased platelets.

EV-302 Study: 440 patients with previously untreated la/mUC (PADCEV in combination with pembrolizumab)

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab. The most common serious adverse reactions (≥2%) were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%). **Fatal adverse reactions** occurred in 3.9% of patients treated with PADCEV in combination with pembrolizumab including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%).

Adverse reactions leading to discontinuation of PADCEV occurred in 35% of patients. The **most common adverse reactions (≥2%) leading to discontinuation** of PADCEV were PN (15%), rash (4.1%) and pneumonitis/ILD (2.3%). Adverse reactions leading to dose interruption of PADCEV occurred in 73% of patients. The **most common adverse reactions (≥2%) leading to dose interruption** of PADCEV were PN (22%), rash (16%), COVID-19 (10%), diarrhea (5%), pneumonitis/ILD (4.8%), fatigue (3.9%), hyperglycemia (3.6%), increased ALT (3%) and pruritus (2.5%). Adverse reactions leading to dose reduction of PADCEV occurred in 42% of patients. The **most common adverse reactions (≥2%) leading to dose reduction** of PADCEV were rash (16%), PN (13%) and fatigue (2.7%).

EV-103 Study: 121 patients with previously untreated la/mUC who were not eligible for cisplatin-containing chemotherapy (PADCEV in combination with pembrolizumab)

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab; the most common (≥2%) were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), sepsis (3.3%), pneumonia (3.3%), hematuria (3.3%), pneumonitis/ILD (3.3%), urinary retention (2.5%), diarrhea (2.5%), myasthenia gravis (2.5%), myositis (2.5%), anemia (2.5%), and hypotension (2.5%). **Fatal adverse reactions** occurred in 5% of patients treated with PADCEV in combination with pembrolizumab, including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis/ILD (0.8%). **Adverse reactions leading to discontinuation** of PADCEV occurred in 36% of patients; the most common (≥2%) were PN (20%) and rash (6%). **Adverse reactions leading to dose interruption** of PADCEV occurred in 69% of patients; the most common (≥2%) were PN (18%), rash (12%), increased lipase (6%), pneumonitis/ILD (6%), diarrhea (4.1%), acute kidney injury (3.3%), increased ALT (3.3%), fatigue (3.3%), neutropenia (3.3%), urinary tract infection (3.3%), increased amylase (2.5%), anemia (2.5%), COVID-19 (2.5%), hyperglycemia (2.5%), and hypotension (2.5%). **Adverse reactions leading to dose reduction** of PADCEV occurred in 45% of patients; the most common (≥2%) were PN (17%), rash (12%), fatigue (5%), neutropenia (5%), and diarrhea (4.1%).

DRUG INTERACTIONS

Effects of other drugs on PADCEV (*Dual P-gp and Strong CYP3A4 Inhibitors*) Concomitant use with dual P-gp and strong CYP3A4 inhibitors may increase unconjugated monomethyl auristatin E exposure, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with dual P-gp and strong CYP3A4 inhibitors.

SPECIFIC POPULATIONS

Lactation Advise lactating women not to breastfeed during treatment with PADCEV and for 3 weeks after the last dose.

Hepatic impairment Avoid the use of PADCEV in patients with moderate or severe hepatic impairment.

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on adjacent pages.

1L=first-line; AUC=area under the curve; BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; IV=intravenous; la/mUC=locally advanced or metastatic urothelial cancer; mOS=median overall survival; mPFS=median progression-free survival; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

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PADCEV®
enfortumab vedotin-ejfv
Injection for IV infusion 20 mg & 30 mg vials

astellas ONCOLOGY
Pfizer Oncology

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Injection for IV infusion 20 mg & 30 mg vials

PADCEV® (enfortumab vedotin-ejfv) for injection, for intravenous use

The following is a brief summary of the full Prescribing Information. **Please see the package insert for full prescribing information including BOXED WARNING.**

WARNING: SERIOUS SKIN REACTIONS

- **PADCEV can cause severe and fatal cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which occurred predominantly during the first cycle of treatment, but may occur later.**
- **Closely monitor patients for skin reactions.**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.**

INDICATIONS AND USAGE

PADCEV, in combination with pembrolizumab, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC).

PADCEV, as a single agent, is indicated for the treatment of adult patients with locally advanced or mUC who:

- have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosage

When given in combination with pembrolizumab, the recommended dose of PADCEV is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. Refer to the pembrolizumab Prescribing Information for the recommended dosing information of pembrolizumab.

The recommended dose of PADCEV as a single agent is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Dose Modifications

Table 1. Dose Modifications

Adverse Reaction	Severity[1]	Dose Modification[1]
Skin Reactions	For persistent or recurrent Grade 2 skin reactions	Consider withholding until Grade ≤1, then resume treatment at the same dose level or dose reduce by one dose level.
	Grade 3 skin reactions	Withhold until Grade ≤1, then resume treatment at the same dose level or dose reduce by one dose level.
	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 2-4 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
Hyperglycemia	Blood glucose >250 mg/dL	Withhold until elevated blood glucose has improved to ≤250 mg/dL, then resume treatment at the same dose level.
Pneumonitis/ Interstitial Lung Disease (ILD)	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade ≥3	Permanently discontinue.
Peripheral Neuropathy	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level.
	Grade ≥3	Permanently discontinue.
Other nonhematologic toxicity	Grade 3	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Permanently discontinue.
Hematologic toxicity	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Withhold until Grade ≤1, then reduce dose by one dose level or discontinue treatment.

1. Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Table 2. Recommended Dose Reduction Schedule

	Dose Level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

WARNINGS AND PRECAUTIONS

Skin Reactions

Severe cutaneous adverse reactions, including fatal cases of SJS or TEN occurred in patients treated with PADCEV. SJS and TEN occurred predominantly during the first cycle of treatment but may occur later.

Skin reactions occurred in 70% (all grades) of the 564 patients treated with PADCEV in combination with pembrolizumab in clinical trials. When PADCEV was given in combination with pembrolizumab, the incidence of skin reactions, including severe events, occurred at a higher rate compared to PADCEV as a single agent. The majority of the skin reactions that occurred with combination therapy included maculo-papular rash, macular rash and papular rash. Grade 3-4 skin reactions occurred in 17% of patients (Grade 3: 16%, Grade 4: 1%), including maculo-papular rash, bullous dermatitis, dermatitis, exfoliative dermatitis, pemphigoid, rash, erythematous rash, macular rash, and papular rash. A fatal reaction of bullous dermatitis occurred in one patient (0.2%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Skin reactions led to discontinuation of PADCEV in 6% of patients. Of the patients who experienced a skin reaction and had data regarding resolution (N = 391), 59% had complete resolution and 41% had residual skin reactions at their last evaluation. Of the patients with residual skin reactions at last evaluation, 27% (43/159) had Grade ≥2 skin reactions.

Skin reactions occurred in 58% (all grades) of the 720 patients treated with PADCEV as a single agent in clinical trials. Twenty-three percent (23%) of patients had maculo-papular rash and 34% had pruritus. Grade 3-4 skin reactions occurred in 14% of patients, including maculo-papular rash, erythematous rash, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. The median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 8 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=75), 24% of patients restarting at the same dose and 24% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 3.1% of patients. Of the patients who experienced a skin reaction and had data regarding resolution (N =328), 58% had complete resolution and 42% had residual skin reactions at their last evaluation. Of the patients with residual skin reactions at last evaluation, 39% (53/137) had Grade ≥2 skin reactions.

Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated.

For persistent or recurrent Grade 2 skin reactions, consider withholding PADCEV until Grade ≤1. Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for Grade 3 skin reactions.

Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.

Hyperglycemia

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV.

Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials.

In clinical trials of PADCEV as a single agent, 17% of the 720 patients treated with PADCEV developed hyperglycemia of any grade; 7% of patients developed Grade 3-4 hyperglycemia (Grade 3: 6.5%, Grade 4: 0.6%). Fatal events of hyperglycemia and diabetic ketoacidosis occurred in one patient each (0.1%). The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. The median time to onset of hyperglycemia was 0.5 months (range: 0 to 20 months). Hyperglycemia led to discontinuation of PADCEV in 0.7% of patients. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. Of the patients who initiated insulin therapy for treatment of hyperglycemia, 66% (23/35) discontinued insulin by the time of last evaluation.

Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia.

If blood glucose is elevated (>250 mg/dL), withhold PADCEV.

Pneumonitis/Interstitial Lung Disease (ILD)

Severe, life-threatening or fatal pneumonitis/ILD occurred in patients treated with PADCEV.

When PADCEV was given in combination with pembrolizumab, 10% of the 564 patients treated with combination therapy had pneumonitis/ILD of any grade and 4% had Grade 3-4. A fatal event of pneumonitis/ILD occurred in two patients (0.4%). The incidence of pneumonitis/ILD, including severe events, occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as a single agent. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26 months).

In clinical trials of PADCEV as a single agent, 3% of the 720 patients treated with PADCEV had pneumonitis/ILD of any grade and 0.8% had Grade 3-4. The median time to onset of any grade pneumonitis/ILD was 2.9 months (range: 0.6 to 6 months).

Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations.

Withhold PADCEV for patients who develop Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis/ILD.

Peripheral Neuropathy

When PADCEV was given in combination with pembrolizumab, 67% of the 564 patients treated with combination therapy had peripheral neuropathy of any grade, 36% had Grade 2 neuropathy, and 7% had Grade 3 neuropathy. The incidence of peripheral neuropathy occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as a single agent. The median time to onset of Grade ≥2 peripheral neuropathy was 6 months (range: 0.3 to 25 months). Of the patients who experienced neuropathy and had data regarding resolution (N = 373), 13% had complete resolution, and 87% of patients had residual neuropathy at last evaluation. Of the patients with residual neuropathy at last evaluation, 45% (146/326) had Grade ≥2 neuropathy.

Peripheral neuropathy occurred in 53% of the 720 patients treated with PADCEV as a single agent in clinical trials including 38% with sensory neuropathy, 8% with muscular weakness and 7% with motor neuropathy. Thirty percent of patients experienced Grade 2 reactions and 5% experienced Grade 3-4 reactions. Peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 peripheral neuropathy was 4.9 months (range: 0.1 to 20 months). Neuropathy led to treatment discontinuation in 6% of patients. Of the patients who experienced neuropathy who had data regarding resolution (N = 296), 11% had complete resolution, and 89% had residual neuropathy at the time of their last evaluation. Of the patients with residual neuropathy at last evaluation, 50% (132/262) had Grade ≥2 neuropathy.

Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs.

Permanently discontinue PADCEV in patients who develop Grade ≥3 peripheral neuropathy.

Ocular Disorders

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV as a single agent in clinical trials in which ophthalmologic exams were scheduled. The majority of these events involved the cornea and included events associated with dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy.

Dry eye symptoms occurred in 30% of patients, and blurred vision occurred in 10% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.7 months (range: 0 to 30.6 months). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

Infusion Site Extravasation

Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 720 patients treated with PADCEV as a single agent in clinical trials, 1% of patients experienced skin and soft tissue reactions, including 0.3% who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of enfortumab vedotin-ejfv to pregnant rats during the period of organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures similar to the clinical exposures at the recommended human dose of 1.25 mg/kg.

Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to PADCEV in combination with pembrolizumab at 1.25 mg/kg in 564 patients in EV-302 and EV-103 and PADCEV as a single agent at 1.25 mg/kg in 720 patients in EV-301, EV-201, EV-203 (NCT04995419), EV-101 (NCT02091999), and EV-102 (NCT03070990). Ocular disorders reflect 384 patients in EV-201, EV-101, and EV-102. Among 564 patients receiving PADCEV in combination with pembrolizumab, 59% were exposed for ≥6 months, and 24% were exposed for ≥12 months. In this pooled population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were increased aspartate aminotransferase, increased creatinine, rash, increased glucose, peripheral neuropathy, increased lipase, decreased lymphocytes, increased alanine aminotransferase, decreased hemoglobin, fatigue, decreased sodium, decreased phosphate, decreased albumin, pruritus, diarrhea, alopecia, decreased weight, decreased appetite, increased urate, decreased neutrophils, decreased potassium, dry eye, nausea, constipation, increased potassium, dysgeusia, urinary tract infection and decreased platelets. Among 720 patients receiving PADCEV as a single agent, 37% were exposed for ≥6 months, and 14% were exposed for ≥12 months. In this pooled population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were increased glucose, increased aspartate aminotransferase, decreased lymphocytes, increased creatinine, rash, fatigue, peripheral neuropathy, decreased albumin, decreased hemoglobin, alopecia, decreased appetite, decreased neutrophils, decreased sodium, increased alanine aminotransferase, decreased phosphate, diarrhea, nausea, pruritus, increased urate, dry eye, dysgeusia, constipation, increased lipase, decreased weight, decreased platelets, abdominal pain, dry skin.

The data described in the following section reflects exposure to PADCEV in combination with pembrolizumab from EV-302 and the dose escalation cohort, Cohort A and Cohort K of EV-103. Patients received PADCEV 1.25 mg/kg in combination with pembrolizumab until disease progression or unacceptable toxicity.

The data described in the following section also reflects exposure to PADCEV as a single agent from an open-label, randomized, trial (EV-301) and Cohort 1 and Cohort 2 of an open-label, single arm, two cohort trial (EV-201). Patients received PADCEV 1.25 mg/kg until disease progression or unacceptable toxicity.

Previously Untreated Locally Advanced or Metastatic Urothelial Cancer

EV-302

The safety of PADCEV in combination with pembrolizumab was evaluated in an open-label, randomized, multicenter trial (EV-302) in patients with locally advanced or metastatic urothelial cancer. Patients received either PADCEV 1.25 mg/kg and pembrolizumab (n=440) or gemcitabine and platinum chemotherapy (either cisplatin or carboplatin) (n=433). Among patients who received PADCEV and pembrolizumab, the median duration of exposure for PADCEV was 7 months (range: 0.3 to 31.9 months).

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab. The most common serious adverse reactions (≥2%) were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%).

Fatal adverse reactions occurred in 3.9% of patients treated with PADCEV in combination with pembrolizumab including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%).

Adverse reactions leading to discontinuation of PADCEV occurred in 35% of patients. The most common adverse reactions (≥2%) leading to discontinuation of PADCEV were peripheral neuropathy (15%), rash (4.1%) and pneumonitis/ILD (2.3%).

Adverse reactions leading to dose interruption of PADCEV occurred in 73% of patients. The most common adverse reactions (≥2%) leading to dose interruption of PADCEV were peripheral neuropathy (22%), rash (16%), COVID-19 (10%), diarrhea (5%), pneumonitis/ILD (4.8%), fatigue (3.9%), hyperglycemia (3.6%), increased alanine aminotransferase (3%) and pruritus (2.5%).

Adverse reactions leading to dose reduction of PADCEV occurred in 42% of patients. The most common adverse reactions (≥2%) leading to dose reduction of PADCEV were rash (16%), peripheral neuropathy (13%) and fatigue (2.7%).

Table 3 summarizes the most common (≥15%) adverse reactions in EV-302.

Table 3. Adverse Reactions ≥15% (All Grades) in Patients Treated with PADCEV in Combination with Pembrolizumab in EV-302

Adverse Reaction	PADCEV in combination with pembrolizumab n=440		Chemotherapy n=433	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash[1]	68	15	15	0
Pruritus	41	1.1	7	0
Alopecia	35	0.5	8	0.2
Dry skin	17	0.2	1	0
General disorders and administration site conditions				
Fatigue[1]	51	6	57	7
Pyrexia	18	0.7	16	1.2
Nervous system disorders				
Peripheral neuropathy[1]	67	8	14	0
Dysgeusia	21	0	9	0
Metabolism and nutrition disorders				
Decreased appetite	33	1.8	26	1.8
Gastrointestinal disorders				
Diarrhea	38	4.5	16	1.4
Nausea	26	1.6	41	2.8
Constipation	26	0	34	0.7
Investigations				
Decreased weight	33	3.6	9	0.2
Eye disorders				
Dry eye[1]	24	0	2.1	0
Infections and infestations				
Urinary tract infection	21	5	19	8

1. Includes: multiple terms

Clinically relevant adverse reactions (<15%) include vomiting (12%), pneumonitis/ILD (10%), hypothyroidism (10%), blurred vision (6%), infusion site extravasation (2%) and myositis (0.5%).

Previously Untreated Cisplatin Ineligible Patients with Locally Advanced or Metastatic Urothelial Cancer

EV-103

The safety of PADCEV was evaluated in combination with pembrolizumab in a multi cohort trial (EV-103) in 121 patients with locally advanced or metastatic urothelial cancer who were not eligible for cisplatin-containing chemotherapy and received at least one dose of PADCEV 1.25 mg/kg and pembrolizumab. The median duration of exposure to PADCEV was 7 months (range: 0.6 to 33 months).

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab. The most common serious adverse reactions (≥2%) were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), sepsis (3.3%), pneumonia (3.3%), hematuria (3.3%), pneumonitis/ILD (3.3%), urinary retention (2.5%), diarrhea (2.5%), myasthenia gravis (2.5%), myositis (2.5%), anemia (2.5%), and hypotension (2.5%).

Fatal adverse reactions occurred in 5% of patients treated with PADCEV in combination with pembrolizumab including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis/ILD (0.8%).

Adverse reactions leading to discontinuation of PADCEV occurred in 36% of patients. The most common adverse reactions (≥2%) leading to discontinuation of PADCEV were peripheral neuropathy (20%) and rash (6%).

Adverse reactions leading to dose interruption of PADCEV occurred in 69% of patients. The most common adverse reactions (≥2%) leading to dose interruption of PADCEV were peripheral neuropathy (18%), rash (12%), increased lipase (6%), pneumonitis/ILD (6%), diarrhea (4.1%), acute kidney injury (3.3%), increased alanine aminotransferase (3.3%), fatigue (3.3%), neutropenia (3.3%), urinary tract infection (3.3%), increased amylase (2.5%), anemia (2.5%), COVID-19 (2.5%), hyperglycemia (2.5%), and hypotension (2.5%).

Adverse reactions leading to dose reduction of PADCEV occurred in 45% of patients. The most common adverse reactions (≥2%) leading to dose reduction of PADCEV were peripheral neuropathy (17%), rash (12%), fatigue (5%), neutropenia (5%), and diarrhea (4.1%).

Table 4 summarizes the most common (≥20%) adverse reactions in EV-103.

Table 4. Adverse Reactions ≥20% (All Grades) in Patients Treated with PADCEV in Combination with Pembrolizumab in EV-103

Adverse Reaction	PADCEV in combination with pembrolizumab n=121	
	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders		
Rash[1]	71	21
Alopecia	52	0
Pruritus	40	3.3
Dry skin	21	0.8
Nervous system disorders		
Peripheral neuropathy[1]	65	3.3
Dysgeusia	35	0
Dizziness	23	0
General disorders and administration site conditions		
Fatigue	60	11
Peripheral edema	26	0
Investigations		
Decreased weight	48	5
Gastrointestinal disorders		
Diarrhea	45	7
Nausea	36	0.8
Constipation	27	0
Metabolism and nutrition disorders		
Decreased appetite	38	0.8
Infections and infestations		
Urinary tract infection	30	12
Eye disorders		
Dry eye	25	0
Musculoskeletal and connective tissue disorders		
Arthralgia	23	1.7

1. Includes: multiple terms

Clinically relevant adverse reactions (<20%) include vomiting (19.8%), pyrexia (18%), hypothyroidism (11%), pneumonitis/ILD (10%), myasthenia gravis (2.5%), myositis (3.3%), and infusion site extravasation (0.8%).

Previously Treated Locally Advanced or Metastatic Urothelial Cancer

EV-301

The safety of PADCEV was evaluated as a single agent in EV-301 in patients with locally advanced or metastatic urothelial cancer (n=296) who received at least one dose of PADCEV 1.25 mg/kg and who were previously treated with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy. Routine ophthalmologic exams were not conducted in EV-301. The median duration of exposure to PADCEV was 5 months (range: 0.5 to 19 months).

Serious adverse reactions occurred in 47% of patients treated with PADCEV. The most common serious adverse reactions (≥2%) were urinary tract infection, acute kidney injury (7% each) and pneumonia (5%). Fatal adverse reactions occurred in 3% of patients, including multiorgan dysfunction (1%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis/ILD and pelvic abscess (0.3% each).

Adverse reactions leading to discontinuation occurred in 17% of patients; the most common adverse reactions (≥2%) leading to discontinuation were peripheral neuropathy (5%) and rash (4%).

Adverse reactions leading to dose interruption occurred in 61% of patients; the most common adverse reactions (≥4%) leading to dose interruption were peripheral neuropathy (23%), rash (11%) and fatigue (9%).

Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions (≥2%) leading to dose reduction were peripheral neuropathy (10%), rash (8%), decreased appetite (3%) and fatigue (3%).

Table 5 summarizes the most common (≥15%) adverse reactions in EV-301.

Table 5. Adverse Reactions (≥15%) in Patients Treated with PADCEV in EV-301

Adverse Reaction	PADCEV n=296		Chemotherapy n=291	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash[1]	54	14	20	0.3
Alopecia	47	0	38	0
Pruritus	34	2	7	0
Dry skin	17	0	4	0
General disorders and administration site conditions				
Fatigue[1]	50	9	40	7

Pyrexia[1]	22	2	14	0
Nervous system disorders				
Peripheral neuropathy[1]	50	5	34	3
Dysgeusia[1]	26	0	8	0
Metabolism and nutrition disorders				
Decreased appetite	41	5	27	2
Gastrointestinal disorders				
Diarrhea[1]	35	4	23	2
Nausea	30	1	25	2
Constipation	28	1	25	2
Abdominal Pain[1]	20	1	14	3
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[1]	25	2	35	5
Eye Disorders				
Dry eye[1]	24	0.7	6	0.3
Infections and infestations				
Urinary Tract Infection[1]	17	6	13	3
Vascular disorders				
Hemorrhage[1]	17	3	13	2
Investigations				
Decreased weight	16	0.3	7	0

1. Includes: multiple terms

Clinically relevant adverse reactions (<15%) include vomiting (14%), increased aspartate aminotransferase (12%), hyperglycemia (10%), increased alanine aminotransferase (9%), pneumonitis/ILD (3%) and infusion site extravasation (0.7%).

EV-201, Cohort 2

The safety of PADCEV was evaluated as a single agent in EV-201, Cohort 2 in patients with locally advanced or metastatic urothelial cancer (n=89) who received at least one dose of PADCEV 1.25 mg/kg and had prior treatment with a PD-1 or PD-L1 inhibitor and were not eligible for cisplatin-based chemotherapy. The median duration of exposure was 5.98 months (range: 0.3 to 24.6 months).

Serious adverse reactions occurred in 39% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were pneumonia, sepsis and diarrhea (5% each). Fatal adverse reactions occurred in 8% of patients, including acute kidney injury (2.2%), metabolic acidosis, sepsis, multiorgan dysfunction, pneumonia and pneumonitis/ILD (1.1% each).

Adverse reactions leading to discontinuation occurred in 20% of patients; the most common adverse reaction (≥2%) leading to discontinuation was peripheral neuropathy (7%).

Adverse reactions leading to dose interruption occurred in 60% of patients; the most common adverse reactions (≥3%) leading to dose interruption were peripheral neuropathy (19%), rash (9%), fatigue (8%), diarrhea (5%), increased aspartate aminotransferase (3%) and hyperglycemia (3%).

Adverse reactions leading to dose reduction occurred in 49% of patients; the most common adverse reactions (≥3%) leading to dose reduction were peripheral neuropathy (19%), rash (11%) and fatigue (7%).

Table 6 summarizes the All Grades and Grades 3-4 adverse reactions reported in patients in EV-201, Cohort 2.

Table 6. Adverse Reactions ≥15% (All Grades) or ≥5% (Grades 3-4) in Patients Treated with PADCEV in EV-201, Cohort 2

	PADCEV n=89	
Adverse Reaction	**All Grades (%)**	**Grades 3-4 (%)**
Skin and subcutaneous tissue disorders		
Rash[1]	66	17
Alopecia	53	0
Pruritus	35	3
Dry skin	19	1
Nervous system disorders		
Peripheral neuropathy[1]	58	8
Dysgeusia[1]	29	0
General disorders and administration site conditions		
Fatigue[1]	48	11
Metabolism and nutrition disorders		
Decreased appetite	40	6
Hyperglycemia	16	9
Gastrointestinal disorders		
Diarrhea[1]	36	8
Nausea	30	1
Investigations		
Decreased weight	35	1
Eye disorders		
Dry eye[1]	30	0

1. Includes: multiple terms

Clinically relevant adverse reactions (<15%) include vomiting (13%), increased aspartate aminotransferase (12%), increased lipase (11%), increased alanine aminotransferase (10%), pneumonitis/ILD (4%) and infusion site extravasation (1%).

DRUG INTERACTIONS

Effects of Other Drugs on PADCEV

Dual P-gp and Strong CYP3A4 Inhibitors

Concomitant use with dual P-gp and strong CYP3A4 inhibitors may increase unconjugated monomethyl auristatin E (MMAE) exposure, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with dual P-gp and strong CYP3A4 inhibitors.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. There are no available human data on PADCEV use in pregnant women to inform a drug-associated risk. In an animal reproduction study, administration of enfortumab vedotin-ejfv to pregnant rats during organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures similar to the exposures at the recommended human dose of 1.25 mg/kg. Advise patients of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Lactation

Risk Summary

There are no data on the presence of enfortumab vedotin-ejfv in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with PADCEV and for 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating PADCEV treatment.

Contraception

Females

PADCEV can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

Infertility

Females

Based on findings in animal studies with MMAE-containing antibody-drug conjugates (ADCs), PADCEV may impair female fertility. The effect on fertility is reversible.

Males

Based on findings from animal studies, PADCEV may impair male fertility.

Pediatric Use

Safety and effectiveness of PADCEV in pediatric patients have not been established.

Geriatric Use

Of the 564 patients treated with PADCEV in combination with pembrolizumab, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. Of the 720 patients treated with PADCEV as a single agent in clinical trials, 39% (n=282) were 65-74 years and 24% (n=170) were 75 years or older. No overall differences in effectiveness were observed between patients 65 years of age or older and younger patients.

Patients 75 years of age or older treated with PADCEV in combination with pembrolizumab experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 4% in patients younger than 75 and 7% in patients 75 years or older.

Patients 75 years of age or older treated with PADCEV as a single agent experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 6% in patients younger than 75 years, and 11% in patients 75 years or older.

No significant difference was observed in the pharmacokinetics of PADCEV between patients 65 years and older and younger patients.

Hepatic Impairment

Avoid the use of PADCEV in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and AST any). PADCEV has only been studied in a limited number of patients with moderate hepatic impairment (n=3) and has not been evaluated in patients with severe hepatic impairment. In another ADC that contains MMAE, the frequency of ≥ Grade 3 adverse reactions and deaths was greater in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment compared to patients with normal hepatic function.

CLINICAL PHARMACOLOGY

Immunogenicity

The observed incidence of anti-drug antibody (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of PADCEV or of other enfortumab vedotin products.

In the 0.3-to-55.7-month treatment periods with ADA sampling in eight clinical studies of PADCEV 1.25 mg/kg as a single agent on Days 1, 8 and 15 of a 28-day cycle and in combination with pembrolizumab on Days 1 and 8 of a 21-day cycle in patients with locally advanced or metastatic urothelial cancer, the incidence of anti-enfortumab vedotin-ejfv antibody formation was 3.6% (22 of 617 patients who were tested for ADA) for PADCEV as a single agent and 3.0% (14 of 466 patients who were tested for ADA) for PADCEV in combination with pembrolizumab.

Because of the low occurrence of ADA, the effect of the ADA on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of PADCEV is unknown.

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ONCOLOGY INSTITUTE BRINGS TOGETHER MIP LEADERS AND INDUSTRY PARTNERS

NCODA's annual **Oncology Institute**, now in its sixth year, continues to move forward, bringing together medically integrated oncology practices, industry partners and NCODA leaders with the goal of fostering stronger collaboration between all stakeholders.

More than 200 representatives from more than 65 industry partners and healthcare practices participated this year's August 20-21 Institute in Boston.

Entitled **Partners in Progress: Delivering Equitable Care through Partnership with Industry & the Oncology Community**, the Institute offered presentations on clinical trial engagement, distribution, care delivery, patient services and support, and social determinants of health data.

Participants had the opportunity to:

- Learn how the industry can best engage with providers to drive equitable outcomes for patients;
- Engage with key stakeholders dedicated to enhancing the patient experience from diagnosis to survivorship;
- Showcase how their organization is partnering to drive equitable care delivery;
- Join pivotal conversations about patient-centric services and support systems;
- Partner in discussions to shape the future of oncology drug distribution focused on patient access to innovative treatments; and
- Contribute to the advancement of provider and patient education in oncology.

Each presentation featured a panel of experts speaking on a wide variety of challenges. For example, panelists on the distribution panel include Bill Karnes, Director of National Physician Networks & Strategic Partners for BeiGene, Jason Noto, MBA, Senior Vice President of Market Access at AVEO Oncology, Kathy Oubre, MS, Chief Executive Officer at Pontchartrain Cancer Center, and Christie Smith, PharmD, MBA, Vice President Pharmacy & Payer Strategy at Cencora.

Panelists compared and contrasted the advantages for patients navigating medically integrated pharmacies versus specialty pharmacies, among other issues.

"The most significant callout I will make is the time to start therapy," Smith said. "When the doctor ... writes the prescription, he can send the patient home with the prescription that same day, after diagnosis if the prior authorization is in place. For a cancer patient, that means a lot."

Oubre emphasized the same point. "Sometimes we have it same day ... but usually you're looking at 24 to 48 hours," she said. "Whereas if we have to send it out to a specialty pharmacy — and we've kept all of these data points for years at our organization — you're looking at about five to 15 business days of a delay ... with outliers of 20 to 30 days."

Karnes noted that BeiGene looked at how patients could best be served when setting up its distribution network.

"Independent pharmacies are doing higher-touch models and that's having an impact," he explained. "So, the disease state we're in is more chronic than acute. We're seeing a difference in outcomes, so we're able to invest in that type of practice."

HEALTH EQUITY STEERING COMMITTEE UNVEILED AT OI

A highlight of this year's NCODA Oncology Institute was the formation of the **Health Equity Steering Committee**.

The committee, comprised of leaders from across the United States, was created to provide ideas for more equitable patient access to oncology care. The 14-member committee includes:

- **Sam Abdelghany**, PharmD, MHA, BCOP, Executive Director of Oncology Pharmacy Services, Smilow Cancer Hospital, Yale New Haven Health;
- **Craig Cole**, MD, Medical Oncologist & Assistant Professor, Michigan State University and the College of Lyman Briggs;
- **James Gilmore**, PharmD, Chief Pharmacy & Clinical Services Officer, American Oncology Network;
- **Sybil Green**, JD, RPh, MHA, Vice President & Chief Equity, Diversity & Inclusion Officer, American Society of Clinical Oncology;
- **Sharita Howe**, PharmD, Associate Director of Partner Development & Strategy, NCODA;
- **Dina Dumercy McHenry**, PharmD, MBA, BCOP, CSSGB, Director of Pharmacy Services, Miami Cancer Institute, Baptist Health South Florida;
- **Stacey McCullough**, PharmD, Chief Pharmacy Officer, NCODA;
- **Benyam Muluneh**, PharmD, BCOP, FHOPA, Assistant Professor, UNC Eshelman School of Pharmacy;
- **Kathy Oubre**, MS, Chief Executive Officer, Pontchartrain Cancer Center;
- **Sucharu Prakash**, MD, Director of Quality Services, Texas Oncology;
- **Nicole Radford**, FACHE, MS, MT(ASCP), Vice President, Laboratory Services, Florida Cancer Specialists & Research Institute;
- **Luis Raez**, MD, Medical Director & Chief Scientific Officer, Memorial Cancer Institute;
- **Michael Reff**, RPh, MBA, Executive Director & Founder, NCODA; and
- **Bhavesh Shah**, RPh, BCOP, Vice President & Chief Pharmacy Officer, Boston Medical Center.

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NEW-START ADHERENCE BARRIERS ASSESSMENT AND DOCUMENTATION TEMPLATE FOR ONCOLOGY NURSES

By Elizabeth Bettencourt, MSN, RN, OCN, & Dawn Landolph, BSN, RN, MPA, OCN

NCODA NURSING COMMUNITY SUPPORTS THE MEDICALLY INTEGRATED TEAM IN CARING FOR OAM PATIENTS

"NCODA empowers oncology nurses around the world with tools and resources that help provide better patient care and advance the value of the oncology nurse's role in all practices."

This statement, found on the NCODA Nursing Community webpage, supports the mission of this community to provide ongoing support, and tools and resources to aid oncology nurses in positively impacting patient outcomes.

The NCODA Nursing Community is more than 1,200 oncology nurses strong, coming from a variety of backgrounds and experiences, including advanced practice nurses, oncology-certified nurses, oncology clinic and research-based nurses, and specialty pharmacy oncology nurses.

This active community meets regularly and is comprised of four subcommittees, one of which is dedicated to developing relevant tools and resources for oncology nurses to utilize in their daily practice.

As the oncology treatment landscape continues to evolve with multiple treatment modalities, including oral anticancer agents, the NCODA Nursing Community recognizes the need to support nurses and the entire medically integrated team caring for patients taking oral anticancer medications.

Oral anticancer medication offers advantages over infusion therapies for patients in terms of flexibility in schedule, lifestyle, family, work and travel. However, patients face challenges with adherence to complex treatment regimens that require them to follow strict dosing, administration and monitoring guidelines.

Positive patient outcomes are significantly impacted by oral medication adherence.

Assessing patient barriers to adherence prior to initiating oral anticancer medication (OAM) therapy and intervening early to ensure patients are set up for success is paramount to supporting the best treatment outcome.

Oncology nurses in the clinic are able to have face-to-face interactions with patients at the time an OAM is prescribed to complete this assessment. Following the steps of the nursing process, oncology nurses individualize interventions for each patient through the assessment of the individual patient's learning needs, potential barriers to adherence and the complexity of the required treatment regimen.

Elizabeth Bettencourt

Dawn Landolph

In the recently published Oncology Nursing Society's (ONS) Guidelines to Support Patient Adherence to Oral Anticancer Medications, the expert panel suggests that an adherence risk/barriers assessment is completed for patients starting a new OAM.[1]

The ONS Oral Anticancer Medication Toolkit identifies key areas to assess patients for readiness to start an OAM: physical, lifestyle, financial, treatment and social factors.[2]

A holistic nursing assessment may include determination of the patient's ability to open packaging or swallow their medication, social support in medication administration, availability of transportation and food, ability to refill prescriptions and the ability to communicate with the pharmacy and oncology care team.

Based on this information, the nurse formulates an individualized care plan that addresses identified barriers to medication procurement and patient adherence and outlines a plan that details the frequency of future patient outreach.

The NCODA Nursing Community identified an opportunity to develop a comprehensive barriers assessment tool and documentation template that not only identified needs but provided nurses actionable interventions to implement.

The Nursing Community's Tools and Resources Committee identified four domains in which to organize specific questions: **Patient-related**, **Social**, **Financial** and **Treatment-related** factors. The committee further delineated the categories into subcategories which ensured the social determinants of health were specifically addressed.

Each committee member was assigned a category and tasked with developing patient interview questions within that domain. Additionally, the members identified necessary patient information to be gleaned from a medical record review versus direct patient interview questions.

Each member's work was organized

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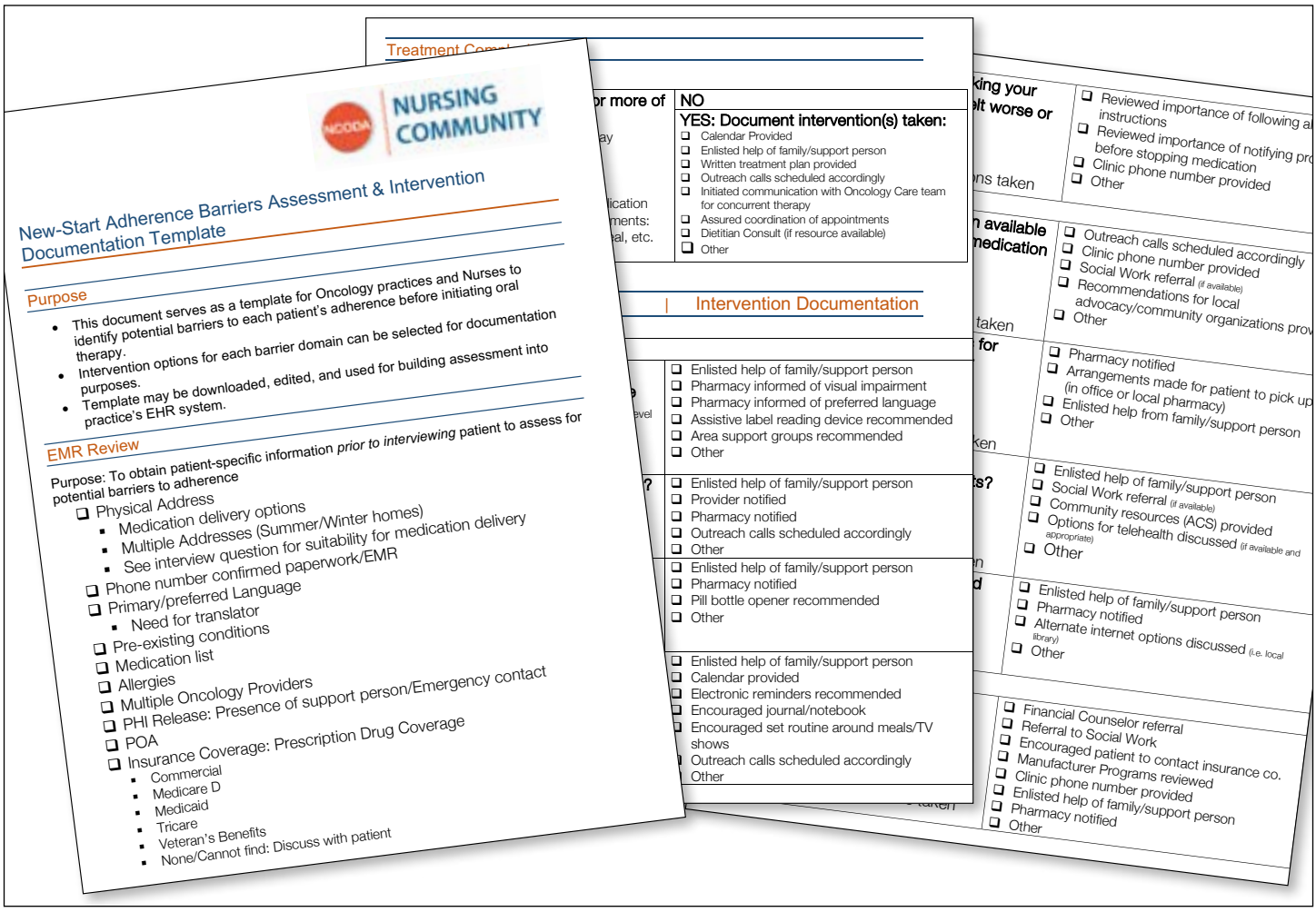

The New-Start Adherence Barriers Assessment Template is now available on the NCODA website.

NURSING TEMPLATE

CONTINUED FROM PREVIOUS PAGE

into a spreadsheet and reviewed by the team. This was the most time-consuming part of the initiative. The primary objective was to streamline the patient interview questions without impacting the quality of the assessment.

The patient interview questions were condensed to 10 core questions that could be answered as "Yes" or "No" and open dialogue for the nurse to tailor personalized interventions to each patient's needs.

The tool was then formatted into a checklist structured document that could be easily adapted into an electronic documentation flowsheet or scanned into the electronic medical record system for documentation of the completed assessment.

A final open review was completed by members of the NCODA Nursing Community resulting in the New-Start Adherence Barriers Assessment and Intervention Documentation Template.

This template, now available in the Nursing Community's Library, is accessible to all NCODA members.

The Nursing Community is pleased to provide resources that assist the entire Medically Integrated care team in delivering high-quality care to patients taking OAMs.

To access **The New-Start Adherence Barriers Assessment Template**, scan the QR code above.

▲ **Elizabeth Bettencourt**, MSN, RN, OCN, is an Oral Oncolytic Nurse Navigator at Palo Alto Medical Foundation/Sutter Health in Sunnyvale, California. **Dawn Landolph**, BSN, RN, MPA, OCN, previously worked as Associate Director of Specialty Pharmacy Nursing Services at Florida Cancer Specialists & Research Institute. Both are members of the NCODA Nursing Community Leadership Team.

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BEYOND THE FIREWALL: ENHANCING CYBERSECURITY IN ONCOLOGY CARE

The Season 7 premiere of **The PQI Podcast** focused on a critical topic that has significantly impacted the healthcare industry: the urgent need for enhanced IT security measures. In this episode, field experts Ben Harkness of Utah Cancer Specialists (UCS), and Mark Moch of American Oncology Network (AON), shared how cutting-edge cybersecurity strategies are reshaping healthcare.

Specifically, the episode looked at the cybersecurity attack earlier this year on Change Healthcare, one of the largest health payment-processing companies in the world. It acts as a clearing house for 15 billion medical claims each year — accounting for nearly 40% of all claims.

Ben Harkness

Mark Moch

PQI: Can you each tell us a little about your organization and what role you perform there?

HARKNESS: I've been with UCS about 23 years. We're a community oncology organization and have 13 locations throughout the intermountain area of Utah. I'm director of IT and facilities.

MOCH: AON has been around for nearly six years and has been rapidly growing. We're now located in 21 states with more than 30 practices in 70 locations across the country. I'm the Chief Information Officer, and one of the executive directors of Meaningful Insights Biotech Analytics, an AON informatics venture in partnership with Ascend Technologies Group.

PQI: How were your organizations affected by the Change Healthcare cyberattack?

MOCH: This was a major event on a national scale that affected anyone using Change Healthcare for claims processing and any insurance-related activities. The outage was very significant and lasted for more than a month.

An unfortunate consequence of that cybersecurity attack was that we essentially got locked out from the ability to process normal billing claims and also our ability to perform prior authorizations to make sure our patients could get their drugs in a timely manner. Obviously, this was a very significant issue for conditions like cancer.

I strongly believe that this incident was severely underplayed on a national scale. I think the media coverage was inadequate. In my mind, this was one of the biggest hacks, if not the biggest hack, in U.S. history.

HARKNESS: It really shows that the trend for cybercrime is evolving. It used to be that they would focus on credit card numbers and financial information, but the new trends are showing that it's far more lucrative for them to go after patient data, where they can get Social Security numbers and other things. I think that's really putting a spotlight on us as healthcare practices.

PQI: In high-level terms, how did your operation respond to the incident?

HARKNESS: For Utah Cancer, there wasn't a lot we could do. We were, for lack of a better word, captive to wait to see how it played out. We met as a team and tried to focus on where we could improve collections in other areas because we couldn't get money in through the Change HealthCare.

MOCH: Obviously, the impact was very significant. The second we heard what was going on, we activated our incident response team and started evaluating what kind of impact it could have across our system. With AON being a single tax ID organization, a lot of our processing and operations resources are centralized, with all claims going through a central system. This provides a lot of benefits to our practices because we can process quicker. But, all of a sudden, this came to a stop.

We started with IT questions: Was there any chance that the attack could spread over to us? Then we started focusing on the operational side. What was the impact on our patients? And how else could we help?

Because this cyberattack was out of our hands, the biggest challenge for us was to reach out to the vendors we are contracted to, and to work with clearinghouses to make sure we could create an ability to use different vendors. We were very successful early on, with an outside vendor helping us to create a simple switch that we could move from Change HealthCare to another clearinghouse and reroute all of our billing.

Operationally, the impact was pretty limited by the time we moved to the other clearinghouse. But it was very impactful to the network, especially from the business standpoint. It interrupted interaction with the cash flow process and everything that happened throughout the revenue cycle.

PQI: What kind of measures should healthcare organizations take to prevent similar attacks in the future?

HARKNESS: We were attacked about two years ago and the effect was equally devastating. It really taught us the lesson that the size of your organization doesn't matter when it comes to measures that you have to take. The things that are recommended are the same things that the regulating bodies are trying to enforce with everyone. You need to do comprehensive risk analysis. You've got to do penetration testing, you've got to do vulnerability scans, things like that. You've got to have backups, you've got to have offline, encrypted backups that you can rely on.

A big one that's often skipped over is employee training. We've really stepped up our training because so many of these attacks are employee-initiated. Because people just don't know; they'll click on whatever comes in their email a lot of times.

MOCH: I agree. No matter what kind of technology you put out there, if someone's giving away the keys to the kingdom, nothing else matters.

For listen to the entire **PQI Podcast** on the topic of cybersecurity, scan the QR code above.

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THE PQI PODCAST

The PQI Podcast, presented by NCODA, hosts clinical and administrative experts in oncology providing insight on important industry topics and how they value the Positive Quality Intervention (PQI) resource for their practice. The podcast also highlights patient stories of hope, determination, and how patient-centered care impacts the cancer journey.

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NCODA | PASSION FOR PATIENTS

ARE YOU AN ONCOLOGY PHARMACIST SEEKING BCPS CERTIFICATION? PAY ATTENTION!

By Eric Christianson, PharmD, BCPS, BCGP

The pursuit of Board-Certified Pharmacotherapy Specialist (BCPS) certification is an important avenue for pharmacists to test their skills and ensure that their clinical knowledge is still up to date.

For those seeking BCPS certification, there are significant changes in the Fall 2024 exam. The biggest shift is the content outline. The Pharmacotherapy section will expand, which is a good thing, in my opinion. I prefer to be tested on drug selection and the appropriate use of medications.

Eric Christianson

The topic areas for pharmacotherapy are better defined. This is a key difference from previous content outlines. In the list below, the "A" topics will get the greatest emphasis on the upcoming exam:

- **A1 Infectious Diseases**
- **A2 Cardiology**
- **A3 Nephrology**
- **A4 Pain Management**
- **A5 Endocrinology**
- **B1 Critical Care**
- **B2 Geriatrics**
- **B3 Pulmonology**
- **B4 Neurology**
- **B5 Emergency Medicine and Toxicology**
- **B6 Gastroenterology**
- **B7 Psychiatry and Mental Health**
- **C1 Oncology and Hematology**
- **C2 Nutrition Support**
- **C3 Women's Health (e.g., gynecology, obstetrics)**
- **C4 Hospice and Palliative Care**
- **C5 Pediatrics**
- **C6 Allergy, Immunology and Rheumatology**
- **C7 Urology**

While the **Statistics and Associated Topics** section no longer appears on the exam, do NOT rejoice. There still will be a significant number of questions — I anticipate 10 to12 — that will be "gettable" if you know statistics. These can make or break your exam and will be a nice bonus for anyone who prepares for them.

FEWER QUESTIONS

Another change to the BCPS is in the number of questions. The total number will drop from 175 to 150.

I'm a little old-school in that I would rather have more questions than fewer, especially if I feel like I have adequately prepared. But 150 is still a fairly big number and you will have some wiggle room to get some of the questions incorrect.

Don't get too frazzled about getting a few questions wrong. Twenty-five of the 150 are NOT graded. Keep your cool during the exam and recognize that you may be getting the non-graded questions wrong.

Note that there will be less time to take the exam — three hours and 45 minutes, down from the four hours and 23 minutes previously allowed.

It will be critical to pace yourself if you have historically been a moderate-to-slow test taker. Practice questions are the best way to assess the length of time it takes you to complete questions.

CONTINUING EDUCATION (CE) REQUIREMENTS

The CE requirements for recertification will go to 80 units of BPS-approved CE. These CE credits can be purchased only through the American College of Clinical Pharmacy (ACCP) and the American Society of Health-System Pharmacists (ASHP).

In addition, 20 units of self-reported CE must be completed (not a big deal since most states require the units).

The other way to recertify is to take a shortened BCPS exam. If you want to recertify via examination, you do NOT have to purchase and obtain the 80 CE credits through ACCP or ASHP or keep track of the CE over the certification period. The 20 units of self-reported CE are required. The recertification exam is shorter in length and has only 100 questions compared to the original exam of 150 questions.

CONTINUOUS TESTING IS NEW

In the future, pharmacists will have more options on when they can take the BCPS exam. In the past, testing was permitted only in April and September. Moving forward, pharmacists will be able to continuously test throughout the year.

This is an awesome change and should make it easier for candidates to plan their schedule better and take it at a time of the year when they are best prepared.

I hope this information helps you prepare for your BCPS exam in 2024 and 2025!

Eric Christianson, PharmD, BCPS, BCGP, is the Founder of Meded101.com, a website dedicated to the clinical education and training of pharmacists and students. His podcast, Real Life Pharmacology, has reached millions of healthcare professionals. For more information, contact mededucation101@gmail.com.

WHAT IS A PNET?

THERE'S A WORLD OF DIFFERENCE BETWEEN PANCREATIC NEUROENDOCRINE TUMORS & PANCREATIC ADENOCARCINOMA

By Nancy Augustine, PharmD, CSP

In the world of clinical oncology, losing a patient is inevitable, and it never gets easier.

When one hears pancreatic cancer, we automatically think of pancreatic adenocarcinoma, which is very different from pancreatic neuroendocrine tumors (PNETs).

Nancy Augustine

I remember losing a patient to a PNET that went undiagnosed and then spread. It is an unfortunate scenario and incredibly sad as well.

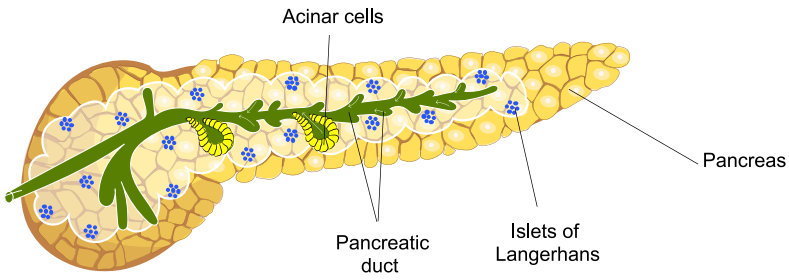
There are many differences in these cancers as seen in **TABLE 1**.

The signs/symptoms for both pancreatic adenocarcinomas and PNETs also can vary as seen on the following page in **CHART 1**, **CHART 2** and **FIGURE 2**.

Among the nine most common symptoms, adenocarcinoma and PNET overlap in the four manifestations of diarrhea, nausea, weight loss and abdominal pain (**FIGURE 2**).

FIGURE 1: PARTS OF THE PANCREAS

The pancreas consists of a wide end called the head (includes neck and uncinate process), a middle part called the body, and a narrow end called the tail.



PNET VARIANTS

MEN1: These variants lead to multiple endocrine neoplasia type 1 (MEN1).

▲ People with this condition can develop a range of tumors like gastronoma or insulinoma, which are types of PNETs.

▲ People with MEN1 also have higher risk for other NETs, including GI and lung neuroendocrine tumors.

VHL: These variants cause von Hippel-Lindau syndrome.

▲ Fewer than one in five people with this will develop a PNET, usually one that doesn't release hormones.

▲ People with VHL may also develop another type of NET called pheochromocytoma.

DIAGNOSIS OF PNET[4,5]

Blood and urine tests can be used to help diagnose PNET:[5]

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TABLE 1: DIFFERENCES BETWEEN PANCREATIC ADENOCARCINOMA & PANCREATIC NEUROENDOCRINE TUMORS[1,2]

	CELL TYPES	PREVALENCE	OUTLOOK
Pancreatic adenocarcinoma	Develops in exocrine cells, which release digestive enzymes	Most common type of pancreatic cancer	Fast-moving disease
Pancreatic neuroendocrine tumors	Forms in endocrine cells, which release hormones – these cells sit in clusters called islets, which is why these tumors are also called islet cell tumors	PNETs are rare, making up only 5%-10% of pancreatic tumors	PNETs grow slowly in most cases

PNET

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▲ Hormones made by different types of PNET cells, such as insulin, gastrin, glucagon, somatostatin, pancreatic polypeptide, and vasoactive intestinal peptide (VIP);

▲ Chromogranin A (CgA); and

▲ Glucose and C-peptide (for insulinomas).

A PNET is either functional (produces hormones) or, more commonly, nonfunctional (does not produce hormones).[4] There are four types of functional PNETs:[4]

1. Gastrinoma

▲ This tumor makes too much gastrin.

▲ Gastrin is a hormone that causes acid production in the stomach.

▲ Too much stomach acid can cause severe ulcers (Zollinger-Ellison syndrome).

2. Glucagonoma

▲ This tumor makes too much glucagon.

▲ Glucagon is a hormone that increases glucose (sugar) levels in the blood.

▲ Too much blood glucose can cause hyperglycemia.

3. Insulinoma

▲ This tumor makes too much insulin.

▲ This can rapidly lower blood sugar (hypoglycemia).

▲ Insulinomas are usually noncancerous.

4. VIPoma

▲ This tumor starts in the cells of the pancreas that make vasoactive intestinal peptide (VIP).

▲ VIP is a hormone that helps move water into the intestines.

▲ Too much VIP can cause chronic, watery diarrhea (Verner-Morrison syndrome).

TREATMENT

Treatment for PNETs is based on:[4]

1. Location

▲ Whether cancer is found in one or multiple areas of the pancreas.

▲ Whether it is in the tail or head of the pancreas (more complicated surgery to remove).

2. Metastases

▲ Whether cancer has spread to lymph nodes or other parts of the body: liver, lung, peritoneum or bone.

Standard treatment for PNETs includes:[4]

▲ Surgery;

▲ Duodenotomy;

▲ Pancreatoduodenectomy;

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CHART 1: TOP NINE SIGNS/SYMPTOMS FOR PANCREATIC ADENOCARCINOMAS[3]

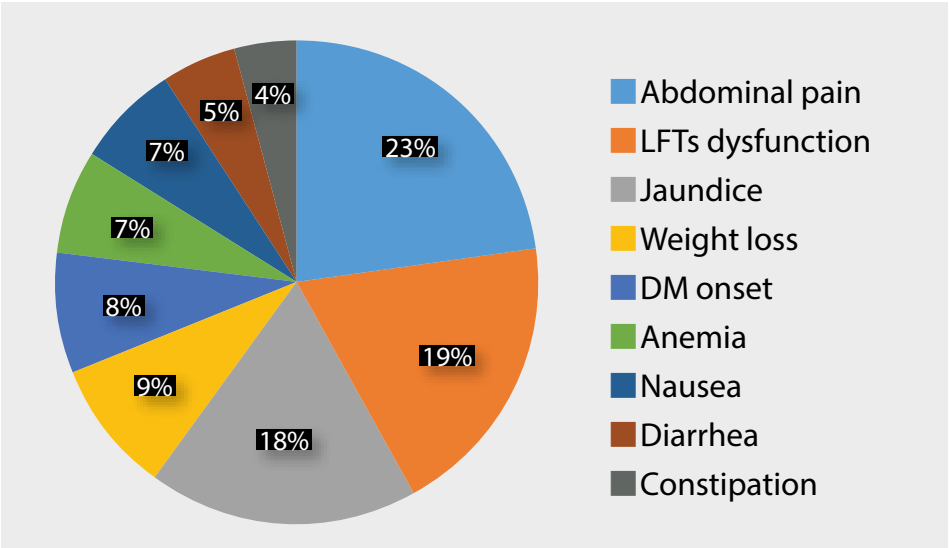


CHART 2: TOP NINE SIGNS/SYMPTOMS FOR PNETS[3]

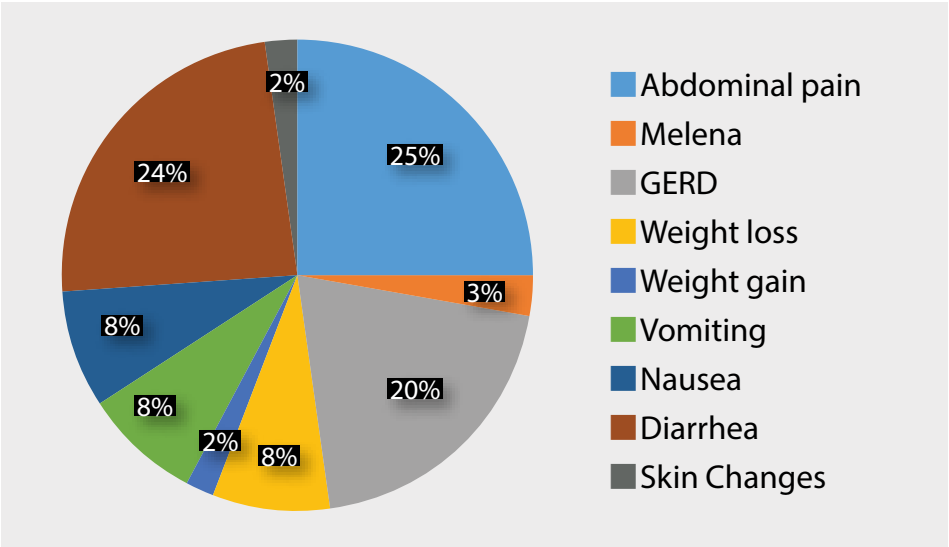
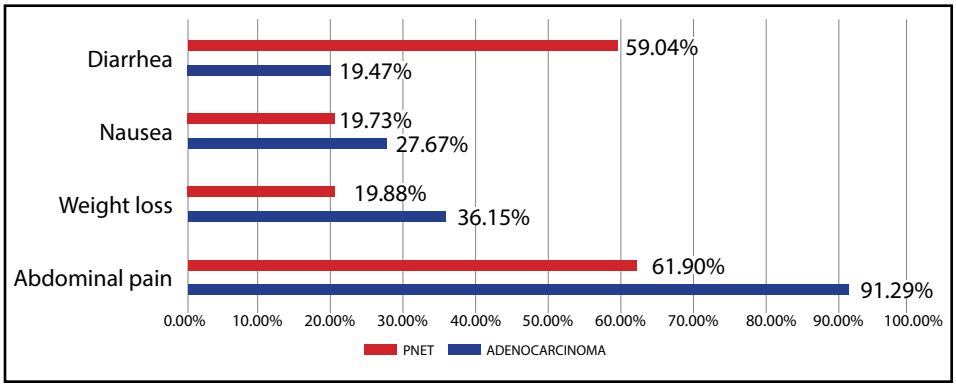


FIGURE 2: TOP NINE MOST COMMON MANIFESTATIONS[3]



PNET

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- Pancreatectomy (distal or total);
- Peripancreatic lymphadenectomy;
- Splenectomy;
- Chemotherapy;
- Hormone therapy;
- Targeted therapy; and
- Supportive care.

Nonfunctioning pancreatic tumors are caused by abnormal growth and reproduction of neuroendocrine cells in the pancreas. Nonfunctioning PNETs often do not show any symptoms related to hormones.[4] Some symptoms include:[4]

- Abdominal pain;
- Nausea;
- Weight loss; and
- Jaundice (yellowing of the skin.)

TESTING

Recommended testing for nonfunctioning PNETs:[4]

- Abdominal with or without pelvis multiphase CT or MRI;

Additional testing may include:[4]

- Somatostatin receptor positron emission tomography CT scan (SSTR-PET/CT) or MRI scan (SSTR-PET/MRI);
- Chest CT with or without contrast;
- Endoscopic ultrasound (EUS);
- Biochemical tests; and
- Genetic counseling and testing for inherited genetic conditions.

Treatment for nonfunctioning PNETs is broken up by locoregional disease and metastatic disease.[4]

Surveillance tests are done at specific times after treatment to check for any cancer recurrence. Surveillance tests can include general health tests such as a medical history and a physical exam, and imaging tests. See **TABLE 2**.[4]

For patients with advanced disease, or metastatic disease (cancer that has spread from primary tumor site to a distant part of the body), treatment options for metastatic disease are based on tumor burden and whether the tumor could be removed by surgery.[4] Testing may include:[4]

TABLE 2: PNETS: SURVEILLANCE TESTS[4]

TIME SINCE RESECTION	TESTS AS NEEDED
12 weeks to 12 months	• General health tests • Biochemical tests • Abdominal multiphase CT or MRI • Chest CT with or without contrast
One year to 10 years (every six to 12 months)	• General health tests • Biochemical tests • Abdominal multiphase CT or MRI • Chest CT with or without contrast
More than 10 years	• Surveillance as needed

- Abdominal with or without pelvic multiphase CT or MRI and chest CT with or without contrast;
- SSTR-PET/CT or SSTR-PET/MRI;
- Biochemical tests; and
- Tumor classification and grade.

For patients with asymptomatic, low tumor burden and stable disease:[4]

- Observe with biochemical tests or abdominal/pelvic multiphase CT or MRI every 12 weeks to 12 months and chest CT with or without contrast (as needed).
- Can consider octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot).

For patients with symptomatic or significant tumor burden or significant progressive disease:[4]

- Manage symptoms.
- Alternative front-line therapy may be given.
- For disease progression, may treat with octreotide LAR (Sandostatin, Bynfezia Pen) or lanreotide (Somatuline Depot).

Overall, PNETs vary from pancreatic adenocarcinomas, and there are many

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TABLE 3: PNETS — DISEASE PROGRESSION AND ALTERNATE FRONT-LINE TREATMENTS[4]

Clinical Trial
Everolimus (Afinitor®)
Sunitinib (Sutent®)
Temozolomide (Temodar®) and Capecitabine (Xeloda®)
PRRT with 177Lu-dotatate, if SSTR-positive and progression on octreotide LAR or lanreotide
Other cytotoxic chemotherapy
Belzutifan (Welireg™) in the setting of gremlin VHL (von Hippel-Landau) alteration
Liver-directed therapy for liver-predominant disease
Palliative RT for symptomatic bone metastases

PNET

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different factors to consider regarding diagnosis and treatment. If patients are experiencing symptoms without any definitive diagnosis, considering a differential diagnosis to get to the root cause of the symptoms is a great option.

Listening to the patient is the key to getting answers and figuring out what is going on with them clinically to further help with treatment.

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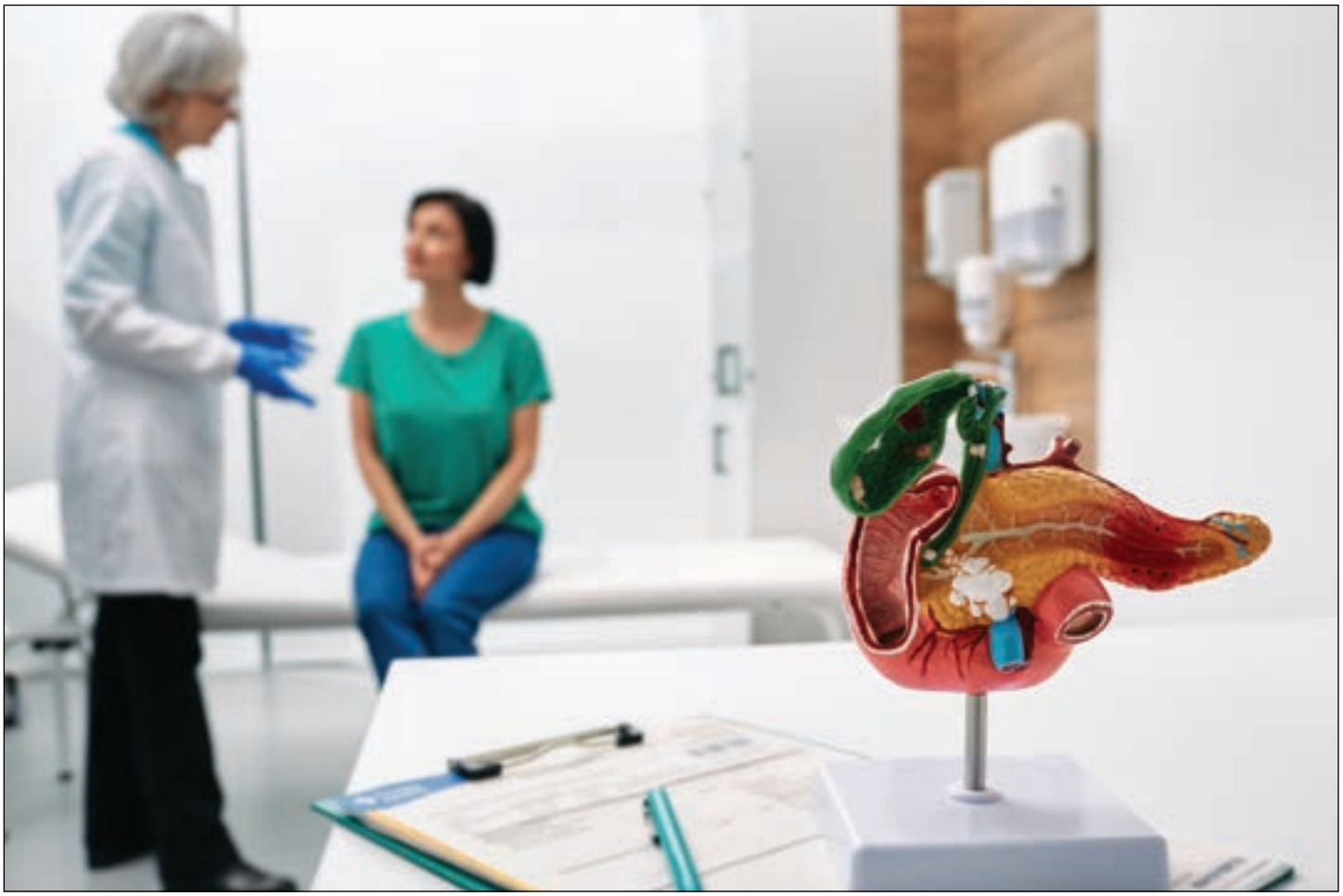
If patients are experiencing symptoms without any definitive diagnosis, considering a differential diagnosis to get to the root cause of the symptoms is a great option. Listening to the patient is the key to getting answers and figuring out what is going on with them clinically to further help with treatment.



TREATING METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

A REVIEW OF NOVEL COMBINATIONS OF PARP & ANDROGEN RECEPTOR SIGNALING INHIBITORS

By Andrew Ruplin, PharmD

Prostate cancer is the most common cancer in males in the United States.[1] An estimated almost 300,000 new cases will be diagnosed in 2024, and prostate cancer remains the second most common cause of cancer death in males after lung cancer.[1]

The overall incidence of prostate cancer declined steadily between 2007 and 2014 but has slowly increased since then at a rate of 3% annually, driven by an increase in the diagnosis of regional and metastatic disease.[2]

Despite being the second most common cause of cancer death in males, prostate cancer has an overall five-year survival rate of 97%.[3] Patients with regional or localized cancer have a greater than 99% five-year survival rate, but unfortunately, only about 36% of patients with distant metastases will be alive at five years.[3]

Andrew Ruplin

Treatment options for prostate cancer vary widely depending on the stage, characteristics, expected survival and individual patients' wishes. These include observation, active surveillance, surgery, radiation or systemic therapy.[4]

Patients with metastatic prostate cancer should be offered systemic therapy, which is also diverse in mechanisms and encompasses androgen deprivation therapy (ADT) such as luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, androgen receptor signaling inhibitors (ARSis), radioligands, traditional cytotoxic chemotherapy, cellular immunotherapy and small-molecule targeted inhibitors.[4]

Although ADT is currently the backbone of treatment for metastatic prostate cancer, resistance to ADT and classification of a patient's disease as castration-resistant prostate cancer (CRPC) are crucial developments in any patient with prostate cancer.[5] The

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transformation to metastatic castration-resistant prostate cancer (mCRPC) portends a poorer prognosis and overall survival.[6]

Poly (ADP-ribose) polymerase (PARP) inhibitors are among the more recently FDA-approved novel therapies for mCRPC. They induce synthetic lethality through inhibition of the DNA-repairing PARP enzymes, primarily PARP1 and PARP2, in persons with homologous recombination repair (HRR) mechanism deficient phenotypes.[7,8]

Breast cancer gene 1 (BRCA1) and 2 (BRCA2)-deficient cells were the first to be identified and studied as targets for PARP inhibition as a cancer-killing mechanism, but additional genes such as CHEK1, ATM, FANCA, CDK12, PALB2, RAD51D and others have been studied. These genes occur in up to 30% of patients with metastatic prostate cancer.[9] This frequency of homologous recombination repair gene alterations (HRRm) in prostate cancer made PARP inhibitors an attractive drug class for investigation.

In May 2020, rucaparib and olaparib were approved for treatment of mCRPC with appropriate HRRm. Since then, research has focused on combining PARP inhibitors with other anticancer mechanisms. As a result, three combinations of PARP inhibitors and anti-androgen therapies are now approved for mCRPC. This review will discuss and compare the use and role of these combinations to treat mCRPC.

PARP INHIBITORS: CLASS CONSIDERATIONS

Two PARP inhibitors are currently approved as monotherapy for treatment of prostate cancer: olaparib and rucaparib. These approvals as monotherapy predate the newer combinations discussed in this review.

Clinicians should be conscientious when selecting a PARP inhibitor as monotherapy or in combination based on patients' individual characteristics, including approved or studied HRR gene alterations and tolerance for expected side effects, as these differ among the PARP inhibitors.

Clinicians should be conscientious when selecting a PARP inhibitor as monotherapy or in combination based on patients' individual characteristics, including approved or studied HRR gene alterations and tolerance for expected side effects, as these differ among the PARP inhibitors.

PARP inhibitors have several adverse effects consistent among the class that are relevant for monotherapy and all three approved PARP inhibitor/anti-androgen combinations.[10-12]

Hematologic toxicity can occur with decreases seen to neutrophils, erythrocytes and platelets.[13-15] For this reason, PARP inhibitors and their combinations require laboratory testing periodically to identify myelosuppression that may warrant treatment interruption.

All PARP inhibitors' prescribing information packets carry a warning for potential development of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML).[13-15] MDS/AML has been reported in patients treated for ovarian cancer, breast cancer, prostate cancer, and others.[16] There is discussion about what predisposing or potentially causative factors exist, such as prior DNA-damaging treatment with chemotherapy or radiation, but for now, all patients considered for treatment with PARP inhibitor should be counseled on the risk.[16]

Patients who develop hematologic toxicity should be evaluated by a hematologist if adequate recovery of cell counts does not occur in a reasonable time frame after stopping treatment, such as four weeks.[14]

Nausea and diarrhea can occur with any PARP inhibitor, and transient increases to serum creatinine and liver function tests (especially aminotransferases) have been seen.[17,18]

NIRAPARIB & ABIRATERONE ACETATE (AKEEGA™)

Niraparib and abiraterone acetate is a combination of the PARP inhibitor niraparib and Cytochrome P450 17 (CYP17) inhibitor abiraterone acetate. It was approved in 2023 for treatment of mCRPC with deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC until disease progression or unacceptable toxicity.[13]

This approval is based on positive radiographic progression-free survival (rPFS) and overall survival (OS) results from cohort 1 of the randomized, double-blind, placebo-controlled, phase 3 MAGNITUDE trial comparing niraparib and abiraterone plus prednisone to abiraterone plus prednisone plus placebo in patients with mCRPC and no prior systemic treatment in this setting.[12]

Systemic therapy was allowed in earlier disease settings (e.g., docetaxel in castration-sensitive disease). Patients also received androgen deprivation therapy through active treatment with LHRH analogs or prior orchiectomy consistent with the standard of care for advanced prostate cancer.

Enrolled patients were prospectively screened for HRR gene alterations, including ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, or PALB2. Fifty-three percent of patients were confirmed BRCAm.[12]

A statistically significant rPFS and OS benefit was seen in the HRRm intention-to-treat cohort 1, and subgroup analyses of the BRCA-only and non-BRCA HRRm patients and analysis of patients in cohort 2 comprised of

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patients without HRR gene mutations demonstrated that BRCAm patients benefitted most from the combination investigational arm. Cohort 2, however, did not see a benefit.[12] Because of these findings, the current FDA approval is limited to BRCAm mCRPC.[13]

Niraparib and abiraterone acetate is unique in that it is the only fixed combination pill among the three combinations of PARP inhibitors and ARSis. The other combinations are achieved by taking the PARP inhibitor and ARSi individually.

The starting dose is 200mg niraparib/1,000mg abiraterone acetate by mouth once daily. Patients also should be prescribed 10mg daily prednisone to prevent the known potential side effect of mineralocorticoid excess seen with abiraterone acetate.[13,19,20]

Unlike for the indication in ovarian cancer, there is no dose adjustment for the niraparib component contingent upon baseline weight or platelet labs.[13]

Patients need to take this treatment on an empty stomach due to the known substantial increases in absorption and resultant blood levels of abiraterone acetate when administered with food.[13,19] If a dose reduction is needed due to toxicity, the FDA approved a 50mg niraparib/500mg abiraterone acetate strength tablet to accommodate the recommended 100mg niraparib/1,000mg abiraterone acetate dose level.[13]

Concomitant use of strong CYP3A4 inducers should be avoided as abiraterone acetate is a substrate of this enzyme.[13] Since abiraterone acetate is a CYP2D6 and 2C8 inhibitor, use sensitive substrates of CYP2D6 with caution or avoid altogether if possible.[13]

There are no dose adjustments recommended for renal or hepatic impairment, but it is recommended to avoid this combination treatment in patients with moderate or severe hepatic impairment.[13] Patients with renal impairment [creatinine clearance (CrCl) ≤ 90 mL/min] should be treated with caution.[13]

Recommended laboratory monitoring is frequent. Weekly complete blood counts are recommended for the first month, every two weeks for the next two months, monthly for the remainder of the first year, then every other month and as clinically indicated.[13]

As hepatotoxicity is a known adverse effect of abiraterone, liver function tests (transaminases and bilirubin) should be monitored at least every two weeks for the first three months, then at least monthly.[19]

OLAPARIB & ABIRATERONE ACETATE

Olaparib and abiraterone acetate is a combination of the PARP inhibitor olaparib administered concurrently with the CYP17 inhibitor abiraterone acetate.[14]

This combination treatment is approved to treat mCRPC with deleterious or suspected deleterious BRCAm until disease progression or unacceptable toxicity. The approval is based on positive rPFS and OS benefits from the randomized, double-blind, placebo controlled, phase 3 PROpel trial comparing the combination of olaparib and abiraterone acetate to abiraterone acetate plus placebo.[11]

All patients received prednisone or prednisolone with abiraterone and ADT in the form of LHRH analogs or prior orchiectomy. Prior systemic therapy was allowed in earlier disease settings but not allowed for the mCRPC setting.

Genes for HRR were assessed retrospectively in PROpel and included ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L.[11] HRRm and BRCAm were detected in 28% and 12% of patients in the treatment arm, respectively.[11]

A post-hoc exploratory analysis of OS was performed for HRRm, non-HRRm, BRCAm, and non-BRCAm subgroups. BRCAm patients showed the most improved rPFS and OS benefits from the combination treatment.[11] For this reason, the FDA has limited the approval of this treatment currently to BRCAm mCRPC.[14]

The combination is prescribed as 300mg olaparib by mouth twice daily and abiraterone acetate 1,000mg by mouth once daily, plus prednisone or prednisolone 5mg twice daily based on what was done in the PROpel trial.[11]

Olaparib can be taken without regard to food, but abiraterone acetate must be taken on an empty stomach.[14,19]

Patients experiencing significant toxicities that warrant dose reduction should have abiraterone reduced in 250mg increments. Olaparib's FDA-approved reductions are 250mg twice daily or 200mg twice daily.[14,19] Because this combination is not fixed, clinicians should use clinical judgment to decide how and for which agent to reduce dosing.

Olaparib is metabolized primarily by CYP3A, and strong or moderate inducers should be avoided.[14] If strong or moderate CYP3A inhibitors cannot be avoided, olaparib should be reduced to 100mg or 150mg twice daily, respectively.[14] As monotherapy, abiraterone's dose can be adjusted if concomitant strong CYP3A4 inducers are administered, but as combination treatment with olaparib, strong inducers of CYP3A need to be avoided outright.[14,19]

Patients with moderate hepatic impairment (Child-Pugh B) prior to initiating treatment should have their abiraterone dose reduced to 250mg once daily.[19] Patients with CrCl 31 to 50 mL/min should have their olaparib dose reduced to 200mg twice daily. CrCl below this is not considered safe for use of olaparib due to lack of data.[14]

Patients should have a complete blood count drawn at least monthly, with liver functions tests every two weeks for the first three months, then at least monthly.[14,19]

The most common adverse reactions (≥ 20%; all grades) in PROpel

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were anemia (50%), fatigue/asthenia (39%), nausea (31%), back pain (22%) and diarrhea (21%).[11]

TALAZOPARIB & ENZALUTAMIDE

Talazoparib and enzalutamide is a combination of the PARP inhibitor talazoparib administered concurrently with the newer-generation androgen receptor inhibitor enzalutamide.[15]

This combination is approved to treat HRRm mCRPC until disease progression or unacceptable toxicity. Approval was based on positive benefits to rPFS seen in the randomized, double-blind, placebo-controlled, multi-cohort, phase 3 TALAPRO-2 trial comparing enzalutamide plus talazoparib to enzalutamide plus placebo.[10]

All patients received ADT in the form of LHRH analogs or prior orchiectomy. Prior systemic therapy was allowed in earlier disease settings but not allowed for the mCRPC setting. HRR genes were prospectively assessed and included BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12.[10] HRRm and BRCA1/2 alteration were detected in 21% and 7% of patients, respectively.[10]

Unlike the results seen in MAGNITUDE but like the results of PROpel, the investigational combination arm of talazoparib and enzalutamide demonstrated improved progression-free survival compared to the control arm in patients without HRR alterations.[10-12] Regardless, the current FDA approval is for HRRm mCRPC.[15]

This combination is prescribed as talazoparib 0.5mg by mouth once daily and enzalutamide 160mg by mouth once daily.[15] Both medications can be taken without regard to food.

If patients experience significant toxicity, talazoparib can be decreased to 0.35mg once daily, then to 0.25mg once daily, and then no less than 0.1mg once daily.[15] Enzalutamide can be reduced to 120mg or 80mg once daily.[21] Because this combination is not fixed, clinicians should use clinical judgment to decide how and for which agent to reduce dosing.

Combinations of PARP inhibitors and ARSis have demonstrated clear benefits in the frontline treatment of mCRPC. Long-term analysis of the overall survival data will continue to elucidate the role of these agents, but for now, each serves as an option for patients with HRR gene alterations, especially and specifically BRCAm for two of the three combinations based on the FDA approvals.

As monotherapy, talazoparib concentrations are known to increase when P-glycoprotein (P-gp) inhibitors are coadministered, and thus it is recommended to reduce the dose of talazoparib.[15] However, in combination with enzalutamide, P-gp inhibitor interactions have not been rigorously studied, and so there are no current dose adjustments recommended for talazoparib in this combination when coadministered with a P-gp inhibitor.[15]

Breast cancer resistance protein (BCRP) inhibitors may also increase concentrations of talazoparib, but there are no initial dose adjustments to talazoparib recommended.[15]

Enzalutamide has numerous drug interactions associated with CYP450 enzymes.[21] Strong inhibitors of CYP2C8 and strong inducers of CYP3A4 should be avoided ideally, but the dose of enzalutamide is suggested to be decreased to 80mg once daily or increased to 240mg once daily if coadministered with a strong CYP2C8 inhibitor or strong CYP3A4 inducer, respectively.[21]

Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C19 and CYP2C9.[21] Medications that are substrates of these enzymes need to be used with caution when co-administered with enzalutamide.[21] The dose of talazoparib should be reduced to 0.35mg for CrCl 30 to 59 mL/min and 0.25mg for CrCl 15 to 29 mL/min.[15]

Hepatic impairment of any severity has not demonstrated significant effects on the pharmacokinetics of talazoparib.[15]

Enzalutamide does not require dose adjustment for renal or hepatic impairment, but it also has not been studied in CrCl < 30 mL/min.[21]

The most common adverse effects in TALAPRO-2 (≥ 20%; all grades) were anemia (66%), neutropenia (36%), fatigue (34%), thrombocytopenia (25%), back pain (22%), leukopenia (22%), decreased appetite (22%) and nausea (21%).[10]

CONCLUSION

Combinations of PARP inhibitors and ARSis have demonstrated clear benefits in the frontline treatment of mCRPC.

Long-term analysis of the overall survival data will continue to elucidate the role of these agents, but for now, each serves as an option for patients with HRR gene alterations.

Clinicians should consider the side effect profiles, administration differences and drug interaction profiles when selecting a specific combination, as well as the potential costs associated with these novel combinations. Trials are ongoing to study PARP inhibitor/ARSi combinations in earlier settings of prostate cancer.

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MANAGING DIABETES MELLITUS IN PATIENTS WITH CHRONIC MYELOPROLIFERATIVE NEOPLASMS

By Ivan Krecak, MD, PhD, Sanja Klobucar, MD, PhD, Marko Skelin, M.Pharm, PhD, & Marko Lucijanic, MD, PhD

Chronic myeloproliferative neoplasms (MPNs) are a group of blood cancers that include essential thrombocythemia (ET), polycythemia vera (PV) and myelofibrosis (MF).

These neoplasms are characterized by constitutively active JAK-STAT signaling due to acquired mutations in the Janus Kinase 2 (JAK2), calreticulin (CALR) or thrombopoietin gene receptor (MPL) genes, which cause overproduction of mature myeloid blood cells in the peripheral blood. This may cause various complications, including blood clots, bleeding and a risk of progression to acute leukemia.[1,2]

Diabetes mellitus (DM), particularly type 2 DM, is a common metabolic disorder characterized by high blood sugar levels due to the body's inability to use insulin effectively.

As both MPNs and DM are chronic conditions that primarily affect older adults, there may be a significant overlap in the populations affected by these diseases.

However, it appears that DM is less frequent in MPN patients than may be expected. Thus, diagnosing and managing DM in patients with MPNs may present unique challenges and could require a tailored approach due to the specific biological and clinical characteristics of MPNs.

THE UNIQUE CHALLENGES OF DIAGNOSING DM IN MPN PATIENTS

Diagnosing DM in patients with MPNs could be more complex than in the general population due to several factors related to the underlying disease and its treatment.

Ivan Krecak

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One of the primary concerns is that MPNs themselves can affect glucose metabolism. In fact, MPN cells display increased energy requirements and metabolic reprogramming, which leads to hypoglycemia. This effect has been shown in MPN mouse models where hypoglycemia correlated with more pronounced erythrocytosis, increased glycolysis and oxidative phosphorylation.[3]

Similarly, patients with MPNs often present with artifactual hypoglycemia in peripheral blood samples caused by increased glucose uptake by the proliferating leukocytes.[4]

Additionally, short red blood cell life span in MPNs may cause lower glycated hemoglobin (HbA1c) levels,[5] a measure of long-term glucose control.

Other issues include chronic inflammation, a hallmark of MPNs, as well as the effects of certain therapies used to treat inflammation in MPNs, such as corticosteroids, which are known to raise blood sugar levels.

Also, hydroxyurea, a medication widely used to treat MPNs, may cause an expansion of HbF which can also cause falsely lower HbA1c levels. Actually, erythrocyte count, hematocrit and hemoglobin levels do not seem to correlate with HbA1c levels in MPN patients.[6]

Also, some symptoms of MPNs — such as fatigue, weight loss, and night sweats — can overlap with those of poorly controlled DM, potentially leading to delayed or missed diagnoses.

Moreover, routine blood tests used to monitor MPNs, like complete blood counts, do not typically include blood glucose or HbA1c levels, meaning that DM could go undetected unless specifically tested for.

Finally, oral glucose tolerance test (OGTT) is independent of the aforementioned laboratory artifacts and blood counts, but it is unlikely that this particular test is routinely used to screen all MPN patients for DM presence. Therefore, low frequency of DM among MPN patients is somewhat unexpected, since both DM and MPNs are typically encountered in the elderly with other chronic comorbidities.

However, all of abovementioned issues may cause DM to be diagnostically "missed" among MPN patients in everyday clinical practice.[7]

HOW MPNS IMPACT DM MANAGEMENT AND THE POTENTIAL ROLE OF DIFFERENT DM MEDICATIONS

Managing DM in patients with MPNs requires careful consideration of the disease's unique characteristics.

The chronic inflammation associated with MPNs can exacerbate insulin resistance, making blood sugar levels harder to control. Furthermore, the risk of thrombotic events (blood clots) is already elevated in MPN patients, and poorly controlled

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DM can further increase this risk.[6,7]

Given the complexities of managing diabetes in MPN patients, regular monitoring and adjustment of treatment plans are essential. Blood sugar levels should be closely watched, especially when starting or changing medications. HbA1c should be regularly monitored to assess the effectiveness of the treatment regimen, as its higher values have been associated with inferior outcomes in MPNs.[6]

Additionally, the potential interactions between MPN therapies and DM medications need to be considered. For example, patients with myelofibrosis on corticosteroids for symptom management may experience elevated blood sugar levels, necessitating adjustments in their DM treatment.

On the other hand, treatments like interferon-alpha, which are increasingly used in MPNs, can have complex effects on blood sugar control, potentially requiring closer monitoring.

It is also important to understand that the pharmacological management of DM in patients with MPNs may differ from the general DM population. However, none of the studies so far have specifically assessed the safety and efficacy of different medications used for the treatment of DM in MPN patients.

Nevertheless, several classes of DM medications may be considered for use in patients with MPNs, each with its own set of advantages and potential drawbacks:

▲ **Sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors):** These medications, which work by reducing glucose reabsorption in the kidneys, potently reduce thrombotic risk in the general population, and have raised some concerns about their effects on the cardiovascular system in MPNs, which is already vulnerable in MPN patients, mostly due to the propensity of these medications to promote erythrocytosis.

Smaller case series have shown that erythrocytosis caused by SGLT2 inhibitors may unmask an underlying MPN and that their use could potentially be associated with higher thrombotic risk,[8] although it is unclear whether this effect is caused by SGLT2 inhibitors or by underlying cardiovascular comorbidities in these patients for whom these drugs were specifically prescribed.

On the other hand, these drugs may also offer potential benefits, such as reducing inflammation and plasma volume in MPNs,[9-12] and lowering the risk of chronic kidney disease[13] and heart failure,[14] but more research is needed to understand their safety and efficacy in the context of MPNs.

▲ **Metformin:** Commonly prescribed as a first-line treatment for type 2 DM, metformin works by reducing the liver's glucose production and improving insulin sensitivity. Although some studies have suggested that metformin might lower cancer risk,[15] including that of MPNs,[16] this remains an area of ongoing research, and it is not yet clear if it offers specific benefits for MPN patients beyond its glucose-lowering effects.

Whether targeting of increased glycolysis and oxidative phosphorylation in MPNs with metformin may potentially control both DM and MPNs warrants further studies.[17,18]

However, metformin is associated with gastrointestinal disturbances; these burdensome symptoms are quite frequent in MPNs and may potentially limit the widespread use of metformin.

▲ **Sulfonylureas:** These drugs increase insulin production from the pancreas. While effective in lowering blood sugar, their use in MPN patients should be carefully monitored due to the risk of hypoglycemia and weight gain. Although weight gain may be beneficial for some, it can be a health burden for other MPN patients, especially considering that ruxolitinib, a JAK1/JAK2 inhibitor used for treatment of MPN, can act in a similar fashion.[19,20] Therefore, studies specifically assessing efficacy and safety of sulfonylureas in MPNs are needed.

▲ **Thiazolidinediones (TZDs):** These drugs improve insulin sensitivity but are associated with an increased risk of weight gain and edema, which could exacerbate the symptoms of MPNs, disorders already associated with higher plasma volume.[9-12] Additionally, their potential impact on heart failure risk is a concern, particularly in older adults with MPNs. None of the studies so far have analyzed safety and efficacy of TZDs in patients with MPNs.

▲ **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors and Glucagon-like Peptide-1 (GLP-1) Receptor Agonists:** These classes of drugs help regulate blood sugar by enhancing insulin secretion in response to meals. They are generally well-tolerated, offer good cardiovascular risk profile and may be beneficial in MPN patients, though their long-term safety and efficacy in this patient population have not been investigated yet.[18] Similarly to metformin, these medications may also be associated with gastrointestinal disturbances which may impair resorption of specific nutrients and other medications.

▲ **Lifestyle modifications:** Lifestyle remains a cornerstone of DM management, and could be particularly beneficial in patients with MPNs who are frequently inactive and sedentary due to significant symptom burden. A balanced diet, regular physical activity and weight management can help improve insulin sensitivity and reduce the risk of complications from both DM and MPNs.

Additionally, exercise treatment during management of different cancers and inflammatory conditions has been shown to improve symptom burden and quality of life, and is also recommended for patients with MPNs.[21,22]

Therefore, balanced diet and physical activity should be an integral part of the treatment plan for MPN patients with DM. However, exercise routines should be tailored to each patient and adapted to avoid overly strenuous activities that could increase the risk of bleeding or thrombosis.

FUTURE DIRECTIONS AND RESEARCH NEEDS

There is a growing need for more

CONTINUED ON NEXT PAGE

DIABETES

CONTINUED FROM PREVIOUS PAGE

research into the specific interactions between MPNs and DM, particularly regarding how different DM treatments affect MPN progression and patient outcomes.

Large-scale studies and clinical trials are needed to identify the best diagnostic approaches to DM in MPNs and to better understand the best practices for managing DM in this unique patient population. These studies may also identify optimal glucose and HbA1c levels in MPNs.

Furthermore, exploring the potential benefits and risks of newer DM medications with proven cardioprotective properties (i.e., SGLT2 inhibitors or GLP1 agonists) in MPN patients could lead to more effective and safer treatment strategies.

Understanding the role of chronic inflammation in both MPNs and DM could also open new avenues for therapeutic interventions that address the root causes of both conditions.

We have started a prospective clinical trial in Croatia that will assess glycated proteins (serum fructosamine and glycated albumin) and use continuous glucose monitoring in MPN patients.

These particular methods are independent of patients' blood counts and may provide better insights into the pathophysiology of dysglycemia in MPN patients and its impact on clinical outcomes in MPNs.

In summary, managing DM in patients with MPNs requires a nuanced approach that takes into account the unique biological and clinical characteristics of MPNs.

While the general principles of DM management apply, the specific risks and challenges associated with MPNs necessitate careful selection and monitoring of treatment strategies.

Patients and healthcare providers should work closely together to develop a multidisciplinary and personalized plan that addresses both DM and MPNs, with regular adjustments as needed to optimize outcomes and minimize complications.

▲ **Ivan Krecak**, MD, PhD, is a hematologist at the General Hospital of Sibenik-Knin County in Sibenik, Croatia. **Sanja Klobucar**, MD, PhD, is an endocrinologist and diabetologist at the Clinical Hospital Center Rijeka in Rijeka, Croatia. **Marko Skelin**, M.Pharm, PhD, is the Deputy Director of the Pharmacy Department at the General Hospital of Sibenik-Knin County, Sibenik, Croatia. **Marko Lucijanic**, MD, PhD, is a hematologist at the University Hospital Dubrava in Zagreb, Croatia.

EDITOR'S NOTE: Information in this story is from an international perspective and may differ from current U.S. guidelines and regulations.

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1L aRCC

#1 PRESCRIBED TKI+IO COMBINATION IN 1L aRCC

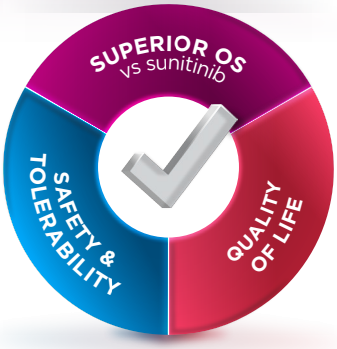
Based on IQVIA claims data as of June 2024. Subject to change without notice.[1]

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

EFFICACY IN BALANCE

CABOMETYX + OPDIVO brings together efficacy, safety, and tolerability data for your 1L aRCC patients[2]

A BALANCE OF DATA*



1L aRCC treatment that offers a balance of data:
superior OS, safety and tolerability, and patient-reported quality of life[2-4] *

*Superior OS vs sunitinib in patients with previously untreated aRCC. Primary analysis OS results: 40% reduction in risk of death with CABOMETYX + OPDIVO vs sunitinib (HR=0.60; 98.89% CI: 0.40-0.89; *P*=0.001); median OS was not reached in either arm. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and **the clinical significance is unknown**.[2,3]

Explore the balance of data

1L=first-line; aRCC=advanced renal cell carcinoma; CI=confidence interval; FKSI-19=Functional Assessment of Cancer Therapy-Kidney Symptom Index 19; HR=hazard ratio; IO=immunotherapy; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

INDICATION

CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. Discontinue CABOMETYX for Grade 3-4 hemorrhage and before surgery. Do not administer to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, and gastrointestinal (GI) perforations, including fatal cases, occurred in CABOMETYX patients. Monitor for signs and symptoms and discontinue in patients with Grade 4 fistulas or GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Fatal thrombotic events have occurred. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension including hypertensive crisis. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information for CABOMETYX on the following pages.

Superior PFS and ORR results in the primary analysis[2]

Primary analysis results
Median follow-up time of 18.1 months; range: 10.6-30.6 months[3]

Primary endpoint, assessed by BICR
P
Double median PFS[2]
16.6 months with CABOMETYX + OPDIVO
(95% CI: 12.5-24.9, n=323)

vs

8.3 months with sunitinib (95% CI: 7.0-9.7, n=328)
HR=0.51 (95% CI: 0.41-0.64; *P*<0.0001)

Secondary endpoint, assessed by BICR
Double ORR[2]
55.7% with CABOMETYX + OPDIVO
(95% CI: 50.1-61.2; n=323)
CR: 8% (n=26/323); PR: 48% (n=154/323)

vs

27.1% with sunitinib (95% CI: 22.4-32.3; n=328);
CR: 4.6% (n=15/328); PR: 23% (n=74/328) (*P*<0.0001)

4-year minimum follow-up analysis
Median follow-up time of 55.6 months; range: 48.1-68.1 months[5]

Primary endpoint
4Y
PFS[5]
16.4 months with CABOMETYX + OPDIVO
(95% CI: 12.5-19.3; n=323)

vs

8.4 months with sunitinib (95% CI: 7.0-9.7; n=328)
HR=0.58 (95% CI: 0.49-0.70)

Secondary endpoint
4Y
ORR[5]
55.7% with CABOMETYX + OPDIVO
(95% CI: 50.1-61.2; n=323)
CR: 13.6% (n=44/323); PR: 42.1% (n=136/323)

vs

27.7% with sunitinib (95% CI: 23.0-32.9; n=328);
CR: 4.6% (n=15/328); PR: 23.2% (n=76/328)

No formal statistical testing was conducted at the time of the updated analysis.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) PREFERRED OPTION

Cabozantinib (CABOMETYX) + nivolumab (OPDIVO) is the first TKI + IO regimen with an NCCN recommendation in both clear-cell and non–clear-cell aRCC[6]

NCCN CATEGORY 1, PREFERRED OPTION IN CLEAR-CELL RCC

- **Category 1**, preferred option across all risk groups in 1L clear-cell RCC[6]
- NCCN Category 1: Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate[6]

NCCN PREFERRED OPTION IN NON–CLEAR-CELL RCC

- **Category 2A**, preferred option in non–clear-cell RCC[6]
- NCCN Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate[6]

NCCN makes no representations or warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. Recommendations made by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer, V.1.2025.[6]

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

Diarrhea: Diarrhea may be severe. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): Withhold CABOMETYX until PPE resolves or decreases to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider withholding CABOMETYX and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Proteinuria: Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria; resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

Impaired Wound Healing: Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Please see additional Important Safety Information throughout and Brief Summary of the Prescribing Information for CABOMETYX on the following pages.

Superior OS outcomes in the primary analysis[3]

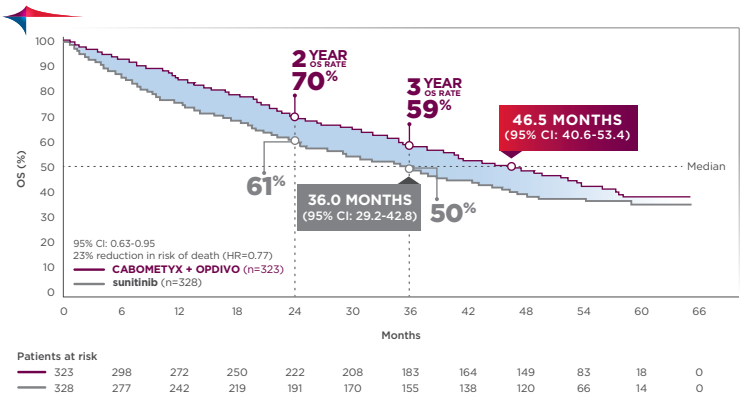
CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

Primary analysis
Median follow-up time of 18.1 months; range: 10.6-30.6 months[3]

Secondary endpoint

P **Superior median OS**[2]
Median OS was not reached with either CABOMETYX + OPDIVO or sunitinib
HR=0.60 (98.89% CI: 0.40-0.89, *P*=0.001)

4Y **4-year minimum follow-up analysis**[5]
Median follow-up time of 55.6 months; range: 48.1-68.1 months



No formal statistical testing was conducted at the time of the updated analysis.

CheckMate-9ER was a randomized (1:1), open-label, Phase 3 trial of CABOMETYX + OPDIVO vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. Quality of life was evaluated as an exploratory endpoint; the clinical significance is unknown.[2,3,7,8]

- **Pre-planned final analysis of OS** (median follow-up: 32.9 months; range: 25.4-45.4 months): Median OS was 37.7 months for CABOMETYX + OPDIVO (95% CI: 35.5-NR; n=323) compared with 34.3 months for sunitinib (95% CI: 29.0-NR; n=328); HR=0.70 (95% CI: 0.55-0.90)[2,8,9]

BICR=blinded independent central review; CR=complete response; NR=not reached; PO=by mouth; PR=partial response.

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Assess for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms during treatment.

Hypocalcemia: Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to fetus. Verify pregnancy status and advise use of effective contraception during treatment and for 4 months after last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are:

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on the following pages.

References: 1. Data on file. IQVIA National Prescription Audit. June 2024. Exelixis, Inc. **2.** CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc. **3.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384(9):829-841. **4.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [supplementary appendix]. *N Engl J Med*. 2021;384(9):829-841. **5.** Bourlon MT, Escudier B, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for previously untreated advanced renal cell carcinoma: results from 55-month follow-up of the CheckMate 9ER trial. Presented at ASCO Genitourinary Cancers Symposium; January 27, 2024. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.1.2025. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed July 1, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. **7.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [protocol]. *N Engl J Med*. 2021;384(9):829-841. **8.** Powles T, Choueiri TK, Burotto M, et al. Final overall survival analysis and organ-specific target lesion assessments with 2-year follow-up in CheckMate 9ER: nivolumab plus cabozantinib versus sunitinib for patients with advanced renal cell carcinoma. Poster presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium; February 17-19, 2022. **9.** Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomized, phase 3 trial. *Lancet Oncol*. 2022;23(7):888-898.

DISCOVER MORE AT CABOMETYXhcp.com

EXELIXIS®

CABOMETYX® (cabozantinib) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

PLEASE SEE THE CABOMETYX PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.
INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE

1.1 Renal Cell Carcinoma
CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of patients with advanced RCC.

1.2 Hepatocellular Carcinoma
CABOMETYX is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

1.3 Differentiated Thyroid Cancer
CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in the RCC, HCC, and DTC studies.

Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

5.2 Perforations and Fistulas
Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX-treated patients.

Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thrombotic events occurred in CABOMETYX-treated patients.

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

5.4 Hypertension and Hypertensive Crisis
CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX-treated patients.

Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

5.5 Diarrhea
Diarrhea occurred in 62% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 10% of patients treated with CABOMETYX.

Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume CABOMETYX at a reduced dose.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-plantar erythrodysesthesia (PPE) occurred in 45% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX.

Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.7 Hepatotoxicity
CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST > 3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

5.8 Adrenal Insufficiency
CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

5.9 Proteinuria
Proteinuria was observed in 8% of patients receiving CABOMETYX.

Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

5.10 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with CABOMETYX.

ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

5.11 Impaired Wound Healing
Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

5.12 Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.13 Thyroid Dysfunction
Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

5.14 Hypocalcemia
CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

5.15 Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed elsewhere in the labeling: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-plantar Erythrodysesthesia, Hepatotoxicity, Adrenal Insufficiency, Proteinuria, Osteonecrosis of the Jaw, Impaired Wound Healing, Reversible Posterior Leukoencephalopathy Syndrome, Thyroid Dysfunction and Hypocalcemia.

6.1 Clinical Trial Experience
The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX as a single agent in 409 patients with RCC enrolled in randomized, active-controlled trials (CABOSUN, METEOR), 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL), in 125 patients with DTC enrolled in a randomized, placebo-controlled trial (COSMIC-311), and in combination with nivolumab 240 mg/m^2 every 2 weeks in 320 patients with RCC enrolled in a randomized, active-controlled trial (CHECKMATE-9ER).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Renal Cell Carcinoma

METEOR

The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received CABOMETYX 60 mg once daily and 322 patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency, were: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of patients were hypertension, diarrhea, fatigue, PPE, hyponatremia, hypophosphatemia, hypomagnesemia, lymphopenia, anemia, hypokalemia, and increased GGT.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received CABOMETYX 20 mg once daily as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to dose interruption occurred in 70% patients receiving CABOMETYX and in 59% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).

Table 1. Adverse Reactions Occurring in ≥ 10% Patients Who Received CABOMETYX in METEOR

Adverse Reaction	CABOMETYX (n=331)[1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	74	11	28	2
Nausea	50	4	28	<1
Vomiting	32	2	14	<1
Stomatitis	22	2	24	2
Constipation	25	<1	19	<1
Abdominal pain[3]	23	4	13	2
Dyspepsia	12	<1	5	0
General				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2

Adverse Reaction	CABOMETYX (n=331) [1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Metabolism and Nutrition				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash[4]	23	<1	43	<1
Dry skin	11	0	10	0
Vascular				
Hypertension[5]	39	16	8	3
Investigations				
Weight decreased	31	2	12	0
Nervous System				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary				
Proteinuria	12	2	9	<1

[1] One subject randomized to everolimus received cabozantinib.
[2] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
[3] Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower
[4] Includes the following terms: rash, rash erythematous, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, genital rash, intermittent leg rash, rash on scrotum and penis, rash maculo-papular, rash pruritic, contact dermatitis, dermatitis acneiform
[5] Includes the following terms hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation

Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestatic (<1%).

Table 2. Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX in METEOR

Laboratory Abnormality	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage (%) of Patients			
Chemistry				
Increased AST	74	3	40	<1
Increased ALT	68	3	32	<1
Increased creatinine	58	<1	71	0
Increased triglycerides	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
Increased ALP	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
Increased GGT	27	5	43	9
Hematology				
Leukopenia	35	<1	31	<1
Neutropenia	31	2	17	<1
Anemia[1]	31	4	71	17
Lymphopenia	25	7	39	12
Thrombocytopenia	25	<1	27	<1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.
NCI CTCAE, Version 4.0
[1] Based on laboratory abnormalities

CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received CABOMETYX 60 mg once daily and 72 patients received sunitinib 50 mg once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib.

Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥5%) in patients treated with CABOMETYX were hypertension, diarrhea, hyponatremia, hypophosphatemia, PPE, fatigue, increased ALT, decreased appetite, stomatitis, pain, hypotension, and syncope.

The median average daily dose was 50.3 mg for CABOMETYX and 44.7 mg for sunitinib (excluding scheduled sunitinib non-dosing days). The dose was reduced in 46% of patients receiving CABOMETYX and in 35% of patients receiving sunitinib. The dose was held in 73% of patients receiving CABOMETYX and in 71% of patients receiving sunitinib. Based on patient disposition, 21% of patients receiving CABOMETYX and 22% of patients receiving sunitinib discontinued due to an adverse reaction.

Table 3. Grade 3-4 Adverse Reactions Occurring in ≥ 1% Patients Who Received CABOMETYX in CABOSUN

Adverse Reaction	CABOMETYX (n = 78)	Sunitinib (n = 72)
	Grade 3-4[1]	Grade 3-4[1]
	Percentage (%) of Patients	
Patients with any Grade 3-4 Adverse Reaction	68	65
Gastrointestinal		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3
Constipation	1	0
General		
Fatigue	6	17
Pain	5	0
Metabolism and Nutrition		
Hyponatremia[2]	9	8
Hypophosphatemia[2]	9	7
Decreased appetite	5	1
Dehydration	4	1
Hypocalcemia[2]	3	0
Hypomagnesemia[2]	3	0
Hyperkalemia[2]	1	3
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
Vascular		
Hypertension[3]	28	21
Hypotension	5	1
Angiopathy	1	1
Investigations		
Increased ALT[2]	5	0
Weight decreased	4	0
Increased AST[2]	3	3
Increased blood creatinine[2]	3	3
Lymphopenia[2]	1	6
Thrombocytopenia[2]	1	11
Nervous System		
Syncope	5	0
Respiratory, Thoracic, and Mediastinal		
Dyspnea	1	6
Dysphonia	1	0
Blood and Lymphatic		
Anemia	1	3
Psychiatric		
Depression	4	0
Confusional state	1	1
Infections		
Lung infection	4	0
Musculoskeletal and Connective Tissue		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
Renal and Urinary		
Renal failure acute	4	1
Proteinuria	3	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase
[1] NCI CTCAE Version 4.0
[2] Laboratory abnormalities are reported as adverse reactions and not based on shifts in laboratory values
[3] Includes the following term: hypertension

CHECKMATE-9ER

The safety of CABOMETYX with nivolumab was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received CABOMETYX 40 mg orally once daily with nivolumab 240 mg over 30 minutes every 2 weeks (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320). CABOMETYX could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in CABOMETYX and nivolumab-treated patients. In this trial, 82% of patients in the CABOMETYX and nivolumab arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving CABOMETYX and nivolumab.

The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either CABOMETYX or nivolumab occurred in 20% of patients: 8% CABOMETYX only, 7% nivolumab only, and 6% both drugs due to the same adverse reaction at the same time. Adverse reactions leading to dose interruption or reduction of either CABOMETYX or nivolumab occurred in 83% of patients: 46% CABOMETYX only, 3% nivolumab only, and 21% both drugs due to the same adverse reaction at the same time, and 6% both drugs sequentially.

The most common adverse reactions reported in ≥20% of patients treated with CABOMETYX and nivolumab were diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Table 4. Adverse Reactions in ≥15% of Patients receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

Adverse Reaction	CABOMETYX and Nivolumab (n=320)		Sunitinib (n=320)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal Pain[a]	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia[b]	15	0	22	0.3
General				
Fatigue[c]	51	8	50	8
Hepatobiliary				
Hepatotoxicity[d]	44	11	26	5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	40	8	41	8
Stomatitis[e]	37	3.4	46	4.4
Rash[f]	36	3.1	14	0
Pruritus	19	0.3	4.4	0
Vascular				
Hypertension[g]	36	13	39	14
Endocrine				
Hypothyroidism[h]	34	0.3	30	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[i]	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
Metabolism and Nutrition				
Decreased appetite	28	1.9	20	1.3
Nervous System Disorders				
Dysgeusia	24	0	22	0
Headache	16	0	12	0.6
Respiratory, Thoracic, and Mediastinal				
Cough[j]	20	0.3	17	0
Dysphonia	17	0.3	3.4	0

Adverse Reaction	CABOMETYX and Nivolumab (n=320)		Sunitinib (n=320)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Infections and Infestations				
Upper respiratory tract infection[k]	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

[d] Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.

[e] Includes mucosal inflammation, aphthous ulcer, mouth ulceration.

[f] Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.

[g] Includes blood pressure increased, blood pressure systolic increased.

[h] Includes primary hypothyroidism.

[i] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis

Table 5. Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

Laboratory Abnormality	CABOMETYX and Nivolumab		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 1-4
	Percentage (%) of Patients			
Chemistry				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
Hematology				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.5	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: CABOMETYX and nivolumab group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years.

Adverse reactions occurring in ≥ 25% of CABOMETYX- treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, asthenia, and decreased appetite. There were 6 adverse reactions leading to death in patients receiving CABOMETYX (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism, upper gastrointestinal hemorrhage).

The median average daily dose was 35.8 mg for CABOMETYX. The dose was reduced in 62% of patients receiving CABOMETYX; 33% of patients required a reduction to 20 mg daily. The most frequent adverse reactions or laboratory abnormalities leading to dose reduction of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 6. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Adverse Reaction	CABOMETYX (n = 467)		Placebo (n = 237)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	<1	12	3
Stomatitis	13	2	2	0
Dyspepsia	10	0	3	0
General				
Fatigue	45	10	30	4
Asthenia	22	7	8	2
Mucosal inflammation	14	2	2	<1
Metabolism and Nutrition				
Decreased appetite	48	6	18	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	17	5	0
Rash[3]	21	2	9	<1
Vascular				
Hypertension[4]	30	16	6	2
Investigations				
Weight decreased	17	1	6	0
Nervous System				
Dysgeusia	12	0	2	0
Endocrine				
Hypothyroidism	8	<1	<1	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	19	1	2	0
Dyspnea	12	3	10	<1
Musculoskeletal and Connective Tissue				
Pain in extremity	9	<1	4	1
Muscle spasms	8	<1	2	0

[1] Includes terms with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] NCI CTCAE Version 4.0

[3] Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected

[4] Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased

Table 7. Laboratory Abnormalities Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Laboratory Abnormality	CABOMETYX N=467		Placebo N=237	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage of Patients			
Chemistry				
Increased LDH	84	9	29	2
Increased ALT	73	12	37	6
Increased AST	73	24	46	19
Hypoalbuminemia	51	1	32	1
Increased ALP	43	8	38	6
Hypophosphatemia	25	9	8	4
Hypokalemia	23	6	6	1
Hypomagnesemia	22	3	3	0
Increased amylase	16	2	9	2
Hypocalcemia	8	2	0	0
Hematology				
Decreased platelets	54	10	16	1
Neutropenia	43	7	8	1
Increased hemoglobin	8	0	1	0

[1] Includes laboratory abnormalities with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, blood lactate dehydrogenase

Differentiated Thyroid Cancer

The safety of CABOMETYX was evaluated in COSMIC-311, a randomized, double-blind, placebo-controlled trial in which 187 patients with advanced differentiated thyroid cancer were randomized to receive CABOMETYX 60 mg orally once daily (n=125) or placebo (n=62) with supportive care until disease progression or unacceptable toxicity. At the time of the primary efficacy analysis, the median duration of treatment was 4.4 months (range 0.0 – 15.7) for patients receiving CABOMETYX and 2.3 months (range 0.3 – 11.6) for patients receiving placebo. The median age was 66 years (range 32 to 85 years), 55% were female, 70% were White, 18% were Asian, 2% were Black, 2% were American Indian or Alaska Native, and 63% received prior lenvatinib.

Adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, PPE, fatigue, hypertension, and stomatitis. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, and stomatitis. Serious adverse reactions occurred in 34% of patients who received CABOMETYX. Serious adverse reactions in ≥2% included diarrhea, pleural effusion, pulmonary embolism and dyspnea. Fatal adverse reactions occurred in 1.6% of patients in the CABOMETYX arm, including arterial hemorrhage (0.8%) and pulmonary embolism (0.8%).

The median average daily dose was 42.0 mg for CABOMETYX. The dose was reduced in 56% of patients receiving CABOMETYX; 22% of patients required a second dose reduction. The most frequent adverse reactions (≥5%) leading to dose reduction of CABOMETYX were PPE, diarrhea, fatigue, proteinuria, and decreased appetite. Dose interruptions occurred in 72% patients receiving CABOMETYX. Adverse reactions requiring dosage interruption in ≥5% of patients were PPE, diarrhea, dyspnea, hypertension, decreased appetite and proteinuria. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 5% of patients.

Table 8. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in COSMIC-311[1]

Adverse Reaction	CABOMETYX (N=125)		Placebo (N=62)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	51	7	3	0
Nausea	24	3	2	0
Vomiting	14	1	8	0
Stomatitis[3]	26	5	3	0
Dry mouth	10	1	2	0
General				
Fatigue[4]	42	10	23	0
Metabolism and Nutrition				
Decreased appetite	23	3	16	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	10	0	0
Vascular				
Hypertension[5]	30	10	5	3
Investigations				
Weight decreased	18	1	5	0
Nervous System				
Dysgeusia	10	0	0	0
Headache	10	2	2	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	10	0	2	0
Pulmonary embolism	5	2	0	0
Renal and Urinary				
Proteinuria	15	1	3	0

[1] Includes terms that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] NCI CTCAE Version 5.0

[3] Includes the following terms: mucosal inflammation, stomatitis

[4] Includes the following terms: fatigue, asthenia

[5] Includes the following terms: hypertension, blood pressure increased, hypertensive crisis

Table 9. Laboratory Abnormalities Occurring in ≥10% of CABOMETYX-Treated Patients in COSMIC-311[1]

Laboratory Abnormality	CABOMETYX N=125		Placebo N=62	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	Percentage (%) of Patients			
Chemistry				
LDH increased[2]	90	10	32	3
AST increased	77	1	18	0
ALT increased	66	2	11	0
Hypocalcemia	36	9	10	2
ALP increased	34	0	15	0
GGT increased	26	2	21	2
Hypomagnesemia	25	2	5	0
Hypoalbuminemia	19	1	7	0
Hypokalemia	18	1	3	0
Hyponatremia	15	0	10	2
Hyperbilirubinemia	12	0	5	0
Hematology				
Leukocytes decreased	38	2	7	2
Neutrophils decreased	31	2	5	2
Platelets decreased	26	0	5	0

[1] Includes laboratory abnormalities that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] Sponsor-defined grades for LDH were as follows: Grade 1 (> ULN to ≤ 2 × ULN), Grade 2 (> 2 × ULN to ≤ 3 × ULN), Grade 3 (> 3 × ULN).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; LDH, blood lactate dehydrogenase

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CABOMETYX

Strong CYP3A4 Inhibitors

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

Strong CYP3A Inducers

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid coadministration of CABOMETYX with strong CYP3A4 inducers. Increase the dosage of CABOMETYX if coadministration with strong CYP3A4 inducers cannot be avoided. Avoid St. John's wort which may also decrease exposure of cabozantinib.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose (see Data). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (approximately 0.12-fold of human area under the curve [AUC] at the recommended dose). Findings included delayed ossification and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.04-fold of human AUC at the recommended dose).

In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg (approximately 1.1-fold of the human AUC at the recommended dose).

In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

8.2 Lactation

Risk Summary

There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX.

Contraception

CABOMETYX can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Infertility

Females and Males

Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of CABOMETYX for the treatment of differentiated thyroid cancer (DTC) have been established in pediatric patients aged 12 years and older.

Use of CABOMETYX in pediatric patients aged 12 years and older with DTC is supported by evidence from adequate and well-controlled studies of CABOMETYX in adults with additional population pharmacokinetic data demonstrating that cabozantinib exposure is within the same range between adults and pediatric patients aged 12 years and older at the recommended dosages.

Physeal widening has been observed in children with open growth plates when treated with CABOMETYX. Based on the limited available data of the effects of CABOMETYX on longitudinal growth, physeal and longitudinal growth monitoring is recommended in children with open growth plates.

The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner's gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physeal hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

8.5 Geriatric Use

In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older. In COSMIC-311, 50% of 125 patients treated with CABOMETYX were age 65 years and older, and 12% were 75 years and older.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 320 patients randomized to CABOMETYX administered with nivolumab in CHECKMATE-9ER, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

8.7 Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

10 OVERDOSAGE

One case of overdosage was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.

Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX.

Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Adrenal insufficiency: Advise patients receiving with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency.

Proteinuria: Advise patients to contact their healthcare provider for signs or symptoms of proteinuria.

Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.

Impaired wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.

Thyroid dysfunction: Advise patients that CABOMETYX can cause thyroid dysfunction and that their thyroid function should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction.

Hypocalcemia: Advise patients that CABOMETYX can cause low calcium levels and that their serum calcium levels should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of hypocalcemia.

Embryo-fetal toxicity:

- Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort.

Important administration information

Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information

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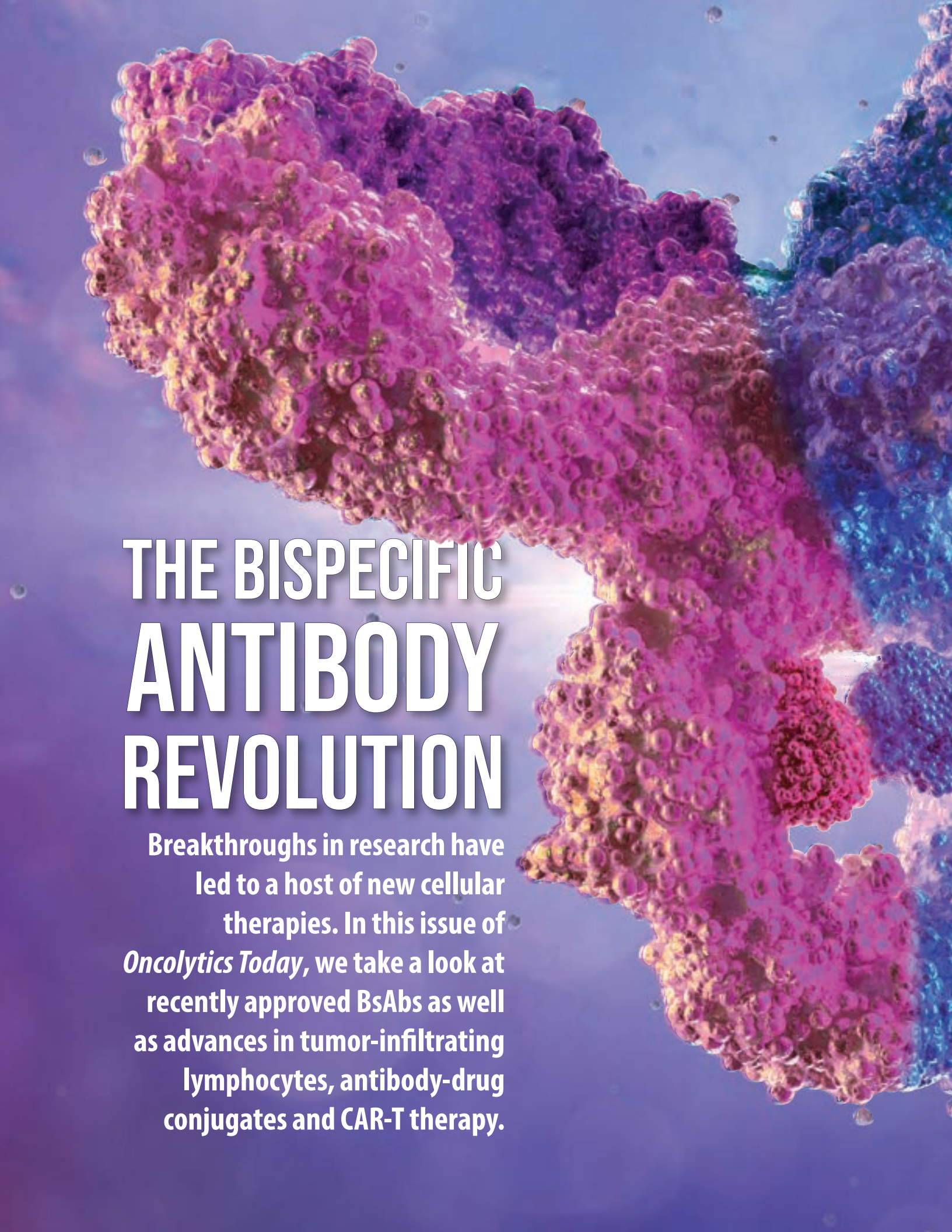

THE BISPECIFIC ANTIBODY REVOLUTION

Breakthroughs in research have led to a host of new cellular therapies. In this issue of *Oncolytics Today*, we take a look at recently approved BsAbs as well as advances in tumor-infiltrating lymphocytes, antibody-drug conjugates and CAR-T therapy.

THE EVOLVING LANDSCAPE OF ONCOLOGY

BISPECIFIC T-CELL ENGAGERS: A NEW FRONTIER IN CANCER TREATMENT

By Lotanna Ezeofor, PharmDc & Kelly Brunk, PharmD, BCOP

T cell-engaging bispecific antibodies (BsAbs) have emerged as a significant advancement in cancer immunotherapy, transforming the treatment landscape for patients with certain hematologic malignancies and solid tumors.

These therapies leverage the body's immune system to target and destroy cancer cells with high specificity,[1] providing new options for patients who may not respond to traditional treatments.

BsAbs are primarily approved for treating patients with relapsed or refractory cancers, but their use is anticipated to extend into earlier treatment stages, both as standalone therapies and in combination with other standard care regimens.[2-7]

Given the rapid advancements in BsAb therapies and their growing importance in oncology, there is a need for an overview that not only examines their historical development and mechanisms of action but also compares their efficacy and safety with CAR-T therapies and evaluates the potential challenges and opportunities they present in clinical practice.

This article will also provide a detailed overview of the adverse effects associated with BsAbs and assess the current outlook for these therapies in cancer care. By addressing these topics, this review aims to equip healthcare professionals with a thorough understanding of BsAbs and their role in modern cancer treatment.

Lotanna Ezeofor

Kelly Brunk

HISTORICAL CONTEXT

The first BsAb to receive U.S. Food and Drug Administration (FDA) approval was blinatumomab, which was approved for the treatment of relapsed or refractory (r/r) B-cell acute precursor lymphoblastic leukemia (BCP-ALL) in 2014.[8]

Recently, there has been a significant uptick in the approval of BsAbs, with eight new agents approved over the past three years. These include mosunetuzumab (2022) and epcoritamab (2024) for r/r follicular lymphoma (FL),[9,10] glofitamab (2023) and epcoritamab (2023) for r/r diffuse large B-cell lymphoma (DLBCL),[10,11] teclistamab (2022), talquetamab (2023) and elranatamab (2023) for r/r multiple myeloma (MM),[12-14] tarlatamab (2024) for second line treatment and beyond (2L+) extensive stage small cell lung cancer (ES-SCLC),[15] and tebentafusp (2022) for HLA-A*02-01 advanced uveal melanoma.[16]

Tables 1-3 (see **Pages 58** to **60**) provide profiles of the FDA-approved BsAbs as of August 15, 2024.

OVERVIEW OF BsAbs MECHANISM OF ACTION

BsAbs are a class of immunotherapeutic agents designed to redirect T cells against cancer cells,[1] offering a novel mechanism of action across various malignancies.

These molecules consist of two single-chain variable fragments linked together, with one binding to the CD3 receptor on T cells and the other targeting a specific antigen on cancer cells, such as CD20, CD19, BCMA, GPRC5D, DLL3, or gp100 peptide-HLA.[1] This dual binding brings T cells close to cancer cells, activating T cells and inducing apoptosis through the release of cytotoxic granules.[1,17]

Additionally, the binding to CD3 triggers T-cell activation, proliferation and cytokine release, enhancing the immune response.[1,17]

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INDICATIONS AND APPLICATIONS

BsAbs have been approved by the FDA for the treatment of hematologic malignancies and solid tumors.

▲ **Hematologic Malignancies:** For adults with r/r MM who have undergone at least four previous lines of therapy, which include a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, teclistamab, talquetamab and elranatamab have received approval.[12-14]

Additionally, mosunetuzumab and epcoritamab are approved for treating adults with r/r FL following two or more lines of systemic therapy.[9,10]

Epcoritamab and glofitamab are also approved for adults with r/r DLBCL after two or more systemic therapies.[10,11]

Blinatumomab has been approved for treating CD19-positive BCP-ALL, including those in first or second complete remission with minimal residual disease (MRD) of 0.1% or greater, r/r CD19-positive BCP-ALL and CD19-positive Philadelphia chromosome-negative (Ph(-)) BCP-ALL during the consolidation phase of multiphase chemotherapy.[8]

▲ **Solid Tumors:** Tebentafusp is approved for treating adult patients who are HLA-A*02:01-positive with unresectable or metastatic uveal melanoma.[16] Tarlatamab is indicated for adult patients with ES-SCLC whose disease has progressed on or after platinum-based chemotherapy.[15]

▲ **Dosing and Administration:** BsAbs typically utilize a step-up dosing regimen during the initial doses,[18] gradually increasing doses to mitigate severe adverse events like cytokine release syndrome (CRS).[18] Administration methods vary depending on the product; some are administered intravenously (IV), while others are administered subcutaneously (SubQ).[19]

▲ **Length of Therapy:** The duration of treatment varies depending on the specific agent, ranging from a set period to indefinite use until disease progression or the onset of intolerable side effects.[20]

EFFICACY

BsAbs have shown significant efficacy across various cancers.

▲ **Hematologic Malignancies:** In r/r FL, epcoritamab and mosunetuzumab have achieved objective response rates (ORR) of about 80%, with complete response (CR) rates of approximately 60% and long durations of response.[9,10,21] For r/r DLBCL, epcoritamab and glofitamab have demonstrated ORRs near 60%, with around 40% CR rates.[10,11,22,23] In r/r MM, teclistamab, talquetamab and elranatamab have shown ORRs between 60% and 75%, with over half of the patients achieving a very good partial response (VGPR) or better.[12-14,24-26]

In leukemia, blinatumomab has proven effective for various indications. In frontline consolidation, alternating blinatumomab with chemotherapy improved overall survival compared to chemotherapy alone, reducing the risk of death from any cause by 58% in patients with MRD negativity.[8] For patients with MRD+ BCP-ALL, single-agent blinatumomab achieved a complete MRD response in 81%, leading to longer relapse-free survival.[8,27] In Ph(-) r/r BCP-ALL, blinatumomab nearly doubled median overall survival compared to standard chemotherapy and provided deep, durable remissions.[8]

▲ **Solid Tumors:** In 2L+ ES-SCLC, tarlatamab demonstrated an ORR of 40%, a disease control rate (DCR) of 70%, a median duration of response (DoR) of 9.7 months and a median overall survival (OS) of 14.3 months.[15,28] For the first-line treatment of HLA-A*02:01 uveal melanoma, tebentafusp achieved an ORR of 9%, a DCR of 46% and improved median OS by approximately six months (21.1 months vs. 16.9 months) compared to the investigator's choice of pembrolizumab, ipilimumab or dacarbazine.[16,29]

SUPPORTIVE CARE CONSIDERATIONS

Supportive measures, including infection prevention, IV hydration and tumor lysis syndrome (TLS) prevention, are often recommended for patients receiving BsAbs.[30-33] Prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) and herpes simplex virus (HSV)/Varicella-Zoster Virus (VZV) is recommended for BsAbs targeting BCMA (teclistamab and elranatamab), GPCR5D (talquetamab) and CD20 (epcoritamab, mosunetuzumab and glofitamab).[9-14] For these agents, routine screening for cytomegalovirus (CMV) might be appropriate depending on epidemiologic risks. For CD19-targeting blinatumomab, PJP and HSV/VZV prophylaxis can be considered.[8] Note that anti-infective prophylaxis is not recommended for agents like tarlatamab or tebentafusp.

Intravenous hydration is recommended with some agents, particularly for patients with low volume status due to the risk of cytokine release syndrome. For example, with tarlatamab, 1 liter of normal saline should be infused over four to five hours immediately following the infusions during cycle 1.[15]

Per the package insert, prophylaxis for TLS using anti-hyperuricemics should be administered when starting treatment with glofitamab.[11]

OVERVIEW OF ADVERSE EFFECTS WITH BsAbs

▲ **Cytokine Release Syndrome (CRS):** CRS is a common and serious adverse effect associated with BsAbs, resulting from the rapid activation of T cells and subsequent cytokine release.[34] Symptoms range from mild flu-like symptoms, such as fever and fatigue, to severe issues like hypotension, hypoxia and multi-organ dysfunction.[34,35]

CRS severity can be graded by the uniform consensus grading system developed by the American Society for Transplantation and Cellular Therapy (ASTCT) (**See TABLE 4**).[35]

Preventive strategies, such as step-up dosing — gradually increasing initial doses to allow the immune system to adjust — are key to managing CRS.[33] This approach can sometimes be initiated in an outpatient setting, depending on the medication's prescribing information.

Protocols often include premedications, like corticosteroids, antihistamines

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TABLE 4: ASTCT CONSENSUS ON CYTOKINE RELEASE SYNDROME GRADING[35]

CRS PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Fever	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or		
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, face mask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

TABLE 5: ASTCT CONSENSUS ON ICANS GRADING FOR ADULTS[35]

NEUROTOXICITY DOMAIN	GRADE 1	GRADE 2	GRADE 3	GRADE 4
ICE score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness, such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad or signs of diffuse cerebral edema on neuroimaging

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and acetaminophen, to further reduce severe reactions. While not guideline-recommended, early trials suggest prophylactic tocilizumab may help prevent CRS.[36] However, it's not FDA-approved for this use, which could pose financial challenges.

▲ **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS):** ICANS is a critical and potentially severe toxicity that requires careful monitoring and management. It typically presents as neurological symptoms ranging from mild confusion and headaches to severe encephalopathy, seizures and cerebral edema.[33,35,37]

ICANS typically begins within a few days of starting treatment.[37] Though the exact mechanism is unclear, ICANS likely involves blood-brain barrier disruption and the infiltration of T cells and cytokines into the central nervous system.[33]

The Immune Effector Cell-Associated Encephalopathy (ICE) score is used to evaluate the severity of neurotoxicity in ICANS, assessing orientation, naming, command-following and handwriting. The ICE score is also a key component of the ICANS grading system developed by ASTCT (**See TABLE 5**).[33,35]

A lower ICE score indicates more severe neurotoxicity, making prompt recognition and intervention essential due to the variability in symptoms and duration. Most cases are mild to moderate (Grade 1 or 2), with more severe cases (Grades 3 or 4) involving seizures or cerebral edema, requiring intensive management.[35]

Management usually includes corticosteroids to reduce inflammation and supportive care, with close monitoring of neurological status.[35] Prompt recognition and intervention are crucial due to the variability in symptoms and duration.

▲ **Other Adverse Effects:** In addition to CRS and ICANS, BsAbs may lead to other adverse effects, such as hematologic toxicities including neutropenia, anemia and thrombocytopenia.[33]

These hematologic issues can elevate the risk of infections and bleeding, requiring careful monitoring and supportive care, like growth factor support or transfusions, to manage these

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complications. Furthermore, there is an increased risk of opportunistic infections with agents used in myeloma, lymphoma or leukemia.[32]

Patients may also experience fatigue, nausea and other gastrointestinal symptoms, impacting their quality of life. These symptoms are generally managed with supportive care measures, such as antiemetics for nausea and adjustments in activity levels to manage fatigue.

UNIQUE ADVERSE EFFECTS OF BsAbs TARGETING GPRC5D

GPRC5D is expressed in malignant bone marrow plasma cells and skin,[38] and targeting this receptor can result in unintended toxicities, including skin, nail and oral adverse events.[39]

▲ **Skin-Related Events:** Patients may experience skin-related adverse effects, such as rash, dryness, or other dermatologic reactions.[39] These events can vary in severity and may require topical treatments or systemic therapies to manage symptoms effectively.

▲ **Nail-Related Events**: Nail toxicity, including changes in nail color, texture, or growth, has been observed in some patients.[39] In studies, nail-related events typically resolved on their own without the need for intervention.

▲ **Oral and Gastrointestinal Events:** GPRC5D targeting can also lead to dysgeusia (altered taste), dry mouth and dysphagia (difficulty swallowing).[39] These symptoms can significantly affect a patient's ability to eat and enjoy food, which may contribute to nutritional challenges. Management strategies include pharmacological treatments, such as dexamethasone, triamcinolone and nystatin as well as dose modification.[39]

REMS PROGRAM FOR BsAbs IN R/R MM

The BsAbs indicated for r/r MM (e.g., talquetamab, teclistamab and elranatamab) are subject to the FDA's Risk Evaluation and Mitigation Strategies (REMS) program to manage serious risks such as CRS and ICANS.[12-14] The program ensures that healthcare providers are trained and certified to prescribe these therapies, enabling them to effectively manage severe adverse events.[40]

Additionally, treatment facilities must be equipped to handle these risks, particularly during the high-risk initial dosing period.

COMPARISON OF CAR-T THERAPY AND BsABs

▲ **Mechanism of Action and Indications:** CAR-T cell therapy and BsAbs operate through different mechanisms with distinct clinical applications.

CAR-T therapies involve genetically modifying a patient's T cells to target specific cancer antigens.[41,42] They are FDA-approved for certain types of non-Hodgkin lymphoma (e.g., DLBCL, primary mediastinal B-cell lymphoma (PMBCL), mantle cell lymphoma (MCL)), r/r MM and r/r B-cell ALL in both adults and children.[43,44]

BsAbs, in contrast, bind directly to T cells and cancer cells to trigger an immune response and are indicated for certain hematologic and solid tumor malignancies, as previously mentioned.[8-16]

For r/r lymphoma and r/r MM, BsAbs and CAR-T therapies are typically considered third or fourth lines of treatment.[45,46] However, both are now being studied in earlier lines of therapy for certain malignancies, which could broaden their application and offer new treatment options at earlier stages of disease management.

In fact, ciltacabtagene autoleucel, a CAR-T cell therapy, was recently approved in April 2024 as a second-line treatment for patients with r/r MM.[47]

▲ **Safety Profile and Accessibility:** Both CAR-T therapies and BsAbs can cause CRS and ICANS , though these events are more common with CAR-T products.[43]

For severe adverse events (Grade 3 or higher), CRS occurred in 46% of CAR-T patients, compared to 4.9% with BsAbs.[43]

Similarly, severe ICANS occurred in 12-32% of CAR-T patients, while BsAbs have a lower incidence, with severe ICANS occurring infrequently.[43]

CAR-T therapy requires a complex process involving apheresis and several weeks for manufacturing , whereas BsAbs are off-the-shelf products.[43] Additionally, CAR-T is a one-time treatment,[43,46] while BsAbs are typically administered weekly, biweekly or monthly, potentially for years.[8-16]

▲ **Clinical Outcomes:** Both CAR-T therapy and BsAbs demonstrate high response rates,[21-29,44] typically after multiple lines of treatment have failed.[48]

For example, in r/r B cell lymphoma and chronic lymphocytic leukemia, CAR-T therapies have shown ORRs of 44% to 91% and CRs of 28% to 68%.[44]

BsAbs, like blinatumomab, also show efficacy, with an ORR just above 40% and around 20% CRs in heavily pretreated DLBCL patients.[49]

A detailed comparison in efficacy between CAR-T and BsAbs is beyond the scope of this article.

BARRIERS AND CONSIDERATIONS FOR IMPLEMENTING BsAbs IN COMMUNITY SETTINGS

In recent years, implementing BsAb administration in community oncology settings has become increasingly feasible and promising.[43]

Key to successfully starting patients on BsAbs in outpatient settings is the careful management of potential adverse effects, such as CRS and ICANS. Healthcare providers must be trained to recognize and manage these toxicities, with resources like tocilizumab and corticosteroids readily available.

With the right infrastructure, including increased staffing and patient education, outpatient initiation of BsAbs, even with step-up dosing, is becoming more practical and likely to become the standard.[7]

Patients can be equipped with home monitoring tools such as a blood pressure cuff, pulse oximeter and thermometer to proactively manage their care and report

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symptoms early. This approach enhances patient safety, reduces the need for frequent hospital visits and improves the overall patient experience.[50-51]

Proper planning and support can address logistical challenges, ensuring that BsAb therapy is effectively managed in outpatient settings. By educating patients and families on the treatment, risks and the importance of reporting symptoms, healthcare providers can mitigate risks and manage adverse effects promptly.

SUMMARY

BsAbs have transformed cancer treatment by utilizing the immune system to specifically target and eliminate cancer cells.

Initially approved for relapsed or refractory cancers, these therapies are now being used in earlier treatment stages, demonstrating their broad potential.[52]

They have shown effectiveness in both hematologic cancers like multiple myeloma, lymphoma and leukemia and solid tumors such as uveal melanoma and small cell lung cancer.

However, their use requires careful management of side effects, notably CRS and ICANS. Compared to CAR-T therapies, BsAbs are more accessible due to their ready-to-use nature and also carry a lower risk of severe CRS and ICANS.

As research advances, these antibodies are becoming a key part of cancer treatment, offering flexible and effective options that add to and complement the existing therapy landscape.

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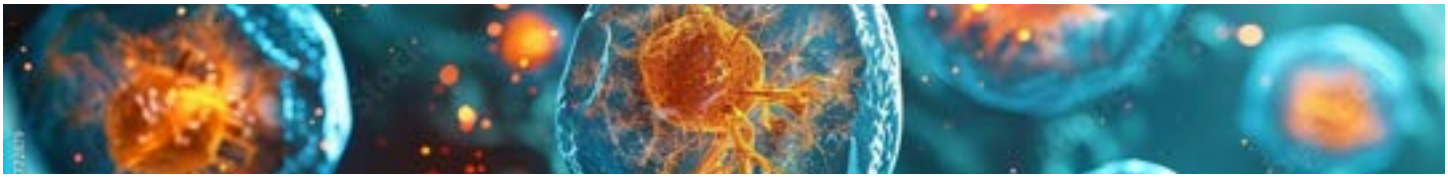

TABLE 1: BsABs IN LYMPHOMA (AS OF AUGUST 15, 2024)

Drug	Mosunetuzumab-axgb (LUNSUMIO™)[1,2]	Epcoritamab-bysp (EPKINLY®)[3,4]	Glofitamab-gxbm (COLUMVI™)[5,6]
Manufacturer	Genentech, Inc.	Genmab US, Inc.	Genentech, Inc.
Target	CD3xCD20	CD3xCD20	CD3xCD20
Indication	R/R follicular lymphoma following 2 or more lines of therapy	1. R/R diffuse large B-cell lymphoma following 2 or more lines of therapy 2. R/R follicular lymphoma following 2 or more lines of therapy	R/R diffuse large B-cell lymphoma following 2 or more lines of therapy
Route of administration	IV	SC	IV
Dosing schedule	C1: Days 1, 8, 15 C2+: Day 1, every 21 days, for up to 8 cycles in CR or up to 17 cycles for PR or SD	C1-3: Days 1, 8, 15, and 22 C4-9: Days 1 and 15 C10+: Day 1, every 28 days until progression	C1: obinutuzumab, Day 1; glofitamab-gxbm Days 8 and 15 C2-12: day 1, every 21 d
CRS mitigation			
Step-up dosing	C1D1: 1mg C1D8: 2mg C1D15: 60mg C2D1: 60mg C3+D1: 30mg	R/R DLBCL C1D1: 0.16mg C1D8: 0.8mg C1D15: 48mg C1D22: 48mg C2D1+: 48mg R/R FL C1D1: 0.16mg C1D8: 0.8mg C1D15: 3mg C1D22: 48mg C2D1+: 48mg	C1D1: obinutuzumab 1,000mg C1D8: 2.5mg (first glofitamab-gxbm dose) C1D15: 10mg C2D1+: 30mg
Premedications	1. A/P 500-1,000mg, 30 minutes prior, for C1 and C2 2. Diphenhydramine 50-100mg (or equivalent), 30 minutes prior, for C1 and C2 3. Dexamethasone 20mg or methylprednisolone 80mg, 1 hour prior, for C1 and C2. Continue all premedications if CRS with prior dose.	1. A/P 650-1,000mg, 30-120 minutes before C1 treatments 2. Diphenhydramine 50mg (or equivalent), 30-120 minutes before C1 treatments 3. Dexamethasone 15mg or prednisolone 100mg (or equivalent), 30-120 minutes before C1 treatments and for three consecutive days after. Continue dexamethasone thereafter if G2 or G3 CRS with prior dose.	1. A/P 500-1,000mg, 30 minutes before all treatments (2) Diphenhydramine 50mg (or equivalent), 30 minutes before all infusions 3. Dexamethasone 20mg (or equivalent), 1 hour before treatment on C1D8, C1D15, C2D1, and C3D1. Continue if CRS with prior dose.
Hospitalization	Not required	C1D15: 24-h admission (DLBCL only), not required for FL	C1D8: 24-h admission
CRS occurrence	G1: 26%; G2: 17%; G3: 1%; G4: 1%; G5: 0% Time course for CRS onset C1D1: 23.3% C1D8: 5.6% C1D15: 36.4% C2D1: 10.3% C3+D1: 2.4% Median time (hours) to CRS onset C1D1: 5 C1D8: 20 C1D15: 27 C2D1: 38	G1: 34%; G2: 15%; G3: 3%; G4: 0%; G5: 0% Time course for CRS onset C1D1 DLBCL 9% FL 14% C1D8 DLBCL 16% FL 7% C1D15 DLBCL 61% FL 17% C1D22 DLBCL 6% FL 49% Median time (hours) to CRS onset All doses: DLBCL 24, FL 59 First full dose: DLBCL 20, FL 61	G1: 47%; G2: 12%; G3: 3%; G4: 1%; G5: 0% Time course for CRS onset C1D8: 42.8% C1D15: 25.2% C2: 26% C3+: 0.9% Median time (hours) to CRS onset C1D8: 13.5 (range: 6-52)
Median duration of CRS	Three days (range: 1-29 days)	Two days (range: 1-27 days)	30.5 hours (range: 0.5-317 hours)
ICANS	G1-2: 3%; G3: 0%; G4: 0%; G5: 0%	G1: 4.5%; G2: 1.3%; G3: 0%; G4: 0%; G5: 0.6%	G1-2: 5%; G3-4: 3%; G5: 0%
Any Grade Adverse Events (with >25% incidence)	Lymphopenia (100%), decreased phosphate (78%), anemia (68%), WBC decreased (60%), neutropenia (58%), thrombocytopenia (46%), cytokine release syndrome (44%), fatigue (42%), glucose increase (42%), rash (39%), AST increased (39%), decreased magnesium (34%), hypokalemia (33%), ALT increased (32%), headache (32%), pyrexia (29%), musculoskeletal pain (28%)	Lymphopenia (87%), anemia (62%), hyponatremia (56%), decreased phosphate (56%), decreased WBC (53%), cytokine release syndrome (51%), neutropenia (50%), thrombocytopenia (48%), AST increased (48%), ALT increased (45%), decreased potassium (34%), decreased magnesium (31%), fatigue (29%), musculoskeletal pain (28%), injection site reactions (27%)	Lymphopenia (90%), decreased fibrinogen (84%), anemia (72%), cytokine release syndrome (70%), decreased phosphate (69%), neutropenia (56%), thrombocytopenia (56%), hyponatremia (49%), hypocalcemia (49%), infection (35%), hypokalemia (32%)
Grade 3 or > Adverse Events (with >25% incidence)	Lymphopenia (98%), decreased phosphate (46%), increased glucose (42%), neutropenia (40%)	Lymphopenia (77%), neutropenia (32%)	Lymphopenia (83%), neutropenia (26%), decreased phosphate (28%)
REMS Program	No	No	No
Drug Approval	December 2022	May 2023 (DLBCL), June 2024 (FL)	June 2023
Pivotal Trial	GO29781	EPCORE NHL-1	NP30179

ABBREVIATIONS: A/P: Acetaminophen; **ALL:** Acute Lymphoblastic Leukemia; **ALT:** Alanine Aminotransferase; **AST:** Aspartate Aminotransferase; **BCMA:** B-Cell Maturation Antigen; **BCP:** B-cell Precursor; **CRS:** Cytokine Release Syndrome; **C:** Cycle; **CD**: Cluster of Differentiation; **D:** Day; **DLBCL:** Diffuse Large B Cell Lymphoma; **DLL3:** Delta-like ligand 3; **ES-SCLC:** Extensive Stage Small Cell Lung Cancer; **FL:** Follicular Lymphoma; **G1:** Grade 1; **G2:** Grade 2; **G3:** Grade 3; **G4:** Grade 4; **G5:** Grade 5; **GPRC5D:** G-protein-coupled receptor, class C, group 5, member D; **HLA:** Human Leukocyte Antigen; **ICANS:** Immune Effector Cell-Associated Neurotoxicity Syndrome; **IV:** Intravenous; **MRD:** Minimal Residual Disease; **NR:** Not Reported; **NS:** Normal Saline; **PR:** Partial Response; **R/R:** Relapsed/Refractory; **SC:** Subcutaneous; **WBC:** White Blood Cell

TABLE 2: BsABs IN MULTIPLE MYELOMA (AS OF AUGUST 15, 2024)

Drug	Teclistamab-cqyv (TECVAYLI®)[7,8]	Talquetamab-tgvs (TALVEY™)[9,10]	Elranatamab-bcmm (ELREXFIO™)[11,12]
Manufacturer	Janssen Biotech, Inc.	Janssen Biotech, Inc.	Pfizer
Target	CD3xBCMA	CD3xGPRC5D	CD3xBCMA
Indication	RRMM following four or more lines of therapy	RRMM following four or more lines of therapy	RRMM following four or more lines of therapy
Route of administration	SC	SC	SC
Dosing schedule	C1: days 1, 3, 5 C2+: weekly until progression For patients who have achieved and maintained a CR or better for >6 months, consider biweekly dosing	Weekly C1: days 1, 4, 7 C2+ weekly until progression Biweekly C1: days 1, 4, 7, 10 C2+: every two weeks until progression	C1: days 1, 4, 8 C2+: once weekly through week 24 Week 25+: biweekly
CRS mitigation Step-up dosing	C1D1: 0.06mg/kg C1D3 (within two to four days after dose1): 0.3mg/kg C1D5 (within two to four days after dose 2): 1.5 mg/kg C2D1 (one week after first treatment dose): 1.5mg/kg weekly	Weekly dosing C1D1: 0.01 mg/kg C1D4 (between 2-4 days of previous dose): 0.06mg/kg C1D7 (between 2-4 days of previous dose): 0.4mg/kg C2D1 (one week after first treatment dose): 0.4mg/kg once weekly Biweekly dosing C1D1: 0.01mg/kg C1D4 (between 2-4 days of previous dose): 0.06mg/kg C1D7 (between 2-4 days of previous dose): 0.4 mg/kg C1D10 (between 2-7 days after dose 3): 0.8mg/kg C2D1: 0.8 mg/kg every two weeks	C1D1: 12mg C1D4 (min of two days between dose 1 and 2): 32mg C1D8 (min. of three days between dose 2 and 3): 76mg C2D1 (one week after first treatment dose; min. of six days between treatment doses): 76mg
Premedications	(1) A/P 650-1,000mg (or equivalent), one to three hours prior, for C1 treatments (2) Diphenhydramine 50mg (or equivalent), one to three hours prior, for C1 treatments (3) Dexamethasone 16mg, one to three hours prior, for C1 treatments	(1) A/P 650-1,000mg (or equivalent), one to three hours prior, for C1 treatments (2) Diphenhydramine 50mg (or equivalent), one to three hours prior, for C1 treatments (3) Dexamethasone 16mg (or equivalent), one to three hours prior, for C1 treatments	(1) A/P 650mg (or equivalent), ~1 hour prior, for C1 treatments (2) Diphenhydramine 25mg (or equivalent), ~1 hour prior, for C1 treatments (3) Dexamethasone 20mg (or equivalent), ~1 hour prior, for C1 treatments
Hospitalization	For 48 hours after administration of step-up doses	For 48 hours after administration of step-up doses	For 48 hours after administration of first step-up dose, and for 24 hours after administration of second step-up dose
CRS occurrence	G1: 50%; G2: 21%; G3: 0.6%; G4: 0%; G5: 0%	G1: 57%; G2: 17%; G3: 1.5%; G4: 0%; G5: 0%	G1: 44%; G2: 14%; G3: 0.5%; G4: 0%; G5: 0%
	Time course for CRS onset C1D1: 42% C1D3: 35% C1D5: 24% Subsequent doses: 3%	Median time (h) to CRS onset All doses: 48	Time course for CRS onset Weekly dosing C1D1: 29% C1D4: 44% C1D7: 30% Biweekly dosing C1D7: 33% C1D10: 12%	Median time (h) to CRS onset All dose: 27 (range 0.1-167)	Time course for CRS onset C1D1: 43% C1D4: 19% C1D8: 7% C1D1: 1.6%	Median time (d) to CRS onset All doses: 2 (range: 1-9)
Median duration of CRS	Two days	17 hours (range 0-622 hours)	Two days (range: one to 19 days)
ICANS	Any grade: 6%	Any grade: 9%	Any grade: 3.3%
Any Grade Adverse Events (with >25% incidence)	Cytokine release syndrome (72.1%), neutropenia (70.9%), anemia (52.1%), thrombocytopenia (40%), lymphopenia (34.5%), diarrhea (28.5%), fatigue (27.9%), nausea (27.3%), pyrexia (27.3%), injection-site reaction (26.1%)	Lymphopenia (90%), pyrexia (83%), cytokine release syndrome (76%), WBC decreased (73%), dysgeusia (70%), anemia (67%), neutropenia (64%), thrombocytopenia (62%), albumin decreased (66%), nail disorder (50%), Alk phos increased (49%), phosphate decreased (44%), musculoskeletal pain (43%), skin disorder (41%), rash (38%), ALT increased (33%), AST increased (31%), hypokalemia (31%), hyponatremia (31%), weight loss (35%), dry mouth (34%), xerosis (30%), fatigue (37%)	Lymphopenia (91%), WBC decreased (69%), anemia (68%), neutropenia (62%), thrombocytopenia (61%), cytokine release syndrome (58%), decreased albumin (55%), fatigue (43%), increased AST (40%), increased creatinine (38%), injection site reaction (37%), hypokalemia (36%), diarrhea (36%), rash (35%), upper respiratory tract infection (34%), musculoskeletal pain (34%), Alk phos increased (34%), diarrhea (32%), decreased CrCl (32%)
Grade 3 or > Adverse Events (with >25% incidence)	Neutropenia (64.2%), anemia (37%), lymphopenia (32.7%)	Lymphopenia (80%), WBC decreased (35%), neutropenia (35%), anemia (30%)	Lymphopenia (84%), neutropenia (51%), anemia (43%), decreased WBC (40%), thrombocytopenia (32%)
REMS Program	Yes	Yes	Yes
Drug Approval	October 2022	August 2023	August 2023
Pivotal Trial	MajesTEC-1	MonumenTAL-1	MagnetisMM-3

ABBREVIATIONS: **A/P:** Acetaminophen; **ALL:** Acute Lymphoblastic Leukemia; **ALT:** Alanine Aminotransferase; **AST:** Aspartate Aminotransferase; **BCMA:** B-Cell Maturation Antigen; **BCP:** B-cell Precursor; **CRS:** Cytokine Release Syndrome; **C:** Cycle; **CD**: Cluster of Differentiation; **D:** Day; **DLBCL:** Diffuse Large B Cell Lymphoma; **DLL3:** Delta-like ligand 3; **ES-SCLC:** Extensive Stage Small Cell Lung Cancer; **FL:** Follicular Lymphoma; **G1:** Grade 1; **G2:** Grade 2; **G3:** Grade 3; **G4:** Grade 4; **G5:** Grade 5; **GPRC5D:** G-protein-coupled receptor, class C, group 5, member D; **HLA:** Human Leukocyte Antigen; **ICANS:** Immune Effector Cell-Associated Neurotoxicity Syndrome; **IV:** Intravenous; **MRD:** Minimal Residual Disease; **NR:** Not Reported; **NS:** Normal Saline; **PR:** Partial Response; **R/R:** Relapsed/Refractory; **SC:** Subcutaneous; **WBC:** White Blood Cell

TABLE 3: BsABs IN OTHER INDICATIONS (AS OF AUGUST 15, 2024)

Drug	Blinatumomab (BLINCYTO®)[13-16]	Tebentafusp-tebn (KIMMTRAK®)[17,18]	Tarlatamab-dlle (IMDELLTRA™)[19,20]
Manufacturer	Amgen, Inc.	Immunocore Commercial LLC	Amgen, Inc.
Target	CD3xCD19	CD3xgp100peptide-HLA	CD3xDLL3
Indication	(1) MRD+ BCP-ALL (2) R/R BCP-ALL (3) BCP-ALL in the consolidation phase	HLA-A*02:01-positive unresectable or metastatic uveal melanoma	ES-SCLC following progression on platinum-based chemotherapy
Route of administration	IV	IV	IV
Dosing schedule	MRD+ BCP-ALL and BCP-ALL in consolidation phase Induction Cycle 1: days 1-28 then 14 days off Consolidation Cycles 2-4: days 1-28 then 14 days off R/R BCP-ALL Induction C1 and C2: days 1-28 then 14 days off Consolidation C3-5: days 1-28 then 14 days off Continued Therapy C 6-9: days 1-28 then 56 days off	Once weekly until progression	C1: days 1, 8 ,15 C2+: days 1 and 15; every 28 days until progression
CRS mitigation			
Step-up dosing	R/R BCP-ALL, Induction Cycle 1: Days 1-7: 9mcg/day Days 8-28: 28mcg/day Note: see PI for dosing for patients under 45kg	C1D1: 20mcg C1D8: 30mcg C1D15: 68mcg C2D1+: 68mcg once weekly	C1D1: 1mg C1D8+: 10mg C1D15: 10mg C2D1+: 10mg every two weeks
Premedications	MRD+ BCP-ALL and BCP-ALL in consolidation phase Corticosteroid (IV): Prednisone 100mg (or equivalent) prior to D1 dose in each cycle For adults with R/R B-cell precursor ALL Corticosteroid (IV): Dexamethasone 20mg prior to D1 dose in each cycle, prior to a step-up dose, and when restarting an infusion after interruption of ≥4 hours	None	(1) Dexamethasone 8mg IV (or equivalent), one hour before treatment on C1D1 and C1D8 (2) 1L NS IV over four to five hours immediately after infusion completion on C1D1, C1C8, and C1D15
Hospitalization	MRD+ BCP-ALL and BCP-ALL in consolidation phase: C1 (3 d) and C2 (2 d) R/R BCP-ALL: C1 (9 d), C2 (2 d)	Appropriate healthcare setting: Optional (monitor for 16 hours after infusion completion for first three doses; then as clinically indicated)	Appropriate healthcare setting: Optional (monitor for 22 to 24 hours from start of infusion on C1D1 and C1D8, 6-8 h post-infusion on C1D15, three to four hours post-infusion on C2D1 and C2D15, and two hours post-infusion on all subsequent infusions)
CRS occurrence	MRD+ BCP-ALL (any grade): 15% R/R BCP-ALL (any grade): 7% BCP-ALL in consolidation phase: 16%	G1: 12%; G2: 76%; G3: 0.8%; G4: 0%; G5: 0%	G1: 34%; G2: 19%; G3: 1.1%; G4: 0.5%; G5: 0%
	Time course for CRS onset: NR Median time (d) to CRS onset: All doses: 2	Time course for CRS onset C1D1: ~85% C1D8: ~75% C1D15: ~60% C2D1: ~30% C2D8: ~10% Median time to CRS onset: All doses: within the day of the infusion	Time course for CRS onset C1D1: 39% C1D8: 28% C1D15: 6% C1D1: 2% Median time (h) to CRS onset: All doses: 13.5 (range: 1-268)
Median duration of CRS	Five days	Two days	Four days (IQR two to six days)
ICANS	Any grade: 7.5%	N/A	G1: 5.3%; G2 or greater: 3.7%; G5: 0%
Any Grade Adverse Events (with >25% incidence)	Pyrexia (91%), Infusion-related reactions (77%), headache (39%), infections-unspecified (39%), tremor (31%), neutropenia (31%), anemia (25%), chills (28%)	Cytokine release syndrome (89%), rash (83%), pyrexia (76%), pruritus (69%), chills (47%), nausea (43%), fatigue (41%), hypotension (38%), dry skin (29%), vomiting (26%)	Cytokine release syndrome (55%), fatigue (51%), pyrexia (36%), dysgeusia (36%), decreased appetite (34%), musculoskeletal pain (30%), constipation (30%), anemia (27%)
Grade 3 or > Adverse Events (with >25% incidence)	Neutropenia (28%)	N/A	Decreased lymphocytes (57%)
REMS Program	No	No	No
Drug Approval	December 2014	January 2022	May 2024
Pivotal Trial(s)	BLAST, TOWER, ECOG-ACRIN E1910	IMCgp100-202	DeLLphi-301

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'ENGAGING' BISPECIFICS IN THE COMMUNITY SETTING

By Sarah Rockwell, PharmD, BCOP

T Cell Engaging Bispecific Antibodies (BsAbs) have recently become an attractive treatment option in relapsed/refractory multiple myeloma, follicular lymphoma, diffuse large B-cell lymphoma, and most recently, small cell lung cancer.


Sarah Rockwell

At time of publication, there have been seven new BsAbs approved in less than two years, with more on the way.[1,2] As such, these therapies are gaining a lot of attention in the oncology world, and the need to adapt and adopt these therapies is becoming increasingly important.

Compared to chimeric antigen receptor (CAR) T-cell therapy, BsAbs have gained a lot of attention in that they are considered "off-the-shelf" therapies that can be acquired similar to other traditionally manufactured drugs.

Conversely, CAR T-cell therapy requires a multi-step process prior to administration, including patient-specific T-cell manufacturing that could take several weeks, a luxury not all patients have.[3]

While CAR T-cell therapy has been shown to be highly efficacious and is a great treatment option for many patients, BsAbs offer an alternative when CAR T-cell therapy is not logistically, clinically or financially feasible for a patient, or if the patient has already progressed on CAR T-cell therapy.[3-5]

WHAT MAKES BsAbs SO UNIQUE?

T cell-engaging BsAbs work by selectively bringing T cells, a patient's healthy immune system cell, directly to the cancer cell target to activate the T cells and elicit an immune response leading to cancer cell destruction.[3,6]

However, this same mechanism that is responsible for efficacy of the BsAbs can also result in significant adverse effects, such as Cytokine Release Syndrome (CRS) and neurotoxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).[3,6,7]

Accordingly, many BsAbs are associated with unique components in order to mitigate and/or monitor for these adverse effects, including, but not limited to, the following:

- SET-UP DOSING AND SUPPORTIVE CARE
- INPATIENT MONITORING AND/OR COMPLEX MONITORING
- RISK EVALUATION MITIGATION STRATEGY (REMS) PROGRAMS

Additionally, BsAbs are associated with significant cytopenias and infection risk, requiring close management and follow-up of patients on continuous therapy.[3,6-8]

Uniquely, talquetamab, a GPRC5D-targeted BsAb, is associated with serious dermatologic and oral toxicities that may require engagement of tertiary support such as nutrition and dermatology to monitor and manage throughout therapy.[9]

While all of these factors, and more, must be carefully considered when deciding to adopt BsAbs into practice, they are simply pieces of the puzzle. With a strategic approach, collaboration and standardization in place, BsAbs can be adopted into the community setting in a manner that is safe for patients and efficient for the practice.

MAINTENANCE THERAPY IN THE COMMUNITY SETTING

One approach to adopting BsAbs in the community setting is by starting with "Maintenance Therapy." This can mean something different for each drug, but in general, refers to doses following the step-up dosing period.

The risk of CRS and ICANS is typically highest at therapy initiation and during dose increases (also known as step-up dosing), which typically occur during the first cycle.[7]

Step-up dosing is typically when hospitalization and/or complex monitoring requirements are in place, although it can vary per drug and per patient. Following step-up dosing, the risk of CRS and ICANS, while still present, decreases significantly for subsequent doses/cycles.[7,9]

For community practices unable to accommodate complex monitoring either due to limitations in infrastructure, staffing or other resources, choosing to adopt BsAbs after this high-risk monitoring period may be a feasible option.

KEY SELECT CONSIDERATIONS FOR IMPLEMENTING BsAbs

However, it is important to note that even if the step-up dosing/complex monitoring periods are circumvented by adopting BsAbs as maintenance therapies in the community setting, there are still several factors that must be considered to safely adopt these therapies. While discussion of all factors of a successful BsAb maintenance program is beyond the scope of this article, select

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COMMUNITY

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considerations have been included.

Providers, nursing and pharmacy staff must be educated on these unique therapies — not only in terms of CRS and ICANS risk and management, but also prolonged infection risk, supportive care requirements and unique drug-specific toxicities as mentioned.

Drug education webinars or in-person presentations, internal learning system modules, standard operating procedures (SOPs), and drug manufacturer trainings are all methods that can be utilized to engage and educate members of the care team prior to implementing BsAbs in the community setting.

In addition to education, SOPs must be developed, not only to maintain compliance with those drugs requiring REMS programs, but also to standardize monitoring and management approaches, especially with regard to CRS and ICANS management, blood count monitoring/cytopenia management and infection prophylaxis, monitoring, and management.[7,8]

REMS program implementation is another important piece of the puzzle for those drugs requiring REMS programs. Appropriate SOPs must be developed, and key operational representatives for the REMS programs must be established, in addition to program enrollment by the facilities and prescribers.

PRACTICE EDUCATION AND TRAINING: PROVIDERS, NURSING, PHARMACY

STANDARD OPERATING PROCEDURES (SOP): CLINICAL (E.G., TOXICITY MANAGEMENT) AND OPERATIONAL

REMS PROGRAM IMPLEMENTATION AND COMPLIANCE

CONCLUSION

As T cell-engaging BsAbs continue to gain traction in the oncology space, enlisting our community practice providers in the management of these patients and implementation of these therapies is imperative and key to improving patient access.

Implementing these therapies with step-up dosing may not be a feasible option for all community practice settings. But starting with maintenance therapy can be an effective, efficient and safe first step to improve access to patients while exposing community providers and staff to BsAbs.

▲ **Sarah Rockwell**, PharmD, BCOP, is a clinical oncology pharmacist and cellular therapies specialist at Florida Cancer Specialists and Research Institute in Tampa, Florida.

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TARLATAMAB: A NOVEL BISPECIFIC T-CELL ENGAGER FOR SMALL CELL LUNG CANCER

A PRIMER FOR SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) is an aggressive neuroendocrine tumor that accounts for about 15% of all lung cancers.[1] SCLC is difficult to treat and has a poor prognosis, with patients typically relapsing after responding to first-line treatment and having a median survival of about six months, if responsive to second-line therapy.[2,3]

SCLC is categorized into limited and extensive stages, where limited stage is confined to the ipsilateral hemithorax. Up to 80% of patients initially diagnosed with SCLC have extensive stage, which has limited treatment options.[4]

Unlike targeted therapies for non-small cell lung cancer (NSCLC) successful in prolonging overall survival, the search for potential biomarkers and targeted therapies for SCLC has not been as successful, despite identifying several genetic mutations.[5]

The mainstay of treatment for extensive stage SCLC is systemic therapy consisting of a platinum (cisplatin or carboplatin) and etoposide with immunotherapy targeting programmed death ligand 1(PD-L1; atezolizumab or durvalumab) followed by maintenance immunotherapy.[2]

The addition of immunotherapy has provided an increase in overall survival of about two to three months compared with chemotherapy alone.[6,7] Other recommended regimens include the use of irinotecan instead of etoposide.

For patients who have disease progression or relapse after initial treatment, the options are limited. In addition to clinical trial enrollment, some recommended regimens include re-treatment with platinum-based doublet, oral or intravenous topotecan, irinotecan, nivolumab, pembrolizumab, and newer agents such as lurbinectedin and tarlatamab.[2,8]

By Edgardo Mendoza, PharmD

Tarlatamab is a bispecific T-cell engager (BiTE) with a novel mechanism of action for the treatment of adults with extensive stage SCLC. This therapy is the first of its kind for a major solid tumor.

The U.S. Food and Drug Administration (FDA) granted accelerated approval to tarlatamab in May 2024 for the treatment of extensive stage SCLC that have progressed on or after platinum-based chemotherapy.

Edgardo Mendoza

Tarlatamab targets delta-like ligand 3 (DLL3) on cancer cells and CD3 on T cells.[9] The linking of DLL3-positive cancer cells with CD-3 positive T cells leads to T-cell activation and release of granzyme and perforin, which leads to tumor cell lysis.[10] DLL3, an inhibitory ligand, is part of the Notch pathway involved in the development of lung neuroendocrine cells.[5,9]

About 85% to 94% of SCLC is characterized by an overexpression of DLL3 on the surface neuroendocrine tumor cells. Meanwhile, DLL3 is normally localized intracellularly in healthy cells, making it a good therapeutic target.[7,10]

Other agents targeting DLL3 have been tested in previous trials. One such agent is an antibody-drug conjugate (ADC) rovalpituzumab tesirine (Rova-T) targeting DLL3. While Rova-T initially showed promising results in a phase 1 study, subsequent phase 3 trials failed to show superiority compared to standard of care.

Furthermore, because of the drug's side effect profile — including severe edema, serous effusions and thrombocytopenia — in addition to its modest clinical benefit, further studies on Rova-T were stopped.[5,10]

In contrast, the clinical trials have thus far shown tarlatamab to be a promising therapy for extensive stage small cell lung cancer.

DeLLphi-300 is a phase 1, open-label, international, dose-escalation study evaluating the safety and antitumor activity by modified Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) in 107 patients with relapsed/refractory SCLC.

In terms of the primary endpoint, the most common treatment-related adverse event was cytokine release syndrome (CRS), which occurred in 56 of 107 patients (52%).

Other common adverse effects were pyrexia (~40%) and constipation (~30%). The results for the secondary efficacy endpoints were as follows: objective response rate (ORR) of 23.4% (95% CI, 15.7 — 32.5), median duration of response (DOR) of 12.3 months (95% CI, 6.6 — 14.9), disease control rate (DCR) of 51.4% (95% CI, 41.5 — 61.2), median progression-free survival (PFS) of 3.7 months (95% CI 2.1 — 5.4), and overall survival (OS) of 13.2 months (95% CI, 10.5 — not reached).[11]

DeLLphi-301 is a phase 2, open-label, international trial evaluating tarlatamab at two dose levels, 10mg and 100mg, administered intravenously every two weeks in 220 patients with advanced SCLC who had disease progression on or after platinum-based chemotherapy and at least one other line of prior therapy.

The primary endpoint was objective

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TARLATAMAB

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response per RECIST 1.1. Another major efficacy endpoint was duration of response as assessed by blinded independent central review. The overall response rate (ORR) for the patients who received the 10mg dose (FDA-approved dose) was 40% (95% CI 29 – 52) and the DOR was ≥6 months in 59% and ≥9 months in 29% of patients. The median PFS for the 10mg group was 4.9 months (95% CI 2.9 – 6.7), and the median OS was 14.3 months.[9]

The promising results of this clinical trial has led to the accelerated approval of tarlatamab for the treatment of extensive stage small cell lung cancer with disease progression on or after platinum-based chemotherapy.

Results from phase 1 and 2 studies have shown that tarlatamab has manageable adverse effects. Tarlatamab has a boxed warning for serious and life-threatening cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS).

Most of the CRS that occurred were grade 1 or 2 in severity, occurring in about 50% of patients.

Other common adverse effects include fatigue (51%), pyrexia (36%), dysgeusia (36%), decreased appetite (34%), musculoskeletal pain (30%), constipation (30%), anemia (27%) and nausea (22%).

Common laboratory abnormalities include decreased lymphocytes, decreased sodium, increased uric acid, decreased total neutrophils, decreased hemoglobin, increased activated partial thromboplastin time, and decreased potassium.[9,11,12]

Based on the phase 1 and phase 2 clinical trial data, the approved dosing of tarlatamab involves a step-up dose of 1mg on cycle 1 Day 1, followed by 10mg on cycle 1 Day 8 and Day 15. Tarlatamab is dosed every two weeks, starting from cycle 2 onwards.[9,11,12]

To reduce the risk of CRS, 8mg of intravenous dexamethasone is given within one hour of tarlatamab infusion on Day 1 and Day 8 of cycle 1. Prophylactic hydration with 1 liter of normal saline is given after the infusion on each day of cycle 1. Patients are monitored for 22 to 24 hours after the first two doses (step-up doses) of tarlatamab and remain within one hour of an appropriate healthcare setting for a total of 48 hours.

After the first two doses, extended monitoring in a healthcare setting is not required unless the patient experiences Grade ≥2 CRS, or ICANS during prior treatments.

Furthermore, the duration of monitoring recommended for subsequent doses are as follows: for cycle 1 Day 15 and cycle 2 doses, six to eight hours after the infusion; for cycles 3 and 4, three to four hours after the infusion; and for cycle 5 onwards, two hours after the infusion.[12]

CONCLUSION

Tarlatamab is a BiTE that presents a new therapeutic approach for the treatment of previously treated extensive stage SCLC. The results from phase 1 and phase 2 clinical trials have thus far been promising for this patient population that has few therapeutic options. The continued approval of tarlatamab is dependent upon the results from the ongoing phase 3 DeLLphi-304 trial.

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LIFILEUCEL: AN FDA-APPROVED TUMOR-INFILTRATING LYMPHOCYTE THERAPY FOR ADVANCED MELANOMA

By Katelyn Yamartino, PharmD, BCOP

Skin cancer represents the most common type of malignancy in the United States, with invasive melanoma representing about 1% of all skin cancers diagnosed.[1]

Despite only representing a small proportion, invasive melanoma is responsible for the most deaths associated with skin cancer. In 2024, it is estimated that there will be 100,640 incidence cases with an estimated 8,290 deaths associated with melanoma.[2]

Katelyn Yamartino

Melanoma is a type of skin cancer that originates from melanocytes, which are specialized skin cells that produce the pigment melanin. This type of skin cancer involves multiple signaling pathways, making advanced melanoma difficult to treat.

Fortunately, most patients are diagnosed when the disease is at the localized or regional stage and is primarily treated with surgical resection.[3] Individuals with localized and regional melanoma have a five-year relative survival of 100% and 74.8%, respectively.

However, as the melanoma spreads, it becomes more difficult to treat, and we see a significant reduction in five-year relative survival. For patients diagnosed with metastatic melanoma, the five-year relative survival decreases to around 35%.[2]

IMMUNE CHECKPOINT INHIBITORS

The introduction of immune checkpoint inhibitors (ICIs) and target therapies over the past decade has significantly improved survival outcomes in patients with melanoma.

Combination treatment with ipilimumab, a cytotoxic T-lymphocyte antigen 4 (CTLA-4), and nivolumab, a programmed death 1 (PD-1) protein, has been associated with a 53% response rate in patients with metastatic melanoma and is currently the standard of care for most patients.[3,4]

BRAF/MEK inhibitors, such as dabrafenib and trametinib, have also been shown to be beneficial in patients with metastatic melanoma who have the relevant mutations with response rates greater than 60%. However, only 35% to 50% of patients with advanced melanoma have these targetable mutations.[5,6,7]

Despite the success of these agents, many patients who received single or combination ICI may still progress. ICI primary resistance is seen in about 40% to 65% of patients and acquired resistance is seen in about 30% to 40% of patients.

In addition, BRAF plus MEK inhibitor therapy has also been associated with resistance, and patients may have rapid disease progression on relapse.

There are limited treatment options that have shown significant benefit for patients who have progressed after treatment with ICI and BRAF/MEK inhibitors.

Cytotoxic chemotherapy has been shown to have a limited response rate of only 4% to 12% with an overall survival (OS) of about seven months. Retreatment with ICI has been associated with response rates ranging from 9% to 29%, with OS of five to 26 months.[8]

TUMOR-INFILTRATING LYMPHOCYTE THERAPY

Due to limited options for patients with metastatic melanoma who progress after first-line treatment, there has been significant need to identify new and safe treatment options following ICI failure.

Lifileucel is the first U.S. Food and Drug Administration- (FDA) approved tumor-infiltrating lymphocyte (TIL) therapy. Lifileucel was granted accelerated approval based on objective response rate for adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.[9]

Lifileucel is a tumor-derived autologous T-cell immunotherapy that produces polyclonal patient-specific TIL (CD8+ and CD4+ T cells) that migrate to tumor sites and target tumor associated neoantigens and mediate tumor cell lysis.[8]

Adoptive cell therapy with the use of TILs was initially developed in the 1980s by Steven Rosenberg, MD, PhD, and his colleagues. They discovered that TIL therapy could shrink tumors in patients with metastatic melanoma.

TIL is similar to CAR-T therapy in which the product is made utilizing a patient's own T cells to target malignant cells.[10]

In CAR-T therapy, T cells are collected from the circulating blood and are genetically modified to recognize malignant cells. These are then expanded, cryopreserved and sent back to the institution for administration. CAR-T therapy is typically used in hematologic cancers such as acute lymphocytic leukemia (ALL), lymphomas and multiple myeloma.[11]

In TIL therapy, T cells are collected directly from the patient's tumor. These cells are then sent to a manufacturer where TILs are isolated from the tumor tissue, expanded and cryopreserved, and returned to the institution administering the therapy.

Unlike CAR-T cells, which are genetically modified to recognize tumor cells, TILs are not modified before being

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expanded. This is due to the cells ability to already recognize and navigate to the tumor since they were collected directly from the tumor tissue.[8]

ADMINISTRATION

Lifileucel must be administered at an inpatient hospital setting with an intensive care unit (ICU) and specialists who are skilled in cardiopulmonary or intensive care medicine.

Prior to lifileucel infusion, the patient must undergo a non-myeloablative lymphodepleting regimen with cyclophosphamide and fludarabine. Cyclophosphamide 60mg/kg IV with mesna is given for two days followed by fludarabine 25mg/m2 IV daily for five days. Lifileucel should then be infused as soon as possible after 24 hours but no later than four days after the last fludarabine dose.

Lifileucel is dosed between 7.5 x 109 and 72 x 109 viable cells and may be suspended in up to four bags. The patient should be premedicated with acetaminophen and diphenhydramine or another H1 antagonist 30 to 60 minutes prior to lifileucel administration. Lifileucel is given at a rate of 1 mL per minute for the first five minutes, then 5-10 mL per minute thereafter.[12]

Interleukin-2, also known as IL-2 (aldesleukin), should then be administered beginning three to 24 hours after lifileucel administration in order to expand the TILs in vivo. The dosing for IL-2 is 600,000 IU/kg every eight to 12 hours for up to a maximum of six doses.

Patients should receive filgrastim or a biosimilar starting the day after lifileucel and continued until the absolute neutrophil count (ANC) is greater than 1,000/mm3 for three consecutive days, or per institutional standard of neutropenia. All patients should also receive prophylactic antimicrobials.[12]

EFFICACY

Lifileucel was given accelerated approval by the FDA in February 2024 due to the results from the C-144-01 clinical trial. Efficacy data from 153 participants was reported in a pooled analysis of consecutive cohorts (66 patients from Cohort 2 and 87 patients from Cohort 4) from the C-144-01 study.

Eighty-three patients (54.2%) had cutaneous melanoma, with a minority having mucosal or acral, and 47 patients (30.7%) had either unknown primary or insufficient information. Additionally, 47.1% of patients had baseline liver and/or brain metastasis.

Patients in the study had a median of three lines of prior treatment with all patients receiving prior anti-PD-1/PD-L1 therapy. Also, 81.7% of patients received anti-CTLA-4 therapy, 53.6% received a combination anti-PD-1/anti-CTLA-4 therapy and 25.5% received BRAF/MEK inhibitors. Out of the group, 83 patients (54.2%) were considered refractory to anti-PD-1/PD-L1 therapy.[8]

Primary outcomes from the study included objective response rate (ORR), complete response and partial response. The ORR from these cohorts was reported at 31.4%, with eight patients (5.2%) and 40 patients (26.1%) demonstrating a complete and partial response, respectively. The median duration of response (DOR) was not reached at a median follow-up of 27.6 months.

Progression-free survival (PFS) and OS were reported as 4.1 months and 13.9 months, respectively.

Investigators additionally reported that in the 83 patients who were primary refractory to prior anti-PD-1/PD-L1 therapy, ORR was 31.3% with six CRs (7.2%) and 20 PRs (24.1%).[8]

SAFETY

Lifileucel should only be administered in inpatient hospital facilities with access to an ICU with cardiopulmonary and intensive care specialists.

Lifileucel has several boxed warnings, including treatment-related mortality, prolonged severe cytopenias, internal organ hemorrhage, severe infection, cardiopulmonary and renal impairment, and hypersensitivity reactions.[12]

LIFILEUCEL ADVERSE EFFECTS OCCURRING IN ≥30% OF PATIENTS (n=156)[8]

ADVERSE EFFECT	Any Grade (%)	Grade 3/4 (%)
Thrombocytopenia	129 (82.7)	120 (76.9)
Chills	117 (75)	8 (5.1)
Anemia	97 (62.2)	78 (50)
Fever	81 (51.9)	17 (10.9)
Neutropenia	66 (42.3)	45 (28.8)
Febrile neutropenia	65 (41.7)	65 (41.7)
Hypophosphatemia	58 (37.2)	41 (2.3)
Leukopenia	54 (34.6)	42 (26.9)
Hypotension	52 (33.3)	17 (10.9)
Fatigue	51 (32.7)	6 (3.8)
Lymphopenia	49 (31.4)	38 (24.4)
Diarrhea	48 (30.8	2 (1.3)

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The safety analysis from the C-144-01 trial included 156 patients. The most common adverse events (≥ 20%) were chills, pyrexia, fatigue, tachycardia, diarrhea, febrile neutropenia, edema, rash, hypotension, alopecia, infection, hypoxia and dyspnea.

Grade 3/4 treatment-emergent adverse events (TEAEs) occurred in ≥ 30% of the patients and included thrombocytopenia (76.9%), anemia (50%) and febrile neutropenia (41.7%). Most of the TEAEs were manageable and the incidence decreased over the first two weeks following the lifileucel infusion.[8]

In the clinical trial, treatment-related mortality occurred in 7.5% of patients, including two deaths during the lymphodepleting period, six deaths within 30 days of lifileucel administration and four deaths within 38 to 150 days of lifileucel.

Of those that received lifileucel, six patients died within 30 days, four of whom were associated with adverse effects and two related to progression of disease. Three of the four who died due to adverse effects were determined by the investigator to be related to the lymphodepleting therapy and/or related to IL-2.

Cause of death included severe infections, internal organ hemorrhage, acute renal failure, respiratory failure, cardiac arrhythmia, extensive ascites, liver injury and bone marrow failure.[8,12]

IL-2 has black box warnings for capillary leak syndrome, infections and CNS toxicities. Patients may also experience nausea, vomiting, diarrhea, itching and congestion with IL-2 and should be premedicated with antipyretics, H2 antagonists, antiemetics and antidiarrheals.[13]

CONCLUSION

Lifileucel is the first TIL therapy approved by the FDA. Results from the pooled cohorts of the C-144-01 trial demonstrated encouraging efficacy results in a population where treatment options were limited.

In addition to the lymphodepleting regimen and IL-2 treatment, lifileucel is associated with significant side effects and is required to be administered in an inpatient hospital setting with access to an ICU and cardiopulmonary and intensive care specialists.

Nevertheless, the approval of lifileucel offers a promising treatment option for patients with heavily pretreated advanced melanoma.

Lifileucel is associated with significant side effects and is required to be administered in an inpatient hospital setting with access to an ICU and cardiopulmonary and intensive care specialists. Nevertheless, it offers a promising treatment option for patients with heavily pretreated advanced melanoma.

▲ **Katelyn Yamartino**, PharmD, BCOP, is a stem cell transplant and cellular therapy clinical pharmacist at Yale New Haven Hospital in New Haven, Connecticut.

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ANTIBODY-DRUG CONJUGATE PROVIDES NEW HOPE FOR PATIENTS WITH BRAIN METASTASES

Researchers at the University of Texas Health Science Center at San Antonio (UT Health San Antonio) recently completed second-phase clinical trials on sacituzumab govitecan, an antibody-drug conjugate (ADC) that represents a novel approach to cancer treatment.

The drug already has been proven effective in clinical trials focusing on triple-negative breast cancer (TNBC). The UT Health San Antonio trial focused on its effectiveness in treating breast cancer brain metastases as well as primary brain tumors.

The trial was directed by **Andrew Brenner**, MD, PhD, a Professor of Medicine in the Division of Hematology and Oncology at UT Health San Antonio and a specialist in both breast cancer and malignancies of the brain and spinal cord at Mays Cancer Center, home to UT Health San Antonio MD Anderson Cancer Center. In addition to his clinical practice, he is internationally recognized for his work in developing novel therapies to treat breast cancers and central nervous system tumors.

Andrew Brenner

Oncolytics Today recently interviewed Brenner about the trial:

OT: Dr. Brenner, what is the key challenge in treating brain tumors?

AB: We've always had issues in terms of what to do with our patients who have brain metastases because of the blood-brain barrier. It's an active issue because the endothelial cells, the astrocytes and the pericytes that make up this barrier, will physically take anything that makes it across passively and pump it right back into the blood via different transporters. Even if we have something that passively gets across, it often isn't sufficient. We need drugs to physically get across and stay across.

OT: Have ADCs provided a way to deliver drugs past the blood-brain barrier?

AB: Theoretically, you would think, no, they shouldn't because antibodies are big and they can't get passively across. A good example of that is trastuzumab. We really don't see trastuzumab working in the brain. In fact, if you look at patients on trastuzumab, we actually saw an increase in brain metastases because we are making these patients live longer. So, the antibody wasn't getting to the brain.

Yet, we've seen some interesting data in terms of activity of these ADCs in the brain. I think a good example is that we see some decrease in terms of development of brain metastases in patients who receive KADCYLA® for HER2 in the metastatic setting. They tend to end up developing fewer brain metastases. On top of that, there seems to be a stability or even response from previously treated brain tumors.

OT: Can you tell us how ADC differs from previous approaches?

AB: Antibody-drug conjugates are a new development in targeted therapies. They take chemo from being a carpet-bombing strategy and turn it into more of a smart bomb. A good example of systemic chemotherapy in this regard is the parent of the payload that is being used on this ADC. There's a prodrug called irinotecan or CPT-11. Once you give it by IV, it gets converted by the liver to SN38, and SN38 is really what does the work. SN38 gets into the machinery responsible for cells dividing their DNA and, because of that, it is very potent. We've used irinotecan for primary brain tumors for a number of years. But the problem with Irinotecan is that as soon as the liver activates it to SN38, it starts to immediately do something called glucuronidation, which inactivates it and dumps it into the bile.

Antibody-drug conjugates allow us to load on very potent drugs that cannot be given systemically by themselves because they would be too toxic. The ADC carries it specifically to tumor cells because the antibody recognizes a protein on the surface of the cancer cell that is not expressed in normal tissues. On top of that, it protects the normal cells that don't have the protein because the chemotherapy is bound to the antibody. The only way that the chemotherapy gets released is by the antibody interacting with the target cell and dumping its payload.

There are three different parts to ADCs:

- The antibody itself, which recognizes a surface protein;
- A linker that holds the chemotherapy onto the antibody; and
- The payload itself, which in our case was SN38.

OT: Can you tell us how the sacituzumab govitecan trial came about?

AB: We first heard about sacituzumab govitecan back in 2020, when it was in phase two. There was this really great study that showed a high level of activity in patients with TNBC. As you know, TNBC is a significant challenge for us. We don't have a lot of targeted options for it. It was almost entirely chemotherapy, so having an ADC that would work in TNBC was very exciting. But confirmatory studies were needed.

Sacituzumab govitecan recognizes a protein called Trop2. Trop2 is expressed on the surface of breast and other cancers, but it's not typically expressed in normal cells. It's considered a gestational or a trophoblastic protein, so it's usually expressed only during development, but not really much in adult tissues. Cancer cells express it because they degenerate and start to express Trop2, making it a good target for an antibody-drug conjugate.

The question for us was, will it get in the brain? Does it work there? Because TNBC patients develop brain metastases and we wanted to answer that question. We discussed it with the company that was developing the drug and they were interested as well.

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ANTIBODY-DRUG CONJUGATES

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OT: What was your methodology?

AB: The first thing we did was look at mice. We took immunocompromised mice, inoculated TNBC cells directly into the brain, allowed them to grow, and then treated them with sacituzumab govitecan. About one month after inoculating the tumors into the brains, the half of animals that were treated with the test placebo had all died. But the ones that were treated with sacituzumab govitecan were all alive. On top of that, there was also reduction in tumors, which suggested that the drug could treat metastases in the brain. Specifically, triple-negative brain metastases.

Patients with breast cancer often will present with a large lesion because a lot of times it can be silent. They only present when they're symptomatic. For such patients, many times we will just go ahead and take them to surgery to remove the lesion that's making them symptomatic. But they usually don't go to surgery the same day. Usually there's a little bit of time there.

So, we designed the study such that patients the day before their surgery would get a dose of sacituzumab govitecan. We figured that a good amount of the ADC could cross over into the brain in that time period. We started enrolling breast cancer brain metastases patients, as well as patients with primary brain tumors.

OT: Why primary brain tumors?

AB: As I noted earlier, we use irinotecan in primary brain tumors. And while it's not the most effective drug, SN38 is known to cross the blood-brain barrier. We had a hypothesis that the linker that connected the antibody to the drug would be active when it passed through the blood vessels of primary brain tumors because they're very hypoxic with a low pH and the linker is pH-dependent. So, we decided we're going to go look at both breast cancer brain metastases as well as recurrent glioblastoma (GBM).

We started enrolling patients into the study who presented with brain tumors and planned to go into surgery. Most patients were eager because this was a new drug with a lot of promise. We basically allowed any patient slated to have a craniotomy to remove a tumor to participate.

OT: What was the main objective in the trial?

AB: The primary endpoint was the amount of SN38 in the brain metastases a day after administering the drug. We had developed a very reliable method for detecting SN38 in brain tissues with the University of Texas at Austin that was published before we did this study.

We saw pretty substantial levels on SN38 in the tissues, both for breast cancer metastases and for recurrent GBM. The amount that was seen was about 10 times what is known to kill the cancer cells, the IC50 — the concentration at which 50% of the cells are knocked off within a day or two. So, the concentrations we saw certainly seemed sufficient.

We also did a lot of biomarker analysis to try and determine if this function was due to the amount of Trop2 on the cancer cells or more a factor of how hypoxic and low pH these tumors were. The drug levels correlated with the Trop2 expression, but not with the hypoxia, suggesting that it was not a passive release as it passed through the blood vessels, but an actual engagement with the cancer cell and uptake of the antibody, and then release.

OT: Can you tell us a little bit more about what you've specifically witnessed with some of the patients in the trial?

AB: It was pretty incredible. Patients with breast cancer, brain metastases, especially triple-negative, tend not to do really well. Not only did we see excellent responses in a significant number of subjects, but the time it took to progress was consistent with what you see extracranially in the breast cancer itself. And that was really surprising. I have some patients who received the drug and the brain metastases have not come back. They did not receive radiation or anything that would otherwise explain it. They just got the drug and their particular tumors were so sensitive that they haven't come back in the brain. For these patients, it was life-changing.

I have some patients who received the drug and the brain metastases have not come back. They did not receive radiation or anything that would otherwise explain it. They just got the drug and their particular tumors were so sensitive that they haven't come back in the brain. For these patients, it was life-changing.

OT: What does this finding mean for future research?

AB: You see Trop2 on a variety of other cancers, so you would imagine wherever it is expressed there's going to be activity of this ADC. As a matter of fact, there are a number of other ADCs being developed using Trop2 as the target where they're loading other chemotherapies onto the antibody. The ADC field is going to continue exploding as we identify more payloads, more surface antigens and better linkers. Brain metastases can occur from a variety of other cancers, lung cancer, for example. So, knowing that these ADCs work in the brain is really important. We need to build evidence to support that.

On top of that, it might be possible to use this drug for primary brain tumors. We have one study in recurrent GBM, but we're also expanding the number of patients we're analyzing which could result in a change in the label of the drug. This Southwest Oncology Group study is called S2007 and is more than halfway accrued right now.

We're hoping we will have a more definitive answer, not just the number of patients we studied, but a significant number of patients that the FDA can look at and say, "Yes, sacituzumab govitecan works on patients who have HER2 negative brain metastases and this should be considered a treatment option for these patients."

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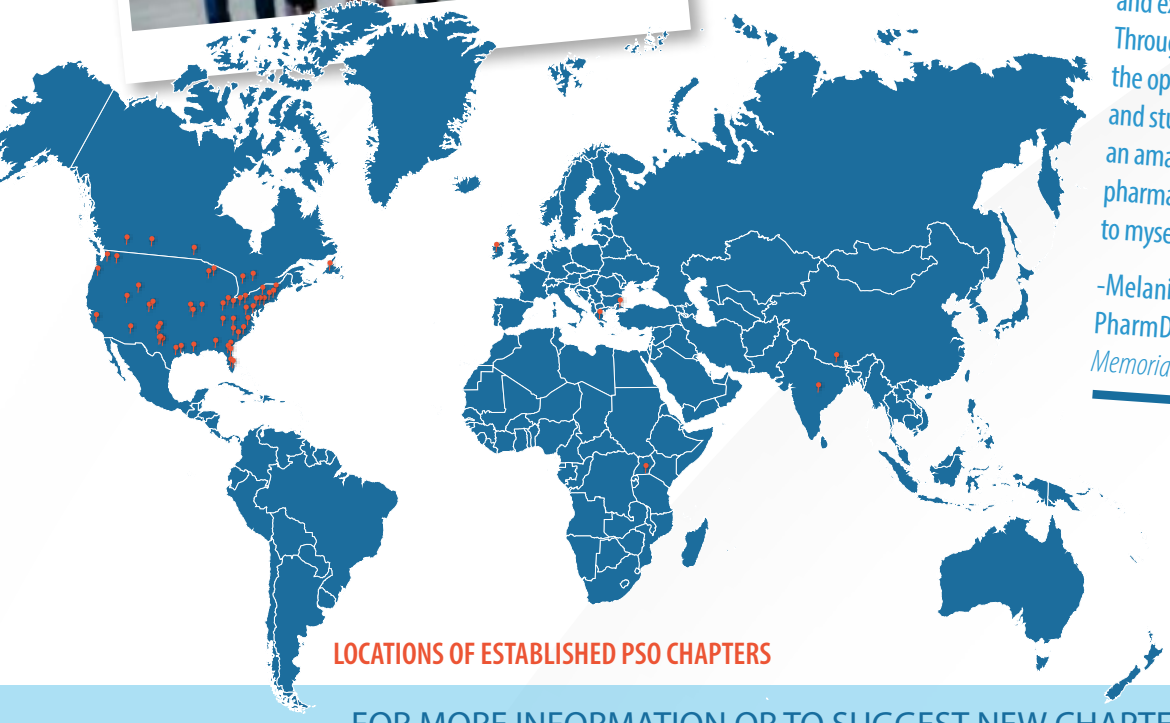
"Being involved with NCODA has been a highlight of my pharmacy school experience! I have been able to enhance my leadership skills, confidence in public speaking and networking, mentorship skills and expand my knowledge of oncology pharmacy. Through being a part of NCODA, I have been given the opportunity to work with pharmacy professionals and students from around the world, which has been an amazing experience. I highly encourage other pharmacy students to join their school's PSO or, similar to myself, start their own chapter at their university!"

-Melanie King
PharmD Candidate | Class of 2025
Memorial University | NCODA PSO IEB President



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WHAT COMES NEXT: FOLLOWING CAR-T THERAPY & MANAGING DELAYED TOXICITIES

By Maggie Nelson, PharmD, BCOP

Hematologic malignancy treatment has changed dramatically since the approval of the first chimeric antigen receptor T-cell (CAR-T) therapy in 2017.

There are currently six CAR-T products on the market — four are directed toward CD-19 and two are directed toward B-cell maturation antigen (BCMA). Malignancies targeted include diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia and multiple myeloma.

Maggie Nelson

A lot has been learned about CAR-T therapy since 2017. In the beginning, anecdotally, it seemed like patients who received this treatment ended up in the intensive care unit and steroids were often avoided. At my institution, we still have a best practice alert restricting steroid orders to our team's attendings attempting to still reduce the amount of steroids given and ensure the appropriateness.

Management of acute toxicities including cytokine release syndrome (CRS) and immune-effector cell therapy-associated neurotoxicity syndrome (ICANS) have now become second nature. While severe adverse effects are still possible, we have learned how to better manage mild to moderate cases.

So, what is our current hurdle? Some of the difficulties we encounter with patients receiving CAR-T therapy happen after they leave the hospital. At our institution, we have close follow-up for the first 30 days, including daily visits until day 14, every other day visits until Day 21, followed by every third day visits until Day 30. If patients live further away, they are often discharged back to their local oncologist on Day 30.

We also require long-term follow-up appointments at Day 100 and Day 180, followed by annual visits.

ADAPTIVE IMMUNITY ISSUES

As we continue to treat patients with CAR-T, we've learned more about complex health issues that can occur from treatment. These patients need to be revaccinated against several pathogens as they receive lymphodepleting chemotherapy prior to their CAR-T cells, which depletes their adaptive immunity. There are also long-term complications related to B-cell aplasia.[1,2]

While engineered CAR-T cells are wildly intricate and intelligent, CD-19 is also found on nonmalignant B-cells and BCMA on nonmalignant plasma cells. CAR-T therapy cannot differentiate between the malignant and nonmalignant cells, putting patients at risk for infections.[1]

Cytopenias after CAR-T therapy can occur and can be difficult to manage. Some patients remain transfusion-dependent for weeks to months after they have received treatment. This can make it difficult to return to "normal life" and can be challenging to manage in patients who live in smaller communities.

A recent meta-analysis focusing on non-relapse mortality (NRM) reported over 50% of deaths were due to infections.[2] Continued close monitoring of patients is essential in the ever-changing landscape that is cellular therapy.

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While there are many studies regarding vaccinations after hematopoietic stem cell transplant (HSCT), this data is not as robust within the cellular therapy realm. Now that there are different targets including CD19-directed and BCMA-directed CAR-T, the data is even more sparse.

Since patients receive lymphodepleting chemotherapy with agents like fludarabine and cyclophosphamide prior to their CAR-T therapy, their adaptive immunity becomes weakened and compromised.[3] As patient's immune reconstitution strengthens over time, we must retrain their immune system to ward off infections with immunizations.

These immunizations protect against Bordetella pertussis, Clostridium tetani, Corynebacterium diphtheriae, inactivated polio, Haemophilus influenzae type B, meningococcal ACWY, Streptococcus pneumoniae, hepatitis B, human papilloma virus (if between the ages of 9 to 45), varicella zoster, measles, mumps and rubella (MMR), as well as a yearly influenza and COVID-19 vaccine.[4]

Vaccine formulations and schedule continue to evolve, adding another layer of complexity in revaccination/supportive care after CAR-T in these patients. Vaccines are often given in a series in which patients receive multiple doses to mount an appropriate immune response, mimicking series seen in infant vaccination.

Practices exist to check titers to ensure an adequate response has been mounted; however, this is not routinely recommended by guidelines. Practitioners who are unfamiliar with these vaccine schedules may find it difficult to track due to multiple doses required at specific time points. Additionally, live vaccines must be administered further out from CAR-T to ensure safe immune reconstitution. This timing may also shift in patients who received maintenance therapy or other supportive care such as intravenous immunoglobulin infusions after CAR-T.

Managing late effects of CAR-T therapy has proven to be challenging and requires a multidisciplinary approach to anticipate needs of patients and ensure access to treat a vast array of possible complications and toxicities.

Moreover, patients may have Medicare insurance, which can further complicate this process. Certain vaccines such as Shingrix™, Pentacel® and MMR must be run through Medicare's prescription drug coverage, thus requiring patients to fill these vaccines in the retail setting as opposed to billing as part of their clinic visit. This can complicate the continuity in vaccine administration documentation.

This is an area that pharmacists can be helpful in creating standard operating procedures (SOPs) that manage stock and schedules of these vaccinations, outlines which vaccines need to be billed through prescription insurance, and provide guidance on appropriate documentation of vaccine administration.

B CELL CONSIDERATIONS

In addition to adaptive immunity, B cells play an intricate role in innate immunity. B cells can differentiate into plasma cells and eventually immunoglobulins, which are important for humoral immunity against bacteria, viruses, and fungi. CD19 often is found on malignant B cells, but also exists on healthy B cells, including naïve B cells and memory B cells.[1]

BCMA, the target for multiple myeloma cellular therapy, is also found on healthy mature B lymphocytes. The downstream effects of cellular therapies on these cell lineages can lead to B-cell aplasia and hypogammaglobulinemia.

As a result, patients are at risk for infections in the early after CAR-T therapy as well as persisting for years. IgG levels below 400mg/dL can be seen in up to 50% of patients after therapy.[1]

This can be managed with intravenous immunoglobulin (IVIG) until IgG levels are more than 400mg/dL. IVIG infusions can come with their own complexities including navigating insurance coverage, coordinating infusion appointments and locations, and managing infusion reactions.

IVIG infusions also affect the ability to administer live vaccines such as MMR due to a diminished response rendering live vaccines less effective.[3]

B-cell aplasia can lead to poor vaccine responses as well. Overall, these off-tumor effects can lead to infectious complications that can be difficult to manage, including fungal infections and pneumocystis pneumonia (PCP).[1]

This is another area in which pharmacists can provide value within the medical team. Pharmacists at our institution aid in monitoring of certain immune levels including IgG and CD4 count. We ensure insurance coverage is in place and appropriate pre-medications are ordered prior to patients receiving IVIG. CD4 counts can help guide antimicrobial prophylaxis selection and timeline most of which can be discontinued between six months and one year after therapy.[4]

COMPLICATIONS FROM CYTOPENIAS

Another complication that can be difficult to manage are cytopenias. Lymphodepleting chemotherapy and inflammation incurred by CAR-T therapy may contribute to cytopenias after therapy, which can increase the risk of bleeding and infection in these patients. These cytopenias may persist for months after CAR-T therapy.

Real-world data surrounding CD19-directed therapies show different

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levels of thrombocytopenia and neutropenia depending on the product. Thrombocytopenia can be seen in up to 43% of patients on Day 30 and up to 11% of patients on days 90 to 100. Neutropenia at Day 30 can be seen in up to 33% of patients and at Day 90 to 100 in 18% of patients.[3]

This suggests that patients should recover from cytopenias over time. However, some may need intervention for severe or persistent cases to prevent additional adverse events.

Transfusion support, growth factor support (GCSF), and epoetin and thrombopoietin receptor agonists may be indicated throughout CAR-T recovery. All of these require coordination and oftentimes insurance approval. GCSF should be given daily until neutropenia resolves, which may be difficult for patients if their insurers require them to come into clinic for their injections.

Eltrombopag, an oral thrombopoietin receptor agonist, can be used to help improve thrombocytopenia and has the potential to improve neutropenia as well.[5] Eltrombopag can be expensive and often requires prior authorization for insurance approval. It also carries side effects and should be used with caution in patients who have a history of pulmonary emboli or deep vein thrombosis. An alternative is romiplostim, which is an injectable version with similar indications.[5]

This is another opportunity for pharmacists to be involved in patient care, including educating patients to ensure they are aware of signs and symptoms of blood clots and other adverse effects. Pharmacists can also aid in supportive care measures for GCSF and epoetin including monitoring and insurance approval.

In conclusion, managing late effects of CAR-T therapy has proven to be challenging and requires a multidisciplinary approach to anticipate needs of patients and ensure access to treat a vast array of possible complications and toxicities.

▲ **Maggie Nelson**, PharmD, BCOP, is a Blood and Marrow Transplant and Cellular Therapy Pharmacist at The University of Kansas Cancer Center in Kansas City, Kansas.

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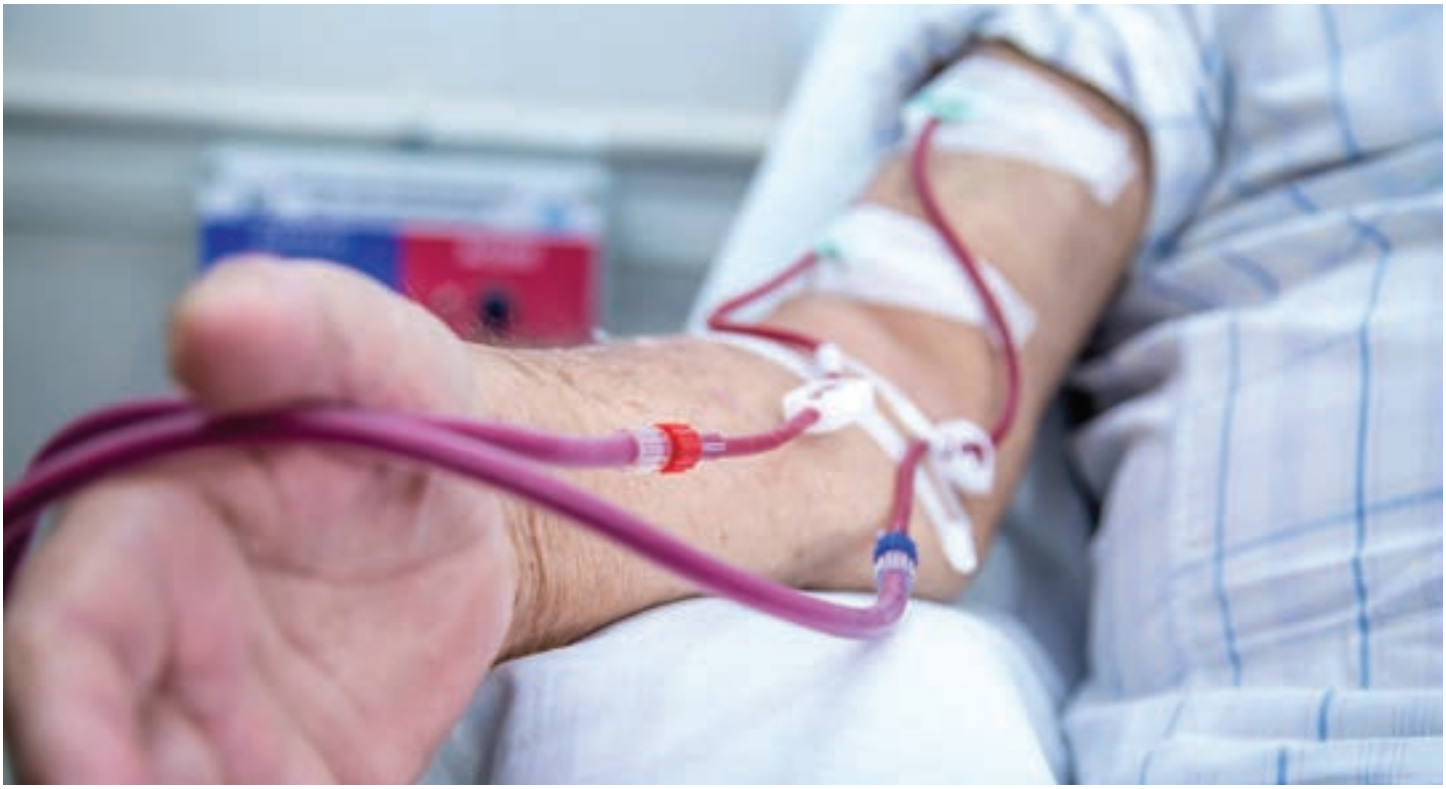

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FDA ANNOUNCES APPROVAL OF 11 NEW ORAL ONCOLYTICS

By Derek Gyori, PharmD, BCOP, & Kirollos Hanna, PharmD, BCPS, BCOP


Derek Gyori


Kirollos Hanna

The U.S. Food and Drug Administration (FDA) approved 11 oral oncology agents from February 15 to August 20, 2024. In the chart below and on the following three pages, the asterisk (*) represents a new indication for a previously approved therapy.

Further information can be found on the FDA website, in the medication-specific prescribing information or clinical trials.

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Tepotinib (TEPMETKO®)[1-3]	2/15/2024	• **Metastatic non–small cell lung cancer with MET exon 14 skipping mutation:** 450mg once daily; continue until disease progression or unacceptable toxicity	**VISION** Multicenter, non-randomized, open-label, multicohort study **Treatment-Naïve** • n=164 • ORR: 57% (95% CI: 49- 65) with 40% of responders having a DOR ≥12 months **Previously Treated** • N=149 • ORR: 45% (95% CI: 37-53) with 36% of responders having a DOR ≥12 months	• ≥20%: Edema, nausea, fatigue, musculoskeletal pain, diarrhea, dyspnea, decreased appetite and rash	• Administer with food at approximately the same time each day • Available as 225mg tablets
Osimertinib (TAGRISSO®)[1,4-5]	2/16/2024*	• **Locally advanced or metastatic non-small cell lung cancer where tumors have EGFR exon 19 deletions or exon 21 L858R mutations (with platinum-based chemotherapy):** 80mg orally once daily	**FLAURA 2** Open-label, randomized trial • PFS: 25.5 months (95% CI: 24.7-NE for osimertinib with platinum-based chemotherapy and 16.7 months (95% CI: 14.1-21.3) for osimertinib monotherapy • OS results were immature at analysis	• ≥ 20%: Leukopenia, thrombocytopenia, neutropenia, lymphopenia, rash, diarrhea, stomatitis, nail toxicity, dry skin and increased blood creatinine	• Administer with or without food • Available as 40mg and 80mg tablets

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Zanubrutinib (BRUKINSA®)[1, 6-7]	3/7/2024*	• **Relapsed or Refractory Follicular Lymphoma:** 160mg taken orally twice daily or 320mg taken orally once daily until disease progression or unacceptable toxicity in combination with obinutuzumab	**ROSEWOOD** • N=217 • ORR: Zanubrutinib + Obinutuzumab 69% (95% CI: 61-76) vs. Obinutuzumab monotherapy: 46% (95% CI: 34-58) (two-sided p-value, 0.0012). • Median DOR: Zanubrutinib + Obinutuzumab: NR (95% CI: 25.3 months, NE) vs. Obinutuzumab monotherapy: 14.0 months (95% CI: 9.2-25.1)	• ≥30%: Decreased neutrophil counts and platelet counts, upper respiratory tract infection, hemorrhage and musculoskeletal pain	• Administer with or without food • Available as 80mg capsules • Consider prophylaxis for herpes simplex virus, Pneumocystis jirovecii pneumonia and other infections in patients at increased risk for infections • Consider benefit-risk of interrupting zanubrutinib treatment for three to seven days prior to and after surgery
Ponatinib (ICLUSIG®)[1,8-9]	3/19/2024*	• **Newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL):** 30mg orally once daily with a reduction to 15mg orally once daily upon achievement of MRD-negative CR at the end of induction, Continue ponatinib with chemotherapy for up to 20 cycles until loss of response or unacceptable toxicity	**PhALLCON** • N= 245 • MRD-negative CR rate at the end of induction: Ponatinib 30% vs. Imatinib 12% (Risk difference 0.18 [95% CI: 0.08-0.28], p-value 0.0004)	• Most common adverse reactions (% not defined): Hepatic dysfunction, arthralgia, rash and related conditions, headache, pyrexia, abdominal pain, constipation, fatigue, nausea, oral mucositis, hypertension, pancreatitis, elevated lipase, peripheral neuropathy, hemorrhage, febrile neutropenia, fluid retention and edema, vomiting, paresthesia and cardiac arrhythmias	• Administer with or without food • Available as 10mg, 15mg, 30mg and 45mg capsules • BBW: Arterial occlusive events, heart failure, hepatotoxicity, Venous thromboembolism
Alectinib (ALECENSA®)[1, 10-11]	4/18/2024*	• **Adjuvant treatment for ALK-Positive NSCLC:** 600mg twice daily for 2 years or until disease progression or unacceptable toxicity, whichever occurs first	**ALINA** • N= 257 **Overall Study population (Stage IB-IIIA)** • Median DFS: Alectinib NR (95% CI: NE) vs Chemotherapy 41.3 months (95% CI: 28.5, NE) (HR 0.24 [95% CI: 0.13, 0.43]; p<0.0001) **•Subgroup Analysis (Stage II-IIIA NSCLC)** • Median DFS: Alectinib NR (95% CI: NE) vs Chemotherapy 44.4 months (95% CI: 27.8, NE) (HR 0.24 [95% CI: 0.13-0.45]; p<0.0001)	• ≥ 20%: Hepatotoxicity, constipation, myalgia, COVID-19, fatigue, rash and cough	• Administer with food • Available as a 150mg capsule

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Tovorafenib (OJEMDA™)[1, 12-13]	4/23/2024	• **Relapsed/Refractory BRAF-altered pediatric low-grade glioma (≥ 6 months of age or older):** Once weekly; dosing is dependent on BSA – refer to package insert for recommendations	**FIREFLY-1** • N= 76 • ORR: 51% (95% CI: 40- 63) • Median DOR: 13.8 months (95% CI: 11.3-NE)	• ≥30%: Rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform & upper respiratory tract infection	• Administer with or without food • Available as a 25mg/mL suspension and 100mg tablets • Do not chew, cut or crush tablets
Selpercatinib (Retevmo®)[1,14-16]	5/29/2024*	• **RET-altered metastatic thyroid cancer or solid tumors in pediatric patients (≥ 2 years of age or older):** Pediatric dosing is based on BSA – refer to package insert for recommendations	**LIBRETTO-121** • N= 25 (Patients age 2 to 20) • ORR: 48% (95% CI: 28-69) • Median DOR: Not Reached, 92% of responders remaining in response at 12 months	• ≥25%: Edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea and headache	• Administer with or without food • Administer with food if patient cannot avoid taking a proton pump inhibitor • Available as 40mg and 80mg capsule and 40mg, 80mg, 120mg and 160mg tablets
	6/12/2024*	• **RET-fusion-positive thyroid cancer:** • Patients ≥50 kg: 160mg twice daily until disease progression or unacceptable toxicity • Patients <50 kg: 120mg twice daily until disease progression or unacceptable toxicity	**LIBRETTO-001** • N= 65 **Previously Treated:** • n= 41 • ORR: 85% (95% CI: 71- 94) • Median DOR 26.7 months (95% CI: 12.1-NE) **Therapy Naïve:** • n=24 • ORR: 96% (95% CI: 79-100) • Median DOR: NE (95% CI: 42.8-NE)		
Repotrectinib (AUGTYRO™)[1, 17]	6/13/2024	• **NTRK gene fusion-positive solid tumors in adults and pediatric patients (Age ≥ 12 years old):** 160mg once daily for 14 days, then increase dose to 160mg twice daily; continue until disease progression or unacceptable toxicity	**TRIDENT-1** • N= 84 • ORR: **TKI-naïve group:** 58% (95% CI: 41- 73) TKI-pretreated group: 50% (95% CI: 35- 65) Median DOR: **TKI-naïve group:** NE (95% CI: NE, NE) **TKI-pretreated group:** 9.9 months (95% CI: 7.4-13.0)	• >20%: Dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness and nausea	• Administer with or without food at approximately the same time each day • Available as 40mg and 160mg capsules

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Adagrasib (KRAZATI®)[1, 18-20]	6/21/2024*	• **KRAS G12C-mutated colorectal cancer:** 600mg orally twice daily until disease progression or unacceptable toxicity in combination with cetuximab	**KRYSTAL-1** • N= 94 • ORR: 34.0% • Median DOR: 5.8 months (95% confidence interval [CI], 4.2-7.6). • Median PFS: 6.9 months (95% CI, 5.7-7.4) • Median OS: 15.9 months (95% CI, 11.8-18.8)	• ≥20%: Rash, nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, headache, dry skin, abdominal pain, decreased appetite, edema, anemia, cough, dizziness, constipation and peripheral neuropathy	• Administer with or without food • Available as 200mg tablets • Moderate or high emetic potential — antiemetics are recommended to prevent nausea and vomiting
Vorasidenib (VORANIGO®)[1,21-22]	8/6/2024	• **Grade 2 Astrocytoma or Oligodendroglioma with a susceptible IDH1 or IDH2 mutation (Age ≥ 12 years old):** 40mg once daily; continue until disease progression or unacceptable toxicity **Pediatric Dosing:** • Patients weighing ≥ 40 kg: 40 mg orally once daily • Patients weighing < 40 kg: 20 mg orally once daily	**INDIGO** • N= 331 • PFS: HR 0.39 (95% CI: 0.27, 0.56), p-value <0.0001 • Median TTNI: NR for vorasidenib and 17.8 months for placebo; HR = 0.26; 95% CI: (0.15- 0.43), p <0.0001	• ≥15%: Fatigue, headache, COVID-19 infection, musculoskeletal pain, diarrhea, nausea and seizure • Hepatotoxicity — requires dosage adjustment	• Administer at approximately the same time each day, with water and with or without food • Available as 10mg and 40mg tablets • Dose adjustments required for hepatotoxicity • Do not split, crush or chew
Lazertinib (Lazcluze® & Leclaza®)[1, 23-24]	8/20/24	• **Locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitutions**: 240mg orally once daily administered in combination with amivantamab	**MARIPOSA** • N=1074 • Median PFS: lazertinib with amivantamab arm 23.7 months (95% CI: 19.1- 27.7) and osimertinib 16.6 months (95% CI: 14.8- 18.5); HR [0.70 (95% confidence interval [CI]: 0.58, 0.85; p-value=0.0002)] • OS results were immature, but no trend towards a detriment was observed	• ≥ 20%: Rash, nail toxicity, musculoskeletal pain, edema, stomatitis, venous thromboembolism, paresthesia, fatigue, diarrhea, constipation, COVID-19 infection, hemorrhage, dry skin, decreased appetite, pruritus, nausea and ocular toxicity	• Administer with or without food • Available as 80mg and 240mg tablet • Risk of venous thromboembolic events (VTE) was observed with lazertinib in combination with amivantamab and prophylactic anticoagulation should be administered for the first four months of therapy

ABBREVIATIONS: **ORR** = Objective Response Rate, **DOR** = Duration Of Response, **CI** = Confidence Interval, **PFS** = Progression-Free Survival, **OS** = Overall Survival, **HR** = Hazard Ratio, **TTNI** = Time To Next Intervention, **MRD** = Minimal Residual Disease, **CR** = Complete Response, **BBW** = Black Box Warning, **DFS** = Disease-Free Survival, **NR** = Not Reached, **NSCLC** = Non-Small Cell Lung Cancer, **TKI** = Tyrosine Kinase Inhibitor

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IDENTIFYING RISK FACTORS FOR HYPERSENSITIVITY REACTIONS TO PEGYLATED-LIPOSOMAL DOXORUBICIN

By Nancy Chukwumezie, PharmD, Dorothy Wang, PharmD, BCOP, & Hansen Ho, PharmD, BCOP

ABSTRACT

Background: Polyethylene glycol-coated (PEGylated) Liposomal Doxorubicin (PLD) is widely used in treating various malignancies, but the risk and mechanisms underlying hypersensitivity reactions (HSR) to PLD remain unclear. Anti-PEG antibodies have been identified in individuals experiencing HSR to PEGylated products, raising concerns about the potential for increased risk following the widespread use of mRNA-PEGylated COVID-19 vaccines during the pandemic. However, guidelines to mitigate HSR risk in PLD therapy are currently lacking.

Objectives: This retrospective cohort study aimed to identify predictors associated with HSR to PLD, assess the characteristics and severity of HSR, and evaluate the relationship between mRNA-PEGylated COVID-19 vaccination and HSR to PLD.

Methods: The study included 322 adult cancer patients who received PLD from June 2015 to June 2022. Multivariable logistic regression identified predictors of HSR, and grading scores were used to evaluate severity.

Results: Multivariate analysis revealed greater than two medication allergies and COVID-19 vaccination status as significant risk factors for HSR to PLD. Patients receiving two or more mRNA-PEGylated COVID-19 vaccines had a higher likelihood of HSR. Most HSRs were of moderate severity.

Conclusion: Previous exposure to the mRNA-PEGylated COVID-19 vaccine and the number of allergies may influence HSR to PLD. Further research is needed to understand the impact of PEGylated moieties on PLD-related HSR.

PEGylated-Liposomal Doxorubicin (PLD) is a medication widely used to treat various disease states, including breast cancer, gynecologic cancers, sarcomas, lymphomas and multiple myeloma. It is a formulation of the antineoplastic doxorubicin that is encapsulated within liposomes and coated with polyethylene glycol (PEG). PEGylation prolongs the drug's circulation time and enhances its therapeutic efficacy.[1]

PLD's prescribing information does not mention premedication before administration.[2] However, there have been reports of hypersensitivity reactions (HSR), which are adverse reactions of the immune system to a particular substance. The reported incidence of these reactions to PLD ranges between 0% and 25%.[3]

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Symptoms may include facial flushing, facial swelling, headache, chest pain, back pain, chills, hypotension, hypertension, dyspnea and even anaphylaxis.[3] These reactions can be concerning and even life-threatening and, if not controlled, may lead to the discontinuation of PLD.

The exact mechanism underlying HSR to PLD has yet to be fully elucidated. However, it has been hypothesized that the PEGylated moiety may be a contributing factor, which is supported by literature that outlines the presence of anti-PEG antibodies after PEG exposure. Anti-PEG antibodies then initiate the complement activation-related pseudo allergy, leading to HSR to PEGylated products.[4–9]

It is noteworthy that during the COVID-19 pandemic the first mRNA vaccines — including those developed by Pfizer-BioNTech and Moderna — were PEGylated to enhance their stability and efficacy, thereby increasing the general population's exposure to PEGylated moieties. This widespread exposure underscores the importance of thoroughly understanding the potential risks associated with PEGylation, particularly in relation to HSRs to other PEGylated therapies, such as PLD. The introduction of these vaccines further emphasizes the need to investigate the implications of PEGylation in the context of PLD treatment.

Currently, there is no standard guidance for initiating prophylactic measures, such as premedications or infusion rate modifications, to mitigate the risk of HSR in patients receiving PLD.[2] However, identifying key risk factors and developing strategies to optimize prophylactic management are crucial steps toward allowing more patients to safely continue PLD, thereby reducing unnecessary avoidance or discontinuation. By understanding the factors contributing to the development of HSR, we can better assess individual patient's risks. Therefore, this study aimed to identify risk factors associated with HSR to PLD and assess the severity of HSR and outcomes of mitigation strategies.

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METHODS

Study Design: This was a retrospective cohort study of patients treated with PLD at The University of California, San Francisco (UCSF) Health from June 1, 2015, through June 30, 2022. Data was extracted from the electronic medical record (EPIC). The study was approved by the UCSF Institutional Review Board.

Population: Eligible patients in the study were adults aged 18 years or older with a diagnosis of breast cancer, gynecologic cancer, sarcoma or other cancer, who received at least one dose of PLD. Patients were excluded from the study if they were pregnant, pediatric or incarcerated during administration of PLD.

Data Collection: Demographic data collected included the following: age, sex, body surface area (BSA), race, weight, height, body mass index (BMI), number of drug allergies, primary diagnosis, previous intravenous chemotherapy received, concomitant chemotherapy, number of previous PLD cycles, albumin level, COVID-19 vaccination status and PLD administration before or during COVID-19 pandemic (Pre-COVID-19 Pandemic Population or COVID-19 Pandemic Population). The presence or absence of HSR was collected and used to divide patients into the two groups for comparison. For patients with a documented HSR, severity and symptoms of reaction were collected, as well as rechallenge action.

Outcomes: The primary outcome was to identify predictors associated with HSR to PLD. Secondary outcomes included assessing the characteristics of HSR to PLD, describing the severity of HSR, and evaluating the relationship between mRNA-PEGylated COVID-19 vaccination status and HSR. Exploratory outcomes included incidence of rechallenge after HSR and PLD rechallenge actions.

Statistical Analysis: All data was analyzed using STATA-BE statistical software version 17.0. Mean and standard deviation, analyzed using the independent samples t-test, were utilized for all continuous parametric data (i.e., age, BMI). Categorical data is presented using frequencies and percentages and analyzed using the Chi-Square Test.

TABLE 1: BASELINE CHARACTERISTICS

VARIABLE	NO HSR N = 282	HSR N = 40	P-VALUE
Median age range during PLD Infusion (years)	62 (53-72)	60 (48-68.5)	0.24
Sex			0.025*
Female	238 (84.4%)	39 (97.5%)	
Male	44 (15.6%)	1 (2.5%)	
Race			0.50
White	167 (59.2%)	24 (60.0%)	
Asian	39 (13.8%)	7 (17.5%)	
Black or African American	20 (7.1%)	0 (0.0%)	
Latinx	34 (12.1%)	5 (12.5%)	
Other/Not Reported	22 (7.8%)	4 (10.0%)	
Weight (in kilograms)†	67.1 (57.2-81.1)	64.3 (54.2-76.7)	0.18
BMI (kg/m²)†	25.2 (22-29)	23.2 (21.3-29.6)	0.32
BSA (m²)†	1.75 (1.6-1.93)	1.7 (1.55-1.9)	0.18
Albumin (g/dL)†	3.5 (3-3.8)	3.65 (2.9-3.9)	0.48
Number of Drug Allergies			<0.001*
No Drug Allergies	137 (48.6%)	13 (32.5%)	
≤ 2 drug allergies	115 (40.8%)	14 (35.0%)	
>2 drug allergies	30 (10.6%)	13 (32.5%)	
Primary Diagnosis			0.74
Breast Cancer	106 (37.6%)	18 (45.0%)	
Gynecologic Cancer	107 (37.9%)	13 (32.5%)	
Sarcoma	23 (8.2%)	2 (5.0%)	
Other	46 (16.3%)	7 (17.5%)	
COVID-19 Pandemic Population			0.030*
Pre-COVID⁺	164 (58.2%)	16 (40.0%)	
During COVID	118 (41.8%)	24 (60.0%)	

Values reported as n (%) unless stated
†Median (interquartile range)
*Statistically significant (p<0.05)
⁺Before 12/31/19

RESULTS

Three-hundred and twenty-four patients who received a PLD dose from June 1, 2015, through June 30, 2022, were identified. Two patients were excluded due to pediatric age. Based on the presence or absence of HSR to PLD, we identified 40 patients with a documented reaction and 282 patients without a reaction to PLD.

With the exception of male participants, number of drug allergies and COVID-19 pandemic population, no significant differences were seen in baseline demographics between reaction and no reaction groups (**Table 1**). The number of patients with more than two allergies experiencing HSR was significantly higher compared to patients experiencing no reaction (13 [32.5%] vs 30 [10.6%]; p <0.001).

Additionally, more patients experienced

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a reaction during the COVID-19 pandemic compared to patients experiencing no reaction [24 (60.0%) vs 118 (41.8%); p<0.030] from December 31, 2019, to June 30, 2022.

No significant differences were found between PLD administration characteristics, including dose, infusion rate, line status, premedication and concurrent chemotherapy (**Table 2**). The use of a peripheral line was higher in the reaction group compared to the no reaction group (18 [46.2%] vs 101 [37.7%]; p = 0.31) but did not reach statistical significance.

The severity of reactions based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, Ohio State Grade, and Brown Grade systems are described in **Table 3**.

Based on the CTCAE v5.0, of the 40 patients who experienced a reaction, three patients (7.8%) had a grade 1 reaction, 28 patients (70%) experienced grade 2 reaction, seven patients (17.5%) experienced a grade 3 reaction, and two patients (5%) experienced a grade 4 reaction.

The most frequent symptoms included flushing (19, 47.5%), chest tightness (16, 40%), shortness of breath (16, 40%) and back pain (15, 37.5%) (**Table 4**).

Approximately 36 patients (90%) with hypersensitivity reaction were rechallenged with PLD. Rechallenge included titration of infusion, addition of premedication, desensitization protocol, no changes, or discontinuation of PLD. (**Figure 1**).

Odds ratio estimates for the multivariate model predicting hypersensitivity reaction are shown in **Table 5**. When controlling for all other factors, patients with more than two drug allergies (3.18 [1.17-8.63; p=0.023]) or received a COVID-19 vaccination (3.27 [1.46 -7.30]; p=0.004) were significantly more likely to have a reaction to PLD.

In a subgroup analysis including only patients who received at least one dose of any available mRNA COVID-19 vaccine (N = 86) at the time of PLD

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TABLE 2: PLD ADMINISTRATION CHARACTERISTICS

VARIABLE	NO HSR N = 282	HSR N = 40	P-VALUE
Line Status			0.31
Central Line	167 (62.3%)	21 (53.8%)	
Peripheral Line	101 (37.7%)	18 (46.2%)	
Pre-Med before Infusion			
Dexamethasone	83 (29.4%)	9 (22.5%)	0.36
Diphenhydramine	6 (2.1%)	1 (2.5%)	0.88
Cetirizine	13 (4.6%)	0 (0.0%)	0.17
Concurrent Chemotherapy			
Carboplatin	49 (17.4%)	7 (17.5%)	0.98
Bevacizumab	51 (18.1%)	10 (25.0%)	0.30
Checkpoint Inhibitor	4 (1.4%)	0 (0.0%)	0.45
PLD Ordered Dose (mg/m²)	40 (30-40)	40 (30-40)	0.17
Administered Dose (mg)	60 (50-70)	69.6 (50.2-70)	0.12
Infusion Rate(mL/hr)	310 (300-608)	307.5 (299-310)	0.05
Values reported as n (%) unless stated †Median (interquartile range) *Statistically significant (p<0.05)			

TABLE 3: HSR SEVERITY SCORING (N=40)

CTCAE SCORE (V5.0)		OHIO STATE GRADE		BROWN GRADE	
Grade 1	3 (7.5%)	**Mild**	8 (22.5%)	**Mild**	9 (22.5%)
Grade 2	28 (70.0%)	**Moderate low-risk**	19 (47.5%)	**Moderate**	25 (62.5%)
Grade 3	7 (17.5%)	**Moderate high-risk**	9 (22.5%)	**Severe**	6 (15.0%)
Grade 4	2 (5.0%)	**Severe**	4 (10.0%)		

TABLE 4: REPORTED SYMPTOMS OF HSR (N=40)

MOST FREQUENT SYMPTOMS		LESS FREQUENT SYMPTOMS		RARE BUT SERIOUS SYMPTOMS	
Flushing	19 (47.5%)	**Abdominal Pain**	7 (17.5%)	**Unresponsive**	2 (5.0%)
Chest Tightness	16 (40.0%)	**Tachycardia**	7 (17.5%)	**Hypoxia**	1 (2.5%)
Shortness of Breath	16 (40.0%)	**Nausea & Vomiting**	7 (17.5%)	**Bradycardia**	1 (2.5%)
Back Pain	15 (37.5%)	**Dizziness**	6 (15.0%)		
		Itching	5 (12.5%)		
		Hypotension	5 (12.5%)		

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administration (**Table 6**), patients with two or fewer COVID-19 vaccines had a significantly lower incidence of reaction (8 [35%] vs 38 [60%]; p=0.036).

DISCUSSION

PLD HSRs have been reported to occur in up to 25% of patients, yet the underlying pathophysiology remains poorly understood. The frequency and contributing factors have been explored in a handful of studies.

For instance, Yamaguchi et al. reported a higher incidence of HSR in patients with allergic history than in patients without allergic history (p = 0.0151). Similarly, Chanan-Khan et al. reported a higher incidence of complement activation (92%) in patients with a HSR to PLD versus (56%) in the nonreaction group.[10]

These findings suggest a potential association between number of allergies and complement activation with HSR. With the advent of mRNA-PEGylated COVID-19 vaccines and reported cases of anaphylaxis to these vaccines,[5] we sought to investigate the relationship between vaccines and HSR to PLD. Our study determined that the presence of greater than two allergies and the administration of more than two mRNA-PEGylated COVID-19 vaccines may increase risk of hypersensitivity to PLD.

Despite the observed rise in HSR during the COVID-19 era, it is reassuring that the majority of these cases seen in our study were classified as Grade 2 or moderate. Importantly, 90% of patients experiencing HSRs were able to continue PLD treatment with appropriate interventions, such as the addition of premedication, modification of infusion rate titration and desensitization protocols. This highlights the effectiveness of current management strategies in allowing continued treatment.[11–13]

To our knowledge, this is the first study to investigate the potential link between mRNA-PEGylated COVID-19 vaccines and increased HSR in patients receiving PLD. Although this study is limited by its retrospective nature and small COVID-19-era cohort size, the findings are particularly significant given that COVID-19 is becoming an endemic virus, with COVID-19 vaccines likely to be recommended for the foreseeable future.[14]

As cancer cases continue to rise globally, with an estimated 20 million new cases in 2022, more individuals will become candidates for PLD therapy.[15] Further research surrounding the potential impact of repeated exposure to mRNA-PEGylated vaccines on the likelihood of HSR to PLD is therefore of critical importance.

CONCLUSION

This study highlights the potential increased risk of HSRs to PLD in patients with multiple drug allergies and those who received mRNA-PEGylated COVID-19 vaccines. The role of PEGylated molecules in sensitizing patients to PLD underscores

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TABLE 5: MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

VARIABLE	ODDS RATIO (95% CI)	P>z
Age	0.99 (0.96-1.01)	0.317
Sex		
Male	0.13 (0.17-1.03)	0.054
Allergies		
≤ 2 drug allergies	1.76 (0.73-4.23)	0.208
>2 drug allergies	3.18 (1.17-8.63)	0.023*
Vaccination Status++		
COVID-19 Vaccinated	3.27 (1.46-7.30)	0.004*
PLD Infusion Rate	0.994 (0.990-0.999)	0.029*

10 patients omitted due to unknown COVID vaccine status (N=312)

++ First COVID vaccine available 12/11/20

FIGURE 1: FOREST PLOT OF HSR RISK

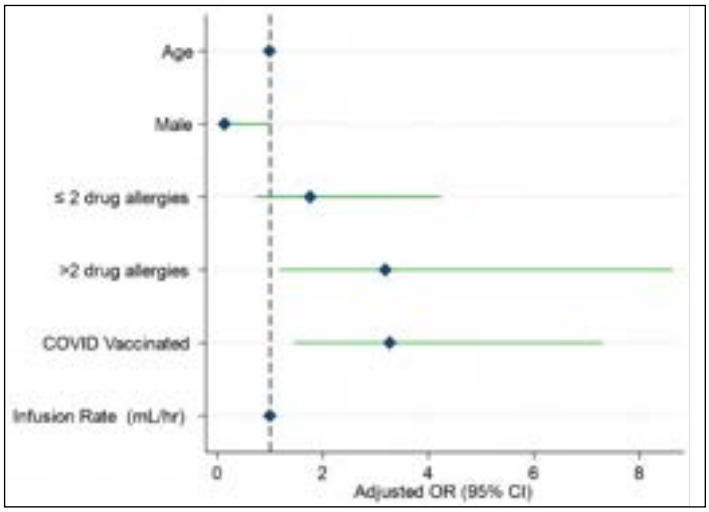

TABLE 6: SECONDARY OUTCOMES: MRNA-PEGYLATED COVID VACCINATION SUBGROUP ANALYSIS

VARIABLE	No HSR N = 63	HSR N = 23	p-value
COVID Vaccination Status			0.36
No COVID Vaccine	17 (27.0%)	4 (17.0%)	
COVID Vaccinated	46 (16.7%)	19 (52.8%)	
Number of COVID Vaccines			0.036*
≤ 2 Vaccines	38 (60%)	8 (35%)	
> 2 Vaccines	25 (40%)	15 (65%)	

N=86; Only includes patients who received any COVID Vaccine

1st mRNA COVID vaccine available 12/11/20. Unknown vaccination status excluded

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the need to consider patient characteristics when administering this therapy.

Further research is necessary to validate these findings, understand the long-term impact of repeated PEGylated vaccine exposure and develop strategies to mitigate HSR risk. Advancing our understanding in these areas will enhance the safety and efficacy of PLD therapy for a broader patient population.

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LONG COVID

A HIDDEN PUBLIC HEALTH CHALLENGE

By Kashyap Patel, MD, Niyati Nathwani, MD, Asutosh Gor, MD, Viral Rabara, MD, & Sashi Naidu, MD

Long COVID is a complex, multi-organ illness that occurs in individuals with a history of SARSCoV-2 infection. Onset typically occurs three months from COVID-19 infection, and symptoms can last for months or years and cannot be explained by an alternative diagnosis, according to the World Health Organization.

Kashyap Patel

Niyati Nathwani

Asutosh Gor

It is believed that Long COVID typically results from ongoing inflammatory changes in multiple tissues.[1] Long COVID is likely to impact 80% of those with a history of COVID-19 infection, with fatigue being the most-reported symptom.[2]

Viral Rabara

Sashi Naidu

More severe cases involve damage to a variety of organ systems, primarily from ongoing inflammatory processes in the lungs, heart, nervous system, kidneys and liver, and thrombotic and cerebrovascular disease. Additional issues may arise from Type 2 diabetes, myalgic encephalomyelitis/chronic fatigue syndrome dysautonomia and postural orthostatic tachycardia syndrome, along with mental health impairment.[3-4]

The pathophysiological pathways may involve direct consequences of the post-infectious inflammatory or autoimmune responses.[5]

More than 200 symptoms have been identified to be associated with Long COVID. It is also believed that Long COVID triggered a 25% increase in the prevalence of anxiety and depression worldwide.[6]

LONG COVID & CARDIOVASCULAR DISEASE[7-11]

Long COVID patients with cardiac involvement have persistent dyspnea, fatigue, chest pain and cough. These symptoms impact approximately in one in five patients three months after the acute SARS-CoV-2 infection.

In the general population, Long COVID-associated cardiac inflammation is reported in 150 cases per 100,000. The risks of myocarditis and pulmonary embolism are reportedly higher than most of the other cardiovascular complications.

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NEUROLOGICAL COMPLICATIONS[12-14]

Neurological manifestations were observed in 33% of patients with Long COVID. These manifestations can impact either the central or peripheral nervous system. The most frequent symptoms include fatigue, "brain fog," headache, cognitive impairment and muscle aches, as well as sleep, mood, smell or taste disorders.

Cognitive dysfunction impacts attention, problem-solving and decision-making. Memory impairment involves both the short- and long-term memory. Younger people (ages 16 to 30) suffer potentially severe symptoms, such as concentration and memory problems, persistent six months after infection.

The study of the anatomical or functional imaging of brain alterations in post-acute sequelae shows consistent changes in many brain areas.

A pronounced loss of gray matter was also seen, as well as an increase in cerebrospinal fluid volume and decrease in whole brain volume with respect to the controls, suggesting an additional diffuse loss of gray matter.

COVID-19 is a risk factor to develop dementia, neurodegenerative diseases and mild cognitive impairments, even in 50-year-old adults.

OTHER MAJOR HEALTH ISSUES[15-16]

Symptoms shown to persist one year after acute disease included mental health disorders, such as depression, anxiety and insomnia, as well as fatigue, muscle and joint pain, and ongoing inflammation.

One prospective study of low-risk individuals that looked at the heart, lungs, liver, kidneys, pancreas and spleen noted 70% of 201 patients had damage to at least one organ, while 29% had multi-organ damage.

Another year-long study of patients with Long COVID found 59% had single-organ damage and 27% multi-organ damage.

COVID-19 is a risk factor to develop dementia, neurodegenerative diseases and mild cognitive impairments, even in 50-year-old adults.

A study of renal functions of veterans infected with COVID 19 reported an increased risk.

LONG COVID, INFLAMMATION & CANCER[17-24]

Approximately 15% to 20% of all cancer cases can be attributed to carcinogenic viral infections. At least seven different human cancer oncogenic viruses have been shown to have strong connections to various forms of cancer in humans, including the Epstein-Barr Virus, human papillomavirus and the hepatitis B and C viruses.

The molecular oncologic mechanisms from viral infections are varied. These mechanisms range from chronic inflammation to immunosuppression, DNA alteration in mitochondrial function, functioning as external oncogenes, over-activating human oncogenes, and inhibiting tumor suppressors.

Chronic inflammation has been identified as an important step in tumorigenesis. For oncogenic viruses to develop, cancer must develop mechanisms that help them evade host immune systems. Second, infections must be capable of inducing mild but persistent inflammation. Chronic inflammation increases the generation of mutations and will consequently increase the risk of tumor development.

Long COVID is essentially associated with activation of the inflammatory pathways. Within six to eight weeks of COVID-19 infection, a significant inflammatory response is observed. In addition, mild or asymptomatic patients have demonstrated neutrophil dysfunction, which in turn increases susceptibility to cancer.

Another potential mechanism may be the "reactivation" of SARS-CoV-2 or other viruses. The residual virus cells could result in long-lasting immunomodulatory effects. This may explain the low-grade inflammation. This chronic inflammation, coupled with oxidative stress, could lead to tissue and DNA damage.

Another mechanism in Long COVID inflammation and cancer may come from the SARS-CoV-2 spike protein, which contains a furin-like cleavage site. This spike protein promotes the activation of the NLRP3 inflammasome and NF-κB inflammatory pathways. Elevated inflammasome pathways may increase oncologic potential.

In summary, in addition to chronic ongoing inflammation, Long COVID may likely be a risk factor for new cancer by following different mechanisms:

- **Chronic viral infection and residual viral proteins;**
- **Chronic Inflammation;**
- **Cell senescence;**
- **The oncogenic potential of SARS-CoV-2; and**
- **Immunosuppression.**

IMPACT ON DISPARITIES[25-28]

The National Institutes of Health Researching COVID to Enhance Recovery Initiative revealed that Black and Hispanic Americans experience more symptoms and health problems related to Long COVID compared to the Caucasian patient population.

This evidence suggests that there are important differences in how Long COVID manifests in different racial and ethnic groups.

Among non-hospitalized COVID-19 patients, Hispanic individuals had higher adjusted odds of being diagnosed with Long COVID across six of eight organ systems, while Black individuals had higher odds of diagnosis across four of

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eight systems. Black patients had twice the risk of diabetes and one-and-a-half times the odds of being diagnosed with chest pain in Long COVID.

These differences may be explained due to interacting biological, environmental and social factors. Immunogenetic differences also exist among populations, affecting the immune cell repertoire and resulting in racial differences in immune profiles.

Black Americans are significantly more likely to carry genetic variants of proinflammatory cytokines. Furthermore, they often bear genotypes (including variants of IL-1, IL-6, IL-10 and TNF-α). This dampening of the immune response leads to inflammatory diseases being more common among Black Americans, which could make them more susceptible to Long COVID.

POPULATION HEALTH IMPACT[29-31]

With more than 600 million individuals infected with COVID-19, it is believed that at least 65 million individuals around the world have Long COVID, based on a conservative estimate of 10% incidence of infected people.

In the U.S., more than 100 million COVID infections occurred by the Fall and Winter of 2022-23. With an estimated 15% to 30% of these individuals developing Long COVID, it is postulated that 7% — or close to 15 million Americans — have been impacted by Long COVID.

Long COVID outpaces diabetes in terms of cost per member for a given health plan, according to *Becker's Payer Issues*. Long COVID is associated with all ages and acute phase disease severities, with the highest percentage of diagnoses between the ages of 36 and 50 years. Most Long COVID cases are in non-hospitalized patients with a mild acute illness.

SUMMARY

This paper presents a compelling case for the urgent need to investigate the intricate relationship between Long COVID, inflammation, heart disease, brain fog and cancer.

With more than 600 million individuals infected with COVID-19, it is believed that at least 65 million individuals around the world have Long COVID, based on a conservative estimate of 10% incidence of infected people.

As leading oncologists as well as population health experts and dedicated scientists, we recognize the potential implications of this emerging health crisis and the impact it may have on patients' long-term well-being.

By analyzing cardiovascular disease, neurological complications, healthcare disparities and the impact of Long COVID on chronic comorbidities, we aim to shed light on the broader population health impact of this condition.

Additionally, we explore the role of COVID-19, mitochondria, microRNA (miRNA), methylation and viruses in the context of cancer development and the associated healthcare costs.

Finally, we examine the trends among community cancer patients before and after the COVID-19 pandemic. By shedding light on these interconnected areas, we aim to encourage oncologists and pharmaceutical companies to support research efforts and collaborate in seeking effective treatments for this complex condition.

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PATIENTS STILL TURNING TO CHARITABLE ASSISTANCE DESPITE MEDICARE REFORMS

By Amy Niles, MBA

High out-of-pocket (OOP) costs for prescription drugs can force patients to delay or forego necessary medications and treatments.

In fact, a Kaiser Family Foundation poll found that 43% of U.S. adults report that they or a family member in their household has put off or postponed needed healthcare due to cost.[1]

Amy Niles

And while pharmaceutical manufacturers can, and do, directly assist uninsured or commercially insured patients with their copays through their patient assistance programs, they are unable to provide direct support to patients enrolled in federally funded insurance programs — including Medicare Part D — due to federal regulations.

Independent charitable patient assistance foundations and healthcare advocacy organizations, like the PAN Foundation, exist to fill this gap in the safety net for thousands of federally insured patients every year who often live on fixed incomes, have multiple chronic illnesses, and face significant challenges affording their OOP prescription medication costs.[2]

Without an organization like the PAN Foundation, these patients would have nowhere else to turn.

NEW MEDICARE REFORMS IN 2025

In 2022, six new Medicare Part D reforms were passed as part of the Inflation Reduction Act, an important step toward healthcare access, affordability and equity for millions of Medicare beneficiaries.[3]

Most notably, these reforms include a $2,000 OOP cap for prescription medications for people with Medicare Part D that goes into effect in 2025. After 2025, the Part D cap will increase each year at the rate of growth per capita Part D costs.

While most other health insurance plans have had a cap on OOP spending for years, this marks the first time those enrolled in Part D plans will have one. This Medicare Part D cap is automatic and applies to everyone enrolled in Part D plans through traditional Medicare and Medicare Advantage plans. It's expected to help all Medicare Part D beneficiaries, especially those who have high OOP prescription medication costs.

In addition to the cap, a new opt-in program, known as the Medicare Prescription Payment Plan, also will go into effect in 2025. Prescription drug plans are required to offer enrollees with Part D coverage the opportunity to opt-in to the plan, which allows OOP prescriptions costs to be spread out monthly throughout the calendar year. Since this is a voluntary program, people must take action to join and take advantage of this new reform.

As with the cap, people with Part D coverage through traditional Medicare and Medicare Advantage programs are eligible to participate in the prescription plan. And while it will not lower OOP costs, the plan offers a way to manage expenses and budget OOP costs more easily.

THE REFORMS IMPACT ON AFFORDABILITY

So, what do these reforms mean when it comes to patient affordability? Through in-depth research by Avalere and our own national polling as part of our Center for Patient Research, we've been at the forefront of understanding how these reforms may impact patients enrolled in Medicare Part D — particularly the new $2,000 OOP cap.[4]

According to our research and polling, many Medicare Part D enrollees will still struggle with affordability even after the new regulations make it easier to begin and continue taking their prescription drugs.

This is especially true among therapeutic areas such as autoimmune conditions, multiple sclerosis and HIV, and other communities experiencing health disparities and inequities, such as indigenous peoples and lower-income individuals.

In fact, Avalere projects that more than 2.6 million adults enrolled in Medicare Part D will have OOP spending high enough to reach the new $2,000 annual cap when it comes into effect in 2025.[5]

And when looking at beneficiaries within only eight key therapeutic areas, Avalere projects about 182,000 to 410,000 people will likely spend more than 10% of their estimated annual income on OOP costs for prescription medication each year.[6] This leaves them

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PAN'S CURRENTLY OPEN FUNDS

PAN currently has more than 20 oncology-related disease funds open — many of which are available for patients with both commercial insurance and Medicare — including:

- Biliary tract cancer
- Chronic lymphocytic leukemia
- Liver cancer
- Mantle cell lymphoma
- Philadelphia chromosome negative myeloproliferative neoplasms
- Small cell lung cancer
- Waldenstrom macroglobulinemia

View all our disease funds and apply today at panfoundation.org/find-disease-fund.

CHARITABLE ASSISTANCE

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effectively underinsured and at increased risk of delaying or forgoing treatment.

WHAT PATIENTS ARE SAYING

For the more than 50 million adults in the U.S. enrolled in Medicare Part D, OOP costs for prescription medications are just one part of their overall cost of care. This doesn't account for their other healthcare costs (e.g., insurance premiums, doctor's office copays, lab tests and other diagnostic tests, etc.) or living expenses, such as housing/rent, food, utilities, clothing, or transportation.

Our national polling found about 75% of adults said it would be difficult to afford $2,000 in OOP prescription costs each year.[7]

Affordability concerns were especially high among Black and Hispanic adults, adults with incomes under $50,000, and adults with chronic or rare diseases.

In fact, about 60% of respondents whose current prescription drug costs don't exceed $2,000 said they would cut back on food-related expenses if they were faced with that total. Others reported they would cut back on utilities or other medical expenses.

To learn more about the **PAN Foundation**, scan the QR code above.

In addition to our polling, we've heard directly from patients from across the country who have indicated they'd still struggle to afford $2,000 in prescription medication costs and need charitable assistance for help.

"The financial strain that it would cause to have to pay $2,000 out of pocket — I wouldn't be able to do what I'm supposed to be doing," said Marlene, a patient from Alabama living with leukemia. "Please keep in mind that those of us who are older and can't make lots of money need these foundations and don't need an extra $2,000 on our plate."

CONTINUED NEED FOR CHARITABLE ASSISTANCE

It's clear that while these reforms are an important step in the right direction, many patients will continue to struggle. And since individuals enrolled in Medicare Part D and other federally funded insurance programs are unable to use manufacturer assistance, they must rely on organizations like us to serve as a safety net when they can't afford their medications.

The PAN Foundation remains committed to providing financial assistance through our 70+ disease funds, including more than 20 oncology-specific funds.

By helping with OOP prescription costs, we allow these patients to focus on what matters most — receiving the treatment they need.

We'll also continue to advocate for improved healthcare access, affordability, and equity so that all people can live the life they deserve.

For as long as patients face high OOP prescription costs and face healthcare access issues, we will be here providing them with financial assistance, advocacy support and educational resources.

▲ **Amy Niles**, MBA, is Chief Mission Officer for the PAN Foundation in Washington, D.C.

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INCORPORATING LARGE LANGUAGE MODELS IN ONCOLOGY

EVER-IMPROVING AI SYSTEMS OFFER NEW OPPORTUNITIES FOR RESEARCHERS, PRACTICES AND CANCER PATIENTS

By Ebaad Khan, Mohid Khan, MSE, Mohamad Hamoudeh, Eman Haque & Waqas Haque, MD, MPH, M.Phil.

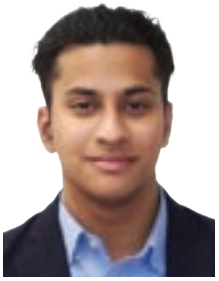
Large language models (LLMs) are sophisticated artificial intelligence (AI) systems capable of understanding and generating human-like text, answering complex questions and adapting to diverse tasks.

These models have undergone a remarkable evolution from their origins as simple statistical, rule-based tools.[1] Fueled by advances in computing power, access to vast datasets, and groundbreaking algorithmic innovations such as neural networks and transformers, LLMs' capabilities have expanded exponentially.

Despite facing challenges like the occasional generation of incorrect information (also known as "hallucinating"), LLMs' impact on process information continues to grow.[2]

Oncology is ripe for LLM implementation due to the role of multidisciplinary communication among medical, radiation and surgical oncologists, along with the role of conveying sensitive and complex information to patients and their caregivers. With the global incidence of cancer projected to reach 35 million cases by 2050, careful deployment of LLMs has the potential to alleviate the increased communications burden among clinicians, patients, administrators and other stakeholders.[3]

LLMs have the potential to not only improve efficiency in performing clinical tasks, but also to have an upstream impact by ensuring better access to care, improving patient health literacy, and identifying novel opportunities in drug discovery. For these technologies to have their maximal impact, it is vital for oncologists and other clinicians to be actively involved in understanding and implementing AI into clinical workflows.



Ebaad Khan

Mohid Khan

Mohamad Hamoudeh

Eman Haque

Waqas Haque

EXAMPLE 1: PATIENT COMMUNICATION

LLMs can assuage patients' concerns and help them better understand their type of cancer and potential treatment options. LLMs have been used to convert difficult-to-understand medical jargon in discharge summaries into more patient-friendly terminology.[4]

In addition, LLMs have even demonstrated potential in providing emotional support to patients by acknowledging the importance of physical and mental well-being, validating patients' emotions and encouraging seeking professional mental health assistance.[5]

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LARGE LANGUAGE MODELS

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Within oncology, LLMs have shown potential in helping answer patients' questions about procedures and treatments.

In one study, researchers asked the AI system ChatGPT (version 3.5) common radiation oncology questions asked by patients. Of 115 radiation oncology questions, 108 responses were considered to have performed the same or better when compared with expert answers from medical professional society websites. However, two responses were deemed to be "potentially harmful," highlighting the potential risk of misinformation.[6]

In another study, LLMs were able to reliably answer questions about five common solid tumors (including breast and prostate cancer) at a college reading level, but were noted to not be very actionable in nature. Both of these studies suggest that LLM-generated responses should be screened by clinicians before being delivered to patients.[7]

EXAMPLE 2: CLINICAL DECISION SUPPORT

LLMs can be effective in enhancing clinical decision-making with innovative approaches to tailored treatment strategies and patient care.

This is demonstrated by a study that included BioMedLM, Perplexity AI and ChatGPT to generate treatment recommendations for ten fictional cancer patients. A manual review by a molecular tumor board found that for every patient case, each LLM produced at least one viable treatment.

For instance, the LLMs identified a unique treatment strategy of antiandrogen therapy for a patient with salivary duct carcinoma with HRAS and PIK3CA variations, which was not suggested by the human expert due to the lack of an immunohistochemistry test.

However, the LLM, understanding that HRAS and PIK3CA co-mutated salivary duct carcinomas usually stain positive for the androgen receptor, recommended antiandrogen therapy even without explicit immunohistochemistry results.[8]

As these technologies continue to evolve, the oncology community eagerly anticipates the trailblazing impacts LLMs will have on patient care, research and treatment outcomes in the near future.

Despite the efficiency of LLMs in clinical settings, a letter in *JAMA Oncology* from earlier this year notes computational limits of answering broad or ambiguous questions. The quality of an LLM-generated answer depends on the specificity of prompt, which is tied to the number of "tokens" (computational power associated with interpreting the query) employed to generate the response.[9]

For example, say a patient were to ask, "How do you treat early-stage, hormone-positive breast cancer?" The response could vary from mentioning common treatment modalities (including chemotherapy, surgery and hormone therapy) to discussing the optimal endocrine backbone or nodal and menopausal status to guide treatment recommendations.

The appropriate response should also be tailored to the user's health literacy — the answer provided to one with no medical knowledge will drastically differ from one given to a medical student, for example.

EXAMPLE 3: DRUG DEVELOPMENT

In addition to clinical practice, LLMs can enhance efficiency in manuscript writing and statistical analysis code generation, particularly benefiting non-native English speakers and researchers with limited programming experience.[10,11,12] The democratization of programming allows a broader range of scientists to contribute more easily to the scientific body of cancer drug development.

On top of clinical research, LLMs have shown significant potential in drug discovery by finding new leads and predicting drug synergy pairings.[13]

To take an example in drug development, researchers compared various LLMs — GPT-2, GPT-3, SciFive and CancerGPT (a fine-tuned GPT-2) — against conventional machine learning methods (such as XGBoost) across a number of relatively data-scarce cancers (including pancreas and soft tissue) to predict potential drug targets.

Traditional models performed better in endometrium, stomach and bone cancers, where data patterns more closely matched common cancers.

Conversely, LLMs, particularly CancerGPT, excelled in liver, soft tissue and urinary tract cancers, which have unique cellular characteristics. Researchers validated the LLM's reasoning against scientific literature, finding mostly accurate explanations.

However, the study was limited by the LLMs' reliance on in vitro data, lack of clinical validation and focus on a specific prediction task. With that limitation in mind, this study demonstrates LLMs' potential to surpass traditional methods in predicting drug synergy for rare cancers.[14]

TRANSPARENCY

Unlike traditional medical devices, such as an ECG or BiPap machine, where a malfunction can be traced back to a specific hardware issue or calibration error, the decision-making process of an LLM is more opaque, making it challenging to pinpoint the exact cause of an erroneous diagnosis or recommendation.

Proposed methods to improve interpretability include a selection inference multistep reasoning framework to generate a series of causal reasoning steps toward the final generated response.[15]

Another method proposes leveraging ChatGPT using chain-of-thought prompting (i.e., step-by-step instructions)

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LARGE LANGUAGE MODELS

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for knowledge graph extraction, where extracted entities and relationships from the raw input text are presented in a structured format, which was then used to train an interpretable linear model for text classification.[15]

DATA PRIVACY

One of the challenges in the validation and implementation of LLMs with real-world clinical patient data would be the risk of leaking confidential and sensitive patient information.

For example, adversarial attacks on a LLM GPT-2 were successful in extracting the model's training data.[15] By querying GPT-2 structured questions, training data including personal identifiable information and internet relay chat conversations were extracted verbatim. Despite anonymizing sensitive patient health information, some algorithms demonstrated the capability to reidentify these patients.[15]

To mitigate these challenges, possible strategies include pseudonymization or filtering patient identifiers, differential privacy, and auditing of LLMs using data extraction attacks.

FUTURE DIRECTIONS

LLMs are evolving through advancements that enhance their efficiency and accuracy.[16] Open-source models, like Meta's recently released Llama 3.1, now rival closed-source counterparts such as Claude 3.5 Sonnet and GPT-4 in performance.[17]

The availability of iterated and alternative LLMs should keep researchers open to ongoing improvements in hallucinations and other concerns that may preclude clinical integration. We can mitigate the risk of biased or inaccurate responses by prioritizing an equity framework from the outset to ensure optimal care for historically underrepresented groups.

As these technologies continue to evolve, the oncology community eagerly anticipates the trailblazing impacts LLMs will have on patient care, research and treatment outcomes in the near future. Close collaboration between technology developers and healthcare providers is crucial to ensure that LLMs are designed to meet the specific needs of oncology and integrate seamlessly into existing clinical practices.

Furthermore, developing comprehensive ethical guidelines for AI use in oncology is essential to address potential biases, maintain patient privacy and ensure an appropriate balance between human expertise and machine assistance.

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ANNEXUSHealth

A heartfelt thank you

We extend our deepest gratitude to our incredible partners at NCODA and the dedicated oncology teams who tirelessly work to achieve positive outcomes through patient-centered, collaborative care. Your efforts are essential, and patients benefit from your dedication every single day.

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An artist's rendering of the building that will house the Greco-Hainsworth Centers for Research in Nashville,Tennessee.

A PRESCRIPTION FOR PROCESS

BUILDING AN INVESTIGATIONAL DRUG SERVICES DEPARTMENT

By Hillary Brown, PharmD, with Ian Flinn, MD, PhD

In healthcare, we recognize that the scientific method is fundamentally about questioning and testing hypotheses. But have you ever thought about applying this approach beyond the development of new drugs or devices? The roles we fulfill in healthcare likely went through a rigorous process of creation and evaluation before becoming integral parts of our daily workflows.

Before becoming the Manager of Investigational Drug Services at Tennessee Oncology, I rarely questioned the established processes. I adhered to standard pharmacy procedures and maintained my routine without much deviation.

However, in August 2023, Tennessee Oncology faced the formidable task of launching a new research program. Under the guidance of the Chief Scientific Officer and other leaders, Tennessee Oncology assembled a five-person team led by an executive director of research operations to build the new research team from scratch under the newly formed Greco-Hainsworth Centers for Research (GHCR). I was brought onboard to establish the research pharmacy for this new initiative.

Hillary Brown

Ian Flinn

Much like the scientific method, developing successful processes and procedures requires extensive questioning and hypothesis testing, especially as GHCR continues to grow. Drawing from my prior experience in other research organizations, I brought elements of established processes and carefully evaluated which aspects would best serve this new division. However, many other questions needed to be answered before we could progress as a fully functional investigational drug pharmacy.

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INVESTIGATIONAL DRUG SERVICES

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QUESTION 1: WHERE WILL WE PUT AN INVESTIGATIONAL PHARMACY?

This was the most daunting and anxiety-inducing challenge we faced. Initially, we were uncertain about where to locate our pharmacy, but we knew we needed a space with ample secure storage for investigational drugs, a dedicated workspace, a sterile compounding area and close proximity to our clinics for timely drug delivery.

With a tight timeline and limited resources, we began searching for a suitable location within Tennessee Oncology. We identified one clinic that met the necessary requirements for investigational drug storage and location. The final piece of this was ensuring that the investigational drug inventory remained exclusively accessible to our team. Given the presence of other staff and patients at this clinic, all investigational drug storage equipment had to be securely locked.

With the support of several Tennessee Oncology team members, we established the required secure storage and workspaces. Just one week before our go-live date, we had a fully equipped space ready to dispense investigational drugs to our first patients under the newly launched GHCR.

We have made several adjustments within the clinic to accommodate our growing team and investigational drug inventory. Currently, we have three desks and space for two refrigerators, two freezers and one ambient temperature cabinet, all securely locked and accessible only to our team. This setup is temporary, and we anticipate relocating to a larger space to support our expanding clinical trials in the future. Our future site is shown in the picture.

QUESTION 2: WHO WILL WORK IN THE PHARMACY?

To ensure a properly functioning investigational pharmacy, especially one in the beginning phases, there is a critical need for a meticulous staff. We needed pharmacists, technicians and dedicated research Electronic Medical Record builders who were all detail-oriented, team players, versatile, self-motivated, adherent to processes, and willing to step in wherever needed. Based on my previous experience as a clinical pharmacist in investigational drug services, I was well-versed in most tasks in an investigational pharmacy and could effectively train the team to handle all aspects of the work. However, it would be advantageous to have staff with experience in research and IV admixtures or, at the very least, those who could be quickly trained in these areas.

From the outset, I was fortunate to play a key role in building the investigational drug services team, such that, on my very first day of orientation in November, interviews for the research technician position were already scheduled. By mid-December, we had a research technician onboard, whose expertise in research and intravenous admixture was instrumental in setting up the pharmacy. This technician helped establish processes for ordering investigational drug products, created courier schedules, and compiled a list and schedule of patients' treatments for the launch date of GHCR. From assisting with the move into the pharmacy to manually receiving investigational drugs while we awaited the accountability system, the technician's contributions have been essential from the start and remain crucial to our daily operations.

After the inauguration of GHCR, our team expanded with the addition of a dedicated Investigational Drug Services pharmacist. Recruiting for this role was crucial, as we needed someone with a research background to navigate the constantly evolving clinical study protocols and pharmacy manuals. This clinical research pharmacist is responsible for reviewing internal protocols and pharmacy manuals, staffing the investigational drug pharmacy, reviewing research EMR builds, and contributing to the development of new processes as we embark on early-phase trials with the GHCR Drug Development Unit (DDU).

As we continue to see an increase in amendments for current studies and new studies in the pipeline, the final crucial addition to our team is a dedicated research EMR builder. This role is essential for integrating protocol-specific investigational drugs, activities, labs and scans into Tennessee Oncology's EMR system. The research EMR builder will also update the system in response to evolving protocol amendments, ensuring that our clinical research team adheres to protocol requirements for each patient.

Determining the optimal staffing levels has been challenging, so we have added team members at different stages as needed. As protocol numbers grow, so will our staffing needs. However, at a minimum, every research pharmacy requires these essential roles to function effectively.

QUESTION 3: HOW WILL WE SAFELY PREPARE AND DISPENSE INVESTIGATIONAL DRUG PRODUCTS TO MULTIPLE CLINICS?

Tennessee Oncology's mission is to deliver high-quality cancer care and clinical research expertise at convenient locations within the community and close to patients' homes. While clinical trial research is crucial in all settings, offering these trials near patients' homes alleviates the significant burden of long-distance travel, enabling them to access extraordinary care that might otherwise be out of reach. To achieve this, it is essential to have robust processes in place to ensure the integrity of investigational drugs from receipt in the investigational drug pharmacy through their transport from the pharmacy to community clinics.

Given the numerous Tennessee Oncology clinics across the state, we established rigorous processes with multiple checkpoints to prevent errors. We work proactively through a "work ahead" process to ensure timely preparation and delivery of investigational drugs to the appropriate clinics, while maintaining excellent communication between the clinical research team and the pharmacy team to ensure alignment and coordination of responsibilities.

To guarantee medication availability, GHCR's investigational pharmacy sets a reorder point for two treatment cycles per patient. Upon receiving shipments, we use a checklist requiring two staff signatures to verify drug integrity, temperature, packing accuracy and proper logging. Shipping documents are uploaded to our accountability system for sponsor review.

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INVESTIGATIONAL DRUG SERVICES

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Our "work ahead" approach entails the research clinical nursing team sending Investigational Product Provided (IPP) forms, which detail the scheduled patients and their corresponding provided drugs to our research pharmacy team. The clinical research pharmacist reviews these orders two business days in advance and obtains a second review from another pharmacist. One business day ahead of treatment, the research technician then prepares the oral investigational drugs and stages the IV investigational drugs. On the day of treatment, the research technician mixes all IV investigational drugs, which are then checked by the research pharmacist. The investigational drugs for that day are packaged in a temperature-controlled cooler and transported by our courier team to the clinic. There, the research nursing team verifies the product's integrity and temperature, as documented on the IPP form, which also serves as the chain of custody form.

To sustain these processes, our team also tracks and documents the return of oral investigational products, monitors temperatures and calibrations, updates internal documents in response to protocol or pharmacy manual changes, quarantines and destroys expired products with sponsor approval, and schedules protocol-specific monitoring visits via a remote system for protocol monitors to review pharmacy activities.

These processes have been rigorously tested and refined by the GHCR research team. It is essential to continue questioning and updating them as circumstances evolve, ensuring that our practices remain effective and responsive to change.

QUESTION 4: WHAT ARE THE IMPORTANT STANDARD OPERATING PROCEDURES TO RELAY TO SPONSORS?

When establishing an investigational drug pharmacy, one of the protocol sponsor's first requests from sites is the Standard Operating Procedures (SOPs) for managing investigational products. These SOPs must be comprehensive yet practical, ensuring long-term viability without imposing unrealistic expectations across different protocols. Effective communication within the research team is essential to prevent conflicts with existing procedures. SOPs should also be readily available to sponsors during monitoring visits to address any procedural questions.

GHCR's Investigational Drug Services SOPs address key areas, such as study initiation, drug accountability, temperature monitoring, preparation, dispensing, transportation, destruction, monitor visits and staff training. They define document provision and site initiation visit protocols, outline how to track drug transactions, specify temperature ranges and monitoring methods, and detail preparation and dispensing workflows. We included a provision to dispense drugs one business day in advance to align with the Interactive Response Technology system. Our transportation protocols cover sending drugs to Tennessee Oncology clinics, and our destruction protocols address on-site disposal of expired drugs. The monitor visit guidelines outline sponsor permissions and scheduling procedures, while staff training SOPs confirm how we remain current with required training.

We continuously update our SOPs to address new challenges. As we learn more, provisions are changed and added. For example, last month's update added a backup temperature monitor provision to simplify handling temperature excursions with a simple note to file, instead of individual reports as required by various pharmacy manuals. Our GHCR team reviews these SOPs twice a year to address new challenges and make any updates necessary.

QUESTION 5: WHAT SYSTEMS WILL WE USE TO MONITOR THE INVESTIGATIONAL DRUG PRODUCT?

As previously discussed, accountability and temperature tracking are both essential in a research pharmacy. Our team approach to these processes ensures accuracy and efficiency.

For accountability, each protocol requires individual configuration within our system. The system tracks each drug shipment from arrival to departure, generates labels, manages IRT access and supports virtual monitoring visits for remote targeted assessment by sponsors. It serves as our digital protocol binder, where we upload all relevant documents, such as temperature logs, temperature monitoring calibration records, patient IV mixing sheets (used by the research technician as a recipe for the investigational IV drug), IRT dispenses, sponsor communications and protocol updates. Tracking pharmacy manual training is also managed through this system. Prior to this, we relied on manual tracking methods, which were significantly improved by this new system after only a few weeks.

Temperature monitoring is another critical area of investigational drug management. Our system records temperatures every five minutes and sends alerts to the team if there are deviations from the acceptable ranges, allowing us to quickly address potential issues. We initially monitored every 15 minutes, but this interval proved insufficient, leading to a temperature excursion — a lesson that prompted us to update our process to five-minute intervals. We have also added a backup temperature monitor, as detailed in our recent SOP updates. These systems are continually evolving, and are refined and adapted as GHCR grows and faces new challenges.

CONCLUSION

The success of launching the research pharmacy hinged not only on the efforts of the investigational drug services team but also on the strong support from Tennessee Oncology and GHCR leadership. Building and maintaining strong relationships both within and outside of our team has been — and will continue to be — crucial in addressing upcoming challenges. Currently, our research team is focused on refining study start-up and amendment processes, with many more processes still to be developed. We are dedicated to rigorously exploring solutions, testing them under pressure, and continually improving to ensure that GHCR becomes the best research program possible.

▲ **Hillary Brown**, PharmD, is a clinical research pharmacist and manager of Investigational Drug Services at Greco-Hainsworth Centers for Research at Tennessee Oncology in Nashville, Tennessee. **Ian Flinn**, MD, PhD, is Chief Scientific Officer at Tennessee Oncology & OneOncology in Nashville, Tennessee.

UNLOCKING SUCCESS IN PHARMA TEAMS: INSIGHTS BEYOND THE OBVIOUS

By Sharita Howe, PharmD, Alex McCafferty, & Pat Connelly, MBA

We know pharma. We are fortunate to work with 85+ pharmaceutical companies. This gives us a unique view into what makes the best, the best. We are incredibly thankful for the support from all our partners.

However, it is true—the best teams act differently. The most successful teams aren't simply good at communication and collaboration—they possess qualities that set them apart in ways only those within the industry can deeply appreciate.

At NCODA, we've seen firsthand what distinguishes the teams that consistently excel. Here are the key traits that make them stand out:

1 COMPREHENSIVE MARKET UNDERSTANDING

The best teams have an unparalleled 360-degree knowledge of the current market and environmental trends. They speak the language of clinical experts, understand the intricacies of patient access, and see the entire picture with clarity.

This deep and broad expertise across the entire team means they can dive into complex challenges, making meaningful progress with fewer, yet more impactful conversations. Their ability to anticipate and address concerns across different stakeholders leads to greater productivity and more successful outcomes.

Sharita Howe

Alex McCafferty

Pat Connelly

But it doesn't stop there. These teams also understand the importance of diversity — diversity of experience, background and perspective. A team with varied insights is better equipped to tackle multifaceted issues because they approach problems from different angles.

Whether it's having members who have worked on the clinical side, in patient advocacy, or in market access, this blend of expertise ensures that the team can address challenges comprehensively.

Diversity isn't just a nice-to-have; it's a critical driver of innovation and success in an industry as complex as ours.

2 EMBRACING COMPLEXITY

Oncology biopharma is inherently complex, and the teams which thrive are those which embrace this complexity rather than shy away from it. They understand that the procurement-to-pay

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PHARMA TEAMS

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process is multifaceted, and they meticulously account for every step in their planning.

These teams navigate obstacles with ease, recognizing that each phase is critical to reaching the end goal. By acknowledging and addressing these challenges head-on, they ensure smoother operations and more consistent success.

Moreover, these teams realize that getting things done means rolling up their sleeves and getting their hands dirty. It's common for team members to step out of their traditional roles and take on tasks that might be considered outside their job descriptions.

Whether it is troubleshooting a logistics issue or working directly with a healthcare provider to resolve a patient access challenge, these teams align well both internally and externally. They understand that success often depends on their willingness to engage at every level and ensure nothing falls through the cracks.

3 SINGULAR FOCUS

Successful teams are masters of focus. They dedicate themselves to one key area, ensuring that all resources and efforts are aligned with moving the needle in that specific domain.

This intense concentration allows them to achieve considerable progress, as they make sure that what needs to get done, gets done — efficiently and effectively. They are clear about their priorities and excel in executing their plans, which drives measurable impact.

To illustrate this point, we have a partner who exemplifies this approach perfectly. They have one message, one goal, and everyone on the team knows it. Everything we work on is aligned toward achieving that goal. They don't allow distractions to pull them away from their focus.

Importantly, they don't move on to the next thing until the current task is completed to their satisfaction. This

NCODA and our pharma partners realize that getting things done sometimes means rolling up your sleeves and getting your hands dirty. It's common for team members to step out of their traditional roles and take on tasks that might be considered outside their job descriptions.

disciplined approach has led to impressive outcomes and serves as a model for other teams striving for excellence.

4 BALANCING RISK & RETURN ON INVESTMENT

Innovation is the lifeblood of progress in biopharma, but it must be balanced with a clear return on investment.

The best teams understand this balance intuitively. They craft pathways that blend traditional approaches with disruptive innovations, ensuring that their efforts not only yield benefits, but also push the envelope of what's possible.

This strategic balance of risk and reward positions them to make substantial contributions while staying aligned with overall business goals.

In an industry where marketing and everything else are increasingly driven by numbers, tracking impact is essential. But these teams understand that it's not just about the numbers; it's also about leadership and education, especially in areas like rare diseases.

The best teams make both moves simultaneously — they follow the numbers, ensuring that their efforts are measurable and impactful, while also driving innovative approaches that push the boundaries of what is possible. They are educators and innovators, guiding the industry forward while keeping a sharp eye on Return on Investment (ROI).

5 ALIGNMENT WITH LEADERSHIP

Finally, alignment with leadership is a hallmark of successful teams. These teams are exceptional in how they communicate their strategies with leadership and involve them in their plans.

By bringing leadership into the fold, they gain access to additional resources and foster a stronger sense of connectivity across the organization. This alignment ensures that everyone is moving in the same direction, maximizing the opportunities to make a real impact.

Through this alignment, these teams can drive more impact and connectivity. They have the best access to resources and decision-makers.

In fact, leaders in oncology are more likely to pick up the phone when it is the head of medical, access, or marketing from these teams calling. This level of access and influence is not easily achieved, but when it is, it accelerates progress and amplifies the team's ability to make a difference in the lives of patients.

THE BOTTOM LINE

These are the qualities that distinguish truly exceptional teams in the pharmaceutical industry. By cultivating a deep understanding of the market, embracing complexity, maintaining a sharp focus, balancing risk with ROI and aligning closely with leadership, these teams are not only more productive but also more impactful in their work.

At NCODA, we see the difference these traits make every day, and we believe they are the key to driving success in this challenging and rewarding field.

▲ **Sharita Howe**, PharmD, is Associate Director of Partner Strategy and Development. **Alex McCafferty** is Associate Manager of Partner Development and Strategy. **Pat Connelly**, MBA, is Chief Development and Strategy Officer. All work at NCODA.

CANCER PREDISPOSITION VARIANTS IN APPARENTLY HEALTHY INDIVIDUALS

NOT ALWAYS A REASON FOR ALARM

By George P. Patrinos, PhD

Imagine that you were told that you have 187 cancer predisposing variants in your genome. Would you be worried?

Well, I was!

George P. Patrinos

Cancer results from a multistep cascade of somatic events involving the accumulation of both genetic and epigenetic changes at various genomic loci, under the influence of a variety of different environmental factors.[1] A considerable number of genomic variants have been previously reported to be causative of, or associated with, an increased risk for various types of cancer.

Single point variants, small insertions/deletions, translocations, gene fusions, copy number changes and loss of heterozygosity represent some of the somatic alterations frequently encountered in cancer, and which can lead to the increased expression of oncogenes or to the silencing of tumor suppressor genes.

Genome-wide association studies (GWASs) have also identified genomic regions that appear to be associated with increased cancer risk. It is to be expected that an improved knowledge of the genomic variants that predispose to tumor initiation, development and progression will be advantageous in the context of informing treatment regimens for cancer patients.

Numerous studies have been performed in an attempt to shed light on the complexity and inter-individual variability of the heritable and tumor genome and to examine the relationship between the possession of specific genomic variants and tumorigenesis, often with ambiguous results.[2] The advent of next-generation sequencing (NGS) has provided unprecedented opportunities to decipher the cancer genome and to dissect the molecular etiology of cancer predisposition.

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Genetic susceptibility to cancer is conferred both by inherited (germline) and tumor-specific (somatic) variants and as such, it is evident in most individuals, not just in those individuals with a personal or family history of cancer. Although the deleterious alleles of cancer risk genes are generally not highly penetrant, the presence of genetic susceptibility variants at multiple loci is generally assumed to increase an individual's overall risk of cancer.

MY PERSONAL EXPERIENCE

Several years ago, while preparing my plenary talk for an oncology conference on the role of next-generation sequencing in cancer genomics, I looked in my own genome analysis to see whether I had any cancer predisposing variant in my genome. The reason was to give a real-life example of the use of NGS in cancer genomics.

One would assume that I expected to have no cancer-predisposing variants as, thank God, there is no cancer history in my family. You can imagine my surprise when my initial search revealed 187 genomic variants predisposing to cancer! My first thought was to start writing my will. But then I realized that some, hopefully the majority of these variants, may not necessarily be deleterious, or in other words truly cancer predisposing.

As such, the next few days after my talk, we initiated a study to look into the genomes of 11 members of two families of Greek descent (one of which was my own, as we already had NGS data to analyze) to identify all genomic variants with the potential to predispose family members to cancer.

In short, we identified a total of 571 variants, of which:

- 47% were disease-associated benign variants;
- 26% were disease-associated benign variants with additional supporting functional evidence;
- 19% were functional variants with in vitro/laboratory or in vivo supporting evidence but no known disease association;
- 4% were putative disease-causing variants but with some residual doubt as to their pathological significance; and
- 3% were disease-causing variants, according to the Human Gene Mutation Database variant annotation.[3]

Subsequent analysis, focused on the latter variant class most likely to be involved in cancer predisposition, revealed two variants of prime interest, namely MSH2 c.2732T>A (p.L911R) and BRCA1 c.2955delC, the first of which is novel.

Also, among the 571 cancer risk-associated variants identified, some were common between the two families considered, whereas others were unique. In particular, 509 variants were found in both family members, while 74 variants were unique to family A and 551 variants were only found in family B.

Commenting on the unique variants obtained, family B comes from northern Greece, a quite distant location from Athens (300.13 km) where family A is from, implying a different genetic origin. For the record, neither of the two abovementioned variants were found in my own genome, which was a big relief for me!

Inherited genomic variants in the BRCA1 gene are well known to confer an increased lifetime risk of developing breast or ovarian cancer. BRCA1 is a tumor suppressor gene that is involved in the maintenance of genome stability (homologous recombination pathway for double-strand DNA repair) and hence, is of paramount importance in hereditary breast and ovarian cancers.

However, the identification of an evidently detrimental BRCA1 variant in a healthy individual is not unlikely. Also, genomic variants in the MSH2 gene are associated with microsatellite instability and cancer (hereditary non-polyposis colorectal cancer, HNPCC) and participates in several DNA repair processes, such as transcription-coupled repair, homologous recombination as well as base excision repair.

CONSULT AN EXPERT

From the above, it is clear that a thorough downstream bioinformatic analysis and a subsequent genetic counseling session should be performed for family members to receive proper genetic advice, without being neither falsely alarmed nor, even worse, falsely reassured.

In other words, direct-to-consumer

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genetic analysis for cancer predisposition should not be performed under any circumstances, as the public may be truly alarmed from these results without being given the proper explanations by an expert.

Looking to the future, whole genome sequencing should ideally be performed once — e.g., at birth, with data analysis frequently interpreted using the continuously updated literature thereafter in order to exploit the wealth of genomic knowledge that is continually becoming available.

Also, family history is of central importance in medical/clinical practice, since it reflects both genetic and environmental exposures within families, while incidental findings and reduced (incomplete) penetrance in cancer complicate decision making even further.

Nowdays, genomic data are hardly integrated in medical decision-making in cancer, given its complexity and as educational initiatives and support from specialists are also lacking. In this context, a community knowledge base has been proposed to facilitate collaborative contributions and open discussions on genomic events to raise general public and even healthcafe professionals' awareness on cancer genomics.

In relation to the diagnosis and prognosis of cancer patients, data interpretation requires a deep understanding of the variation in cancer risk-associated genes in healthy individuals. A crude assessment of the potential extent of the genome-wide cancer susceptibility burden in normal healthy individuals should consider all the (putative) risk-associated genomic variants obtained by the next-generation sequencing analysis.

FUTURE CONCERNS

As whole genome and/or whole exome sequencing approaches begin to be recruited into clinical care, our understanding of detected sequence variations on diagnosis (and prognosis) needs to become more readily accessible to the clinician.

Humans have a large number of genomic variants in their own genome, between 3.5 million to more than 5 million, leading to the extant phenotypic variability both in terms of physiology, namely various physiological traits such as height, skin and eye color, etc., and pathology. It is expected that a large number of 'cancer-predisposing' variants will also be present, the majority of which may NOT necessarily lead to cancer.

This is not a trivial undertaking, especially as the polygenic model proposes that an individual's cancer risk is the net outcome of the presence of multiple genomic variants and environmental factors.[4]

The use of next-generation sequencing is expected to play a crucial role in delineating an individual's variome as well as providing the means to identify novel variants to improve therapeutic modalities.

Signature-based drug-repositioning methods are also known to make use of gene signatures to uncover unknown mechanisms of action of molecules and drugs by coupling the significantly changed genes to computational approaches.

As whole genome sequencing services become more accurate in delivering clinical-grade genome sequences, and whole genome sequencing costs continue to decline, it is expected that this approach will gradually assume an integral role in genomic medicine.

To conclude, humans have a large number of genomic variants in their own genome, between 3.5 million to more than 5 million, leading to the extant phenotypic variability both in terms of physiology, namely various physiological traits such as height, skin and eye color, etc., and pathology. It is expected that a large number of "cancer-predisposing" variants will also be present, the majority of which may NOT necessarily lead to cancer.

To properly understand this information, interested individuals and patients need to be given an informed genetic counseling session from well-trained healthcare professionals to prevent misunderstandings that would lead to unnecessary distress.

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EDITOR'S NOTE: Information in this story is from an international perspective and may differ from current U.S. guidelines and regulations.

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IS YOUR KNOWLEDGE OF CANCER ACTUALLY HARMING PATIENTS?

By Vishal Falke, MBA, & Hardeep Phull, MD

"It's not what happens to you, but how you react to it that matters."

— Epictetus

Is it really someone's fault when they get cancer? This question often haunts many of us, especially when we see a loved one struggle with the disease.

It is commonly observed in clinical practice, for example, that lung cancer patients are often stigmatized due to the strong association between smoking and cancer. Indeed, a recent study revealed that people do tend to blame cancer patients for their condition, particularly if they believed the cancer was preventable or due to smoking.[1]

But is this fair or even accurate? If cancer were as simple as avoiding frozen food or drinking magical juices, we would all be cancer-free, right? But the reality is far more complex.

MISCONCEPTIONS AND REALITIES

Blame culture in cancer is deeply ingrained, yet it is often misguided. Let us explore some common misconceptions:

▲ **Smoking and Lung Cancer:** While smoking is a major risk factor, not every lung cancer patient is a smoker. About 15% of lung cancer patients in the United States have pathologies that are not related to smoking.[1] This misconception overshadows the complexity of the disease, where factors such as genetics and environmental influences also play significant roles.

Indeed, comprehensive market analysis conducted recently on lung cancer drugs illustrated the diversity of treatment options that cater to various types of lung cancer based on tumor gene mutations and other factors beyond those commonly associated with smoking.[2] Patients with certain gene mutations are in fact not associated with any smoking history, and do better on these targeted therapies as compared to standard chemotherapy.[3]

Vishal Falke

Hardeep Phull

▲ **Alcohol:** While certain head and neck cancers and gastrointestinal cancers are associated with moderate to severe alcohol intake, there are no studies suggesting that light intake is detrimental or that alcohol intake alone is the only risk factor in development of these cancers.[4]

Nevertheless, while there have been studies of a possible protective effect with certain cardiovascular diseases, there is no current established threshold at which scientists are aware of when carcinogenic effects can take place, and therefore no safe amount of alcohol intake has been recommended at this time by most cancer societies.[5]

▲ **Dietary Choices:** Though ultra-processed foods, frozen foods, high-sugar foods and even pesticides in our food or water supply can be associated with obesity and cancer, there is no universal diet in the world that has shown conclusively to prevent or treat cancer.[6]

It is generally assumed that foods high in fiber and calcium reduce cancer risk, whereas processed foods, salted or smoked meats, red meats and foods contaminated with mutagens can increase cancer risk.[6]

Overconsumption and obesity can also be linked to cancer, independent of the actual nutritional content of the

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foods consumed. Nevertheless, with the prevalence of food insecurity in the world, it is not fair to assume that all people have access to fresh foods with adequate, safe nutrients or calories.

On the other end of the spectrum, even patients who eat high-quality, organic foods cannot completely prevent a diagnosis of cancer, pointing towards the importance of a balanced dietary approach rather than an overly restrictive one.[6]

▲ **Exercise:** While we know that obesity is a risk factor for vascular disease, diabetes and cancer, the definitions of meaningful exercise or non-sedentary lifestyles have been difficult to define.[6] Indeed, the only consistently proven biometric parameter associated with longevity as well as tolerance to chemotherapy has been muscle mass.[7]

This highlights the importance of activities and exercise regimens that incorporate strength training along with cardiovascular health. It also highlights the need for better strategies to prevent and to address sarcopenia. Indeed, cancer patients with sarcopenia are associated with a worsened prognosis and higher risk of therapy-related toxicity.[8,9]

Ongoing studies into the nuances of body composition beyond body mass index or the overreliance on the presence of adipose tissue have identified the need for new pharmacotherapeutic drugs and strategies in this field.[10]

▲ **Genetics:** Genetics play a crucial role in the development of certain cancers, sometimes being more pivotal than or compounding existing lifestyle choices. Therefore, it is critical for families with patterns of cancer in numerous relatives to be offered genetic screening in order to qualify for earlier cancer screenings or prophylactic procedures to reduce their cancer risk.[11]

Unfortunately, breakdowns in family relationships and/or lack of open communication about illnesses in certain cultures lead to a lack of overall awareness in this regard. This is further compounded by a lack of education or access to healthcare, including the presence of affordable genetic studies, resulting in genetic factors being vastly underscreened in many populations.[11]

We must remind ourselves and our communities that cancer is never a patient's fault. By fostering a culture of empathy and informed awareness, we can improve the quality of life for those affected by this disease.

▲ **Aging:** This is one of the biggest and most reliably studied risk factors for cancer, and yet it cannot be reversed like some of the other known modifiable risk factors.[12] In fact, as the average human lifespan continues to push towards the high 70s, many researchers believe that a cancer diagnosis will be an inevitable norm.[13]

The key concepts of "healthspan" along with lifespan have been juxtaposed. In one of the world's most famous "Blue Zones" in Sardinia, Italy, there are a large number of centenarians (people who live to 100 years of age or older) who maintain a high quality of life.[14] Though it has a smaller number of modern fitness centers, they do exist in this region. Surveys of centenarians suggest that conventional "workouts" are not the secret ingredient to their longevity. Rather, the citizens can be found walking, gardening and engaging in manual labor well into their golden years.

Beyond natural movement, they also have access to clean air, a Mediterranean diet with moderation of intake, fulfilling social networks, and intellectual stimulation in the form of reading and writing.[15]

Despite all of the research studies and attention on this population, the concentration of centenarians in this region, or centenarian ratio, is about 20 to 30 per 10,000 (as compared to five to six worldwide), which is still only 0.3%, thus providing perspective that no given strategy, location, or circumstance is perfect.[16]

▲ **Biological, Environmental and Chemical Carcinogens:** From bacteria like *H. pylori* to viruses like HPV, EBV, hepatitis and HIV, there are numerous known biological carcinogens.[16] Contracting such infections can be associated with socioeconomic factors, diet and basic access (or lack thereof) to vaccines in some cases.

There are also many known environmental toxins that can impact us variably including air pollution, water contaminants and forms of radiation exposure including UV light from sun rays.[17]

Lastly, chemical toxins in the form of industrial, synthetic and naturally occurring compounds or preservatives are ubiquitously distributed throughout the environment, including in everyday consumed products.[16] Recently, even some over-the-counter generic cold medicines have been found to contain cancer-causing benzene.[18]

Moreover, certain occupations, or even populations living in proximity to manufacturing plants or war zones, have been associated with increased incidences of cancer due to these chemical carcinogens.[17]

▲ **Existing Medical Conditions and Treatments:** Patients on certain therapies for rheumatologic conditions, autoimmune disease, organ transplantation, hormonal imbalances, and immunosuppressive conditions have a risk of developing cancer.[19]

In fact, it is known that even chemotherapy medications designed to treat cancer can predispose individuals to develop second therapy-related cancers in the future.[20] In such situations, it is important to consent patients to the potential harms of any treatment, and to always weigh the risks versus benefits when providing a particular therapy.

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▲ **Healthcare Equity, Access and Education:** It is easy to forget in the modern era that there are still millions of people worldwide who either lack access to healthcare or who are underinsured.[21]

Moreover, socioeconomic factors can also lead to a lack of healthcare literacy and education.[21] Certain cultural belief systems can also promote a reliance on superstitions and rituals as a substitute to evidence-based healthcare and screening.

In addition, some regions throughout the world do not have adequate healthcare personnel or facilities to provide population-wide preventive care or routine mammograms, Pap smears, and colonoscopies.[21] In general, the patients living in circumstances with the limitations above have fewer opportunities for early cancer prevention or detection. Unfortunately, the net outcome typically involves a major delay in the diagnosis and treatment of cancer, leading to poor outcomes in these patients.[21]

On the other end of the spectrum, even well-insured patients can have misunderstandings and misgivings about seeking medical attention or prescribing to the allopathic model of medical care, which may lead to a reliance on alternative medicines or unproven theories. Though these can certainly complement modern medicine, they do not replace evidence-based care.

Ultimately, it is also natural human behavior to delay medical appointments and diagnostics, which can lead to unfair culpability being placed on the patient.

THE BLAME GAME'S IMPACT ON PATIENTS

Ultimately, blaming patients does not just harm patients or families emotionally; it may affect their psychological well-being and ultimate recovery.

Studies show that lung cancer patients, for instance, experience higher levels of distress due to this stigma, which may potentially even affect their compliance, tolerance and response to therapy.[1]

This certainly underscores the need for a supportive environment that fosters healing rather than guilt.

WHAT CAN WE DO DIFFERENTLY?

The changes we make should be centered on awareness and empathy. Here are some actionable and practical steps for both healthcare professionals and lay people alike:

1 **Educate:** Raise awareness that cancer is not just a consequence of poor choices. Genetics and many other uncontrollable factors, as discussed above, play significant roles.

2 **Support:** Provide holistic support to patients, emphasizing that it is not their fault while providing equal access to healthcare screening and prevention. Also, address socioeconomic factors and cultural barriers with tailored, global education programs.

3 **Research:** Continue investigating the multifaceted variables, risk factors, and causes of cancer to better inform the public and reduce stigma globally.

4 **Shift Focus:** Essentially, the key focus should be on maximizing healthspan, healthy habits and equitable access to healthcare, while conducting regular cancer screenings with a primary care doctor.

MOVING FORWARD

We must shift from a culture of blame to one of understanding and support. Cancer is a complex disease with a myriad of causes, many beyond our immediate control.

Therefore, we must remind ourselves and our communities that cancer is never a patient's fault. By fostering a culture of empathy and informed awareness, we can improve the quality of life for those affected by this disease.

As professionals, it is our duty to guide this change, starting with our own practices and extending to public education.

It is important to emphasize that a long-term relationship with a doctor that one trusts results in better odds of identifying adequate intervals for screening studies, alarm signs or symptoms warranting more specialized testing. A physician familiar with the patient also is in a better position to identify peculiar patterns in the family history which could provide clues for genetic testing and earlier screening.

This process involves recognizing patterns of unhealthy behaviors or imbalances, which can lead to appropriate diagnostic studies when screening or genetic studies fail to detect certain cancers.

When all of this fails (or "succeeds" in the sense of a screening study finding cancer in the early stage), it is paramount to meet newly diagnosed cancer patients at the ground level. Doctors must help them process and overcome feelings of fear and vulnerability with genuine empowerment, so that they can feel reassured and motivated to reclaim control of their lives.

This act of empowerment simply cannot take place with a culture of pessimism, blame or finger-pointing. It requires a doctor and cancer care team willing to go on a unique journey with a cancer patient, being the trusted advisor, cheerleader and friend that they need and deserve.

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BREAKTHROUGHS IN ONCOLOGY ARE BECOMING ROUTINE THANKS TO NEW CELLULAR THERAPIES

Oncology has continued evolving at an ever-accelerating pace, with a constant stream of breakthroughs now occurring across a wide variety of cancers, many once thought to be untreatable.

Keeping pace with this vast array of new therapies can be a real challenge, let alone understanding how they function and how they should be administered.

Bispecfic antibodies (BsAbs), for instance, offer a significant advancement in cancer immunotherapy.


Michael Reff

BsAbs work by binding to two different types of cells: one arm attaches to the cancer cell, the other to a T cell — one of the human body's primary infection- and disease-fighting mechanisms — allowing the T cell to attack the cancer cell directly. This dual attack provides a more effective method for helping the immune system find and kill cancer cells.

Currently, the U.S. Food and Drug Administration (FDA) has approved BsAbs for the treatment of acute lymphoblastic leukemia, acute myeloid leukemia, B-cell non-Hodgkin lymphomas, multiple myeloma, small cell lung cancer (SLLC) and select solid tumors.

In this issue of ***Oncolytics Today***, we explore BsAbs from several perspectives.

One of our featured articles provides an overview of how BsABs were developed, their mechanism of action, indications and applications, efficacy and adverse effects, as well as pull-out tables for recommended use in various therapies.

Another article looks at strategies for adopting BsAbs in the community setting that are both safe for patients and efficient for the practice.

Other articles look at specific BsAbs and similar cellular therapies that have recently become available:

Tarlatamab, a bispecific T-cell engager, was granted accelerated approval for the treatment of extensive stage SCLC that has progressed after at least two prior systemic therapies.

Lifileucel, the first tumor-infiltrating lymphocyte (TIL), was recently approved by the FDA for the treatment of adult patients with unresectable or certain previously treated metastatic melanomas.

Sacituzumab govitecan — an antibody-drug conjugate already shown to be effective in treating triple-negative breast cancer — also proved to be efficacious in treating breast cancer brain metastases and primary brain tumors in a recently-completed phase 2 trial.

While all these breakthroughs are significant, they are but a snapshot of the new therapies continually being developed.

This wasn't always the case.

Up until the turn of the century, the treatment of most cancers was primarily limited to a relatively small arsenal of intravenous drugs.

All that began to change in 2003 with the completion of the Human Genome Project, a development that allowed oncology research to shift into high gear.

Since then, technical developments in DNA and RNA sequencing have led to the new era of precision medicine. We now can look at a patient's genetics, environment and lifestyle to select the best treatment for each individual.

Keeping our members abreast of these developments is a key part of NCODA's core initiatives:

▲ First, through a multitude of expert webinars.

NCODA offers an International Monthly Webinar on a wide variety of oncology topics. A recent webinar, for instance, featured presentations on strategies to address patient equity, advancements in breast cancer treatment, an overview on capivasertib and a look at the 2025 Medicare reforms.

We also regularly present webinars on other topics, including updates on the latest cancer drugs. Participation, as always, is complimentary for our members.

▲ Then there are NCODA's popular International Spring Forum, Oncology Institute and International Fall Summit — live events where our members can learn about and discuss the latest oncology issues.

These meetings offer unique opportunities to stay updated on the latest industry trends, network with like-minded professionals and gain access to resources that can significantly enhance patient care. NCODA events include complimentary registration, travel and hotel accommodations for practicing members.

▲ Finally, through our publications — ***Oncolytics Today*** and ***Inspire*** — we offer updates on all of the latest clinical updates in oncology, both online and in print.

NCODA's Mission is to empower the medically integrated oncology team to deliver positive, patient-centered outcomes. And keeping you, our members, informed on the latest developments, quality standards and best practices, is an essential component of that Mission.

Michael J. Reff, RPh, MBA
Executive Director & Founder | NCODA

nmdp FIND CURES. SAVE LIVES.

NCODA PASSION FOR PATIENTS

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