ONCOLYTICS TODAY

EMPOWERING THE MEDICALLY INTEGRATED ONCOLOGY PHARMACY PRACTICE | FALL 2021

GOING BEYOND THE FIRST FILL:

ENTERING A WHOLE NEW ERA

NCODA ACCREDITATION
AND PRIME THERAPEUTICS
ARE ABOUT TO CHANGE THE
WORLD OF ORAL ONCOLOGY

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Quality Initiatives in Action:Real World Impact on Patients with Polycythemia Vera

This article, sponsored by Incyte Corporation, is based on paid interviews with Kathy Oubre, CEO, Lacee Blady, Nurse Manager, and Kamie Williams, Advanced Nurse Practitioner, at Pontchartrain Cancer Center.

The quality initiative affords the potential for big impact.

Impact of Implementing a Quality Initiative

Quality is top of mind in oncology. Quality Initiatives (QIs) provide opportunities for practices to refine how they deliver care to their patients, with the goal of helping to improve patient outcomes. Implementing a quality initiative also can have a positive impact on a community practice's value-based care model.

The staff at Pontchartrain Cancer Center, a community oncology practice in southeast Louisiana, implemented a QI to help improve the care they provided to their patients with polycythemia vera (PV), a rare cancer with significant risk of complications. The number of patients with PV managed by the practice was not overwhelming. Therefore, implementing the QI was not expected to be time consuming for the team. The team recognized that small workflow refinements could provide value for their patients, while also allowing the care team to work collaboratively.

"Quality care in oncology is multifaceted. It entails taking a more holistic approach to the patient, rather than just treating the disease. Quality Initiatives offer the opportunity to refine the care we already provide to our patients while showing us where we can improve."

-KATHY OUBRE, CEO

Importance of Actively Monitoring Patients with PV

The goals of care plans for patients with PV are centered on symptom control and decreasing the risk of disease complications, including thrombosis and bleeding.¹ Care plans should focus on lowering the hematocrit (HCT) to normal or near-normal values (<45%), lower the platelet count if the numbers are high, and decrease PV-related symptoms that contribute to morbidity.² In one study in patients with PV, elevated HCT between 45% and 50% was associated with a 4-fold higher rate of cardiovascular death and major thrombosis, compared with HCT <45%.¹ The Pontchartrain QI focused on monitoring lab values for this patient population in order to determine if revisions in their care plan were necessary.

Pontchartrain Developed an Effective Monitoring Strategy

The first step in the QI was to generate data by running a fact-finding query through electronic medical records to quickly identify patients with PV. The medical records and lab report values of these patients, along with their treatment plans, were reviewed. Given the CV risk, this step was critical in helping the oncologist to understand this was a valuable exercise for the practice to focus on. In the Pontchartrain practice, 23 patients with PV were identified. Seven (30%) of these patients had HCT levels >45%.

In the next step of the QI implementation, the nurse manager at Pontchartrain created a workflow and identified areas to discuss with practice leadership. Kamie Williams, a hematology/oncology nurse practitioner (NP) consulted on areas of focus for practice workflow integration. Topics included goals for lab values, how often lab work should be done, and when to use medical intervention, if lab results are not in range. While the workflow required a short time investment upfront, it is essential to integrating the QI into the practice. By collaborating, the team was able to address these issues for multiple patient scenarios and define when additional lab work was needed.

"Our patients mean the world to us, so even if [the Quality Initiative] would've only impacted one patient, it was worth all of the time and effort put into it."

LACEE BLADY, RN

Then they put the workflow into practice. Integrating follow-up lab testing into the workflow allowed a specific, vulnerable subgroup of patients to be better managed. At Pontchartrain Cancer Center, care adjustments were made to care plans—in some cases, multiple times—for the 7 patients identified with HCT levels over 45%.

This PV Ω I addressed the important issue of follow-up. For patients with lab values not within the target range who are at risk for complications, more frequent scheduling and reviewing of lab tests were recommended. While patients were prescribed labs, they were not always fulfilling them. Therefore, more diligent follow-up by the practice was key.

The additional monitoring required minimal time investment for nursing and allied health professionals who were already responsible for direct patient care and management. With guardrails in place, providers may be more likely to incorporate the workflow into the practice's daily routine for patients with PV.

How Pontchartrain Cancer Center Puts QI Steps in Practice



At the beginning of each month, check for upcoming appointments with patients with PV



For any patients identified, determine if they have had 2 elevated HCT or PLT lab results suggesting their PV is not adequately managed and/or that the intervention was inappropriate or inadequate



If any patients are identified, send a "heads up" task to the provider seeing the patient to assess if lab values have improved at this visit. If not, intervention, such as a change in the patient's care plan or therapeutic phlebotomy frequency, may be needed



If intervention is needed, the nurse can contact these patients to ensure they obtain updated lab work on a more frequent basis until values are within acceptable range

This quality initiative has assisted the Pontchartrain Cancer Center in creating a more proficient approach to PV management. It has allowed earlier intervention for patients whose PV is considered uncontrolled.

Tips for Successful Implementation of a QI in Patients with PV

CEO Perspective

- Obtain provider buy-in and include the provider as part of the solution
- Find someone within the practice to champion the QI
- Stay focused on the positive outcomes that it can bring to the patients served by the practice

RN Perspective

- Gain provider feedback on workflows
- Create a spreadsheet to track and monitor patients. Write small updates with each visit highlighting any change in care plan or clinical status
- Run a patient report at the start of each month to identify new patients with a diagnosis of PV that will be seen

NP Perspective

- Collaborate. Identify key roles for nurses, AHPs, and physicians to increase overall efficiency in monitoring patients
- Appoint a leader to oversee the QI to avoid disrupting provider daily workflow
- Include nursing staff to assist in the day-to-day implementation

References: 1. Marchioli, R. Finazzi, G. Specchia, G. et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med.* 2013;368:22-33. **2.** Leukemia Lymphoma Society. Polycythemia Vera Facts. https://www.lls.org/sites/default/files/file_assets/FS13_PolycythemiaVera_FactSheet_final5.1.15.pdf. Accessed Month XX, 2021.



NCODA Cost Avoidance and Waste Tracker

The NCODA Cost Avoidance and Waste Tracker is an online tool created to help practices document the great work they are doing saving money for patients, payers and employers and showcasing the waste produced by outside vendors.

How it works:

Cost Avoidance: Whenever you perform an intervention for a patient that helps prevent an unnecessary Rx from being given to a patient, *record the savings*.

Waste: Whenever a patient brings in medication that was not used at all, record the information.

How to use the data:

Share the information with your administration, payers, employers, etc., to showcase the benefits of your practice over mail-order services.

HELP US CREATE CHANGE AND ACCOUNTABILITY FOR HEALTHCARE SPENDING NATIONWIDE!

Cost Avoidance & Waste Reported To Date by NCODA Members

Cost Avoidance

\$7,190,993

Waste

\$11,673,104

To learn more about the tracker tool, please visit www.NCODA.org/CAWT

ONCOLYTICS TODAY

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NCODA's Mission

is to empower the medically integrated oncology team to deliver positive, patient-centered outcomes by providing leadership, expertise, quality standards and best practices.



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THE MOST IMPRESSIVE ASPECT OF NCODA: THE KNOWLEDGE BASE OF OUR MEMBERS

espite the challenge of the COVID pandemic and the recent resurgence of its new variants, NCODA has continued to flourish.

And while I don't want to dwell on the pandemic, everyone please be sure to take the recommended measures (vaccination, masking, social distancing) so this episode in our medical history can come to a close.

We just completed our first live meetings of 2021 — the Oncology Institute in Scottsdale, Arizona, on Aug. 25-26, and the inaugural Professional Student Organization meeting on



Jim Schwartz

Sept. 16-17 — and by all accounts, they were both well-received and managed in a safe manner.

The representatives that I've spoken to since the Institute have told me they received a great deal of information from this meeting and appreciated the opportunity to meet live, as well as to get the information that will help them in educating our members about their products.

You can read the numbers for yourself on the website, but NCODA just surpassesd 4,000 members. We're growing not only in size, but in importance, and are now recognized as one of the premier resources for information for appropriate use of cancer drugs.

If you haven't been to the NCODA website in a while, take 20 to 30 minutes to go on and look at all the resources available to you and your practice to improve and

The collaboration within NCODA ... has grown into a great opportunity for everyone involved in the treatment of cancer to share knowledge as well as to easily find needed answers from others in the organization.

standardize your treatment of cancer.

The very important NCODA Center of Excellence (CoE) Medically Integrated Pharmacy (MIP) Accreditation Program, under the guidance of Elizabeth Bell (backed and supported by an Executive Accreditation Council and Accreditation Working Group), is moving to begin providing cost-effective oncology-specific accreditation to all NCODA practices.

Unlike most of the current accreditation bodies, this process will be oncology-specific and look at the important issues that you, as a leader in the provision of oncology care, should be using for all patients.

The NCODA accreditation process will be designed to assist you in improving and maintaining your patient-directed care and not be a "check the box" list of less important tasks.

Unlike other pharmacy accreditation programs, the CoE MIP Accreditation Program is patient-centered.

Based on the the Patient-Centered Standards for Medically Integrated Dispensing: ASCO/NCODA Standards established in December 2019, it will focus on adherence, safety, education, speed to therapy, patient satisfaction and financial

assistance.

Currently, several NCODA member practices were selected for the pilot program, which is projected to launch before the end of 2021.

Like all NCODA initiatives, it will assist you in raising and maintaining the quality of care given to your patients. And at a very greatly reduced cost.

NCODA also is working to expand its educational video offerings over the next year. These videos will cover a wide variety of disease states and therapeutic treatment options.

This is yet another tool to assist in educating our patients on the proper way to take their medications as well as on possible side effects and how to manage them appropriately.

The most impressive aspect of NCODA — in my opinion — is the wealth of knowledge contained by our large number of members and their willingness to share expertise and practice-specific processes that enable patients to achieve optimal results from their cancer care.

The collaboration within the organization among providers, nurses, pharmacists, technicians, administrators, lab personnel, etc., has grown into a great opportunity for everyone involved in the treatment of cancer to share their knowledge as well as to easily find needed answers from others in the organization.

This is cancer care at its best, and each of you should be proud of the role you play at your practice, as well as within NCODA, to make this a reality!

James R Schwartz

James R. Schwartz, RPh NCODA President, 2019-2021





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NCODA LOOKING BACK AND LOOKING AHEAD: WHAT A LONG BUT GRATIFYING TRIP IT'S BEEN

CODA has come a long way since 2015. As our organization continues to establish initiatives, advance patient care and grow membership, it's easy to lose perspective on how far it has come in such a short period of time. Oncolytics Today recently interviewed NCODA Founder & Executive Director Michael Reff, RPh, MBA, and two people who played an invaluable role in its start-up: Nancy Egerton, PharmD | Director of Pharmacy New York Oncology Hematology, and Jonas Congelli, Chief of Pharmacy and Ancillary Services | Hematology Oncology Associates of Central New York.

Oncolytics Today: Take us back to the beginning. What were your initial impressions on the idea of NCODA, and what were your expectations when you saw the wheels being set in motion to make the organization a reality?

Egerton: I had no idea that Mike conceptualized this until I went up to visit the practice in Syracuse. He was working there as a pharmacist with Jonas. I basically went up to visit and see how they had laid out their Medically Integrated Pharmacy (MIP) because I was trying to build one in Albany.

I hadn't really seen the practice before — nor either of them — in a long time. I thought it was just a way to reconnect and say hello.

And then Mike said, "You know, I have this idea." And he started talking about the problems associated with patients getting oral oncology



Nancy Egerton

medications. At that point, all of this was unknown to me. I had never dispensed orals from the practice and so I was trying to learn all this. The fact that Jonas had the practice running their MIP gave me some insight, but I was new to the idea and I didn't really know the kinds of issues related to what they were doing.

I don't know even if Mike and Jonas knew at that point but it just seemed like an idea that was, at the time, really relevant because of all the oral cancer medications coming out. It was a great idea, one that I had to be a part of.

Oncolytics Today: Can you pinpoint a moment when you felt that NCODA was going to be a success and you realized that the organization could be sustainable?

Congelli: From day one we had the quality standards, right from the start. We felt that it was important to have that when we were starting the organization. I remember we kept reiterating, "We have to have the quality standards."

I think the big moment when I felt that NCODA had arrived was with the creation of the Oral Chemotherapy Education (OCE) sheets. That was a big project. To create these really valuable education sheets that were way beyond anything else currently out there, it just blew me away.



Jonas Congelli

That was the moment when NCODA arrived.

Oncolytics Today: Mike, how important was it for you to get the right people in place and begin to outline the principles and Mission now synonymous with NCODA?

Reff: I was focused on that right away. We wanted to make sure that we were geographically diverse through New York State. At the time we were really focusing on community oncology. But then the focus quickly shifted from the location to the patients themselves. That's where the passion and the need comes from — it's always on the patient.

Oncolytics Today: Are you able to appreciate the growth and success of NCODA and what has been achieved, or are you ever-focused on what is coming next?

Reff: I am always focused on what's next. There are always more opportunities to grow, and my passion for that never leaves. While we do celebrate our successes, it can be a tough balance because organizations that succeed should never rest on their laurels.

What I do enjoy are stories like starting NCODA and then deciding to partner with Be the Match for three and a half years. Not many nonprofits partner with other nonprofits to provide funding back to their partner. Then there are our Professional Student Organization (PSO) chapters at pharmacy

schools across North America. Students at our Washington State University chapter held a Be the Match Donor Drive and a student was determined

to be a match for someone. This student is going to save someone's life, what a gift! You don't forget things like that. That is what motivates me — those victories, those wins.



Michael Reff

I am always trying to self-improve so I can continue to be a good leader. There's one thing

that we and I need to do better, and that is making sure that people are centered on why we do what we do. Good things will come if we keep staying true to the Mission, Vision and Guiding Values of NCODA.

Oncolytics Today: NCODA has continued to expand its initiatives. How important is it to come up with new, creative and effective ideas that will benefit the patient?

Reff: The motivation has been organic. Had we thought about podcasts before? Yeah, for sure, but then Ginger (Blackmon) just grabbed that and went with it. It is extremely important to put the right people in place. Look at the growth of the Executive Council. We need people who are likeable and want to be a part of it; they have to be collaborative.

Our staff are people who have great hearts. I've selected people who I knew would be a pleasure to work with and share the same vision. That commitment and work has led to our membership surpassing 4,000 members. I never thought that was a possibility at the beginning.

Yet we have always stayed true to our Mission, Vision and Guiding Values and that is what transcends everything we have done. Look at our webinars. We have direct communication with our membership and provide them with information that might help save someone's life. That's about as direct as you can get.

Oncolytics Today: What's next for NCODA?

Reff: Taking what we have done regionally with payers and self-funded employer groups regarding Going Beyond The First Fill, and then executing that on a larger scale. That is NCODA's next big step. And it's a giant leap in the world of oncology and patient care.



DISPARITIES IN ONCOLOGY: PROBLEMS& SOLUTIONS USING CLINICAL TRIALS

By Kashyap Patel, MD, BCMAS, Beth Winkley, PA-C, Emma Gillespie, Hirangi Mukhi, BS, & Gabriel Hansen

"The civility of any society can be measured by evaluating how it treats its most vulnerable."

Mahatma Gandhi

he U.S. healthcare system is in a state of crisis. Per the Commonwealth Fund report, despite spending the highest amount on individual health in the world, the United States is ranked at the bottom of the 17 most developed countries.

While there is room for improvement in every country, the United States has the highest costs and lowest overall performance of all the countries in the report, which included Australia, Canada, France, Germany, the Netherlands, New Zealand, Norway, Sweden, Switzerland, and the United Kingdom.

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Beth Winkley



Emma Gillespie



Hirangi Mukhi



Gabriel Hansen

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DISPARITIES

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Even more concerning, despite having the most expensive healthcare, the United States ranks last among the 11 countries on measures of health system equity, access, administrative efficiency, care delivery and health care outcomes.

The United States spent \$10,207 per person on healthcare in 2018, compared to \$3,943 in the U.K., which ranked first on performance overall.¹

There is extensive spending occurring in healthcare and patients are not seeing any corresponding gains in either lifespan or quality of life.

STATUS OF ONCOLOGY CARE IN THE US

Delivery of cancer care in the U.S. is also facing a crisis, which places an emphasis on volume-based reimbursement versus focusing on value. Despite most oncologists trying to provide optimal care for their patients, their ability to do so is met with a range of barriers.²

According to a report by the Institute of Medicine, factors contributing to these barriers are a growing demand for oncology care, a shrinking oncology work force, rising costs of cancer care, and the complexity of the disease and its treatments.³

The report recommends ways to respond to these challenges, such as strengthening clinicians' core competencies in caring for patients with cancer, shifting to team-based models of care and embracing patient-centered care. The common goal is to improve cancer care delivery.

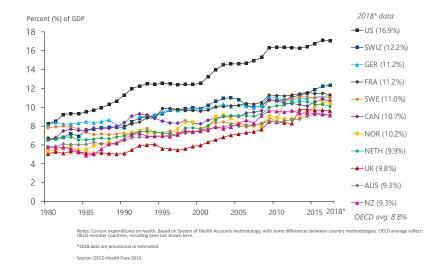
Many changes are needed to improve the barriers, including how we communicate with patients, how we translate research into practice, how we coordinate care and how we measure its quality. Oncology practice has become an umbrella for numerous subspecialties, including radiation and surgical oncology, solidifying the field as a true multidisciplinary team-oriented discipline.

The categorization of malignancies

SPENDING

Health Care Spending as a Percent of GDP, 1980-2018

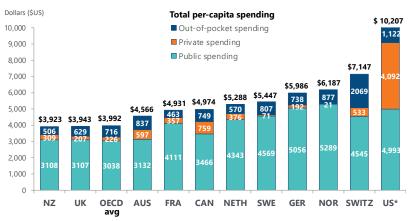
Adjusted for Differences in Cost of Living



SPENDING

Health Care Spending per Capita by Source of Funding, 2018

Adjusted for Differences in Cost of Living



Data reflect current expenditures on health per capita, adjusted using luSS purchasing power parties [PPPs], for 2018 or the most recent year: 2017 for RPA, SVIZ, UK, 1920 for 10, NS, Data for 2018 reflect estimated/providenal values. Numbers may not sum to total due to excluding capital formation of health care providers, and some uncategorized health care spending. Public spending reflects government and compulson spending [HF1], private reflects voluntary schemes [HF2] cord-pocket [HF3] or for the US, Compulsory private insurance schemes' [HF32] category, given that the individual mandate to have health linearance needle in lan 2019. DCED average reflects the average of 36 DCED member countries, including ones not shown here. Source: CDED.

and the appreciation of the complexities of all the diseases of cancer has defined new therapeutics and new specialties in terms of therapy. The complexity of what oncology practice has become reflects a better understanding of the many diseases we treat, and the success of our science.

Treatments for those diseases have vastly improved, becoming less toxic and more accessible. The digital age and

rapid exchange of information ensure oncologists have access to the most current clinical data, regardless of location.

Incorporating this new information into clinical care is challenging. Given the complexity of cancer care, it is difficult to formulate care plans with the necessary speed, precision and quality. As a result, decisions about cancer care are often not sufficiently evidence-based.

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DISPARITIES

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DISPARITIES IN CANCER

The U.S. has significant health disparities among its citizens that are rooted in social, economic, and environmental factors.

A person's place of birth is strongly associated with life expectancy rather than race or genetics. There is a 15-year difference in life expectancy between the most advantaged and disadvantaged citizens in the United States. This difference is correlated with geographic characteristics and health behaviors that are influenced by historical and social factors.

Disparities in cancer care contribute to almost 34% of deaths in people age 25-79, and result in additional spending of \$230 billion dollars. Addressing disparities in cancer care would result in savings of up to a trillion dollars over three years in indirect ways.³

A comprehensive approach is needed to improve disparities and should include support for public policies aimed at a better understanding of the issue by all segments.

The main players at hand are the pharmaceutical companies, researchers, the Health Care Finance Administration (HCFA), adequate funding for federal and local initiatives, considerations of health in community planning and development, and collection of real-world data and evidence.

SOCIAL DETERMINANTS OF HEALTH

Understanding and addressing Social Determinants of Health (SDoH) affecting health outcomes is a pressing issue for all involved in the delivery of healthcare.

SDoH, are defined as "the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life," and are responsible for many health inequalities.⁴

Social determinants are primarily rooted in resource allocation and affect factors at the local, national, and global

Health Care System Performance Rankings

	AUS	CAN	FRA	GER	NETH	NZ	NOR	SWE	SWIZ	UK	US
OVERALL RANKING	3	10	8	5	2	6	1	7	9	4	11
Access to Care	8	9	7	3	1	5	2	6	10	4	11
Care Process	6	4	10	9	3	1	8	11	7	5	2
Administrative Efficiency	2	7	6	9	8	3	1	5	10	4	11
Equity	1	10	7	2	5	9	8	6	3	4	11
Health Care Outcomes	1	10	6	7	4	8	2	5	3	9	11

Source: Eric C. Schneider et al., Mirror, Mirror 2021 — Reflecting Poorly: Health Care in the U.S. Compared to Other High-Income Countries (Commonwealth Fund, Aug. 2021)

Data: Commonwealth Fund analysis

levels. A healthcare delivery model that factors in correlation between SDoH and following factors will enable us to identify role and influence of each of these individually and figure out path forward to bring equity, equality and justice for all — for cancer care.

IMPROVING DIVERSITY IN CLINICAL TRIALS

Diversity in clinical trials (DICT) is critically important for developing therapies that reflect the real world, which includes many ethnic, racial and other populations.

On Nov. 9, 2020, the U.S. Food and Drug Administration (FDA) issued guidance with the agency's recommendations on designing and executing clinical trials of drugs and biologics that include people with different demographic characteristics (e.g., sex, race, ethnicity, age, location of residency) and non-demographic characteristics (e.g., patients with organ dysfunction, comorbid conditions, and disabilities; those at weight range extremes; and populations with diseases or conditions with low prevalence).⁵

This initiative was in response to certain events, including the Black Lives Matter movement in the summer of 2020, as well as healthcare disparities seen during the COVID-19 pandemic, as certain segments of the population (e.g., older adults, pregnant women, children,

and racial and ethnic minorities) were affected in different ways. The FDA's endeavor to include diverse populations is aimed to understand their risks or benefits across all groups.⁵

The pharmaceutical industry has agreed to come together to develop and voluntarily adopt principles on closing the diversity gaps.⁶

The Pharmaceutical Research and Manufacturers of America (PhRMA)

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Disparities in cancer care contribute to almost 34% of deaths in people age 25-79, and result in additional spending of \$230 billion dollars.

Addressing disparities in cancer care would result in savings of up to a trillion dollars over three years in indirect ways.

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DISPARITIES

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represents the country's leading biopharmaceutical researchers and biotechnology companies. In response to the FDA's November release, PhRMA announced the release of industry-wide principles on clinical trial diversity that will focus on four main areas.

The first two principles will focus on building trust and acknowledging the historic mistrust of clinical trials within Black and Brown communities as well as reducing barriers to clinical trial access. The third and fourth principles focus on using real-world data to enhance product information, as well as boost information regarding diversity and inclusion in clinical trial participation.⁶

Each pharmaceutical company has developed their own unique programs and strategies to focus on improving DICT. Understanding these programs and if they are meeting the objectives will enable further DICT programs to be successful and improve this complex issue overall.

PHARMACEUTICAL INITIATIVES

Lin and Bernstein presented a multivariable regression analysis which constructed a temporal network of clinical trial collaborations between large and small-size pharmaceutical companies and institutions to quantify "actors' collaboration network structure, organizational behavior, and partnership characteristics."

They found a positive correlation between the number of successful approved

All five of the top pharmaceutical companies have strategies and initiatives with similar themes but different specific actions.

trials and interdisciplinary collaborations measured by a collaboration diversity metric and concluded that large pharmaceutical companies are more likely to collaborate with a wider range of actors from other specialties, especially smaller industry actors who are newcomers in clinical research, resulting in exclusive access to smaller actors.

Clark et al conducted a review and analysis which investigated barriers impacting minority patients' willingness to participate in trials and formulated potential solutions and tested them across stakeholder groups.⁸ Key themes from solutions were identified that resonated with stakeholders using a transtheoretical model of behavior change and created a communications message map to support a multistakeholder approach for overcoming critical participant barriers.

All five of the top pharmaceutical companies have strategies and initiatives with similar themes but different specific actions.

▲ Johnson and Johnson (J&J) developed three pillars for a global diversity and inclusion strategy, which are "Advance Our Culture of Inclusion and Innovation," "Build a Diverse Workforce for the Future," and "Enhance Business Results and Reputation."

Janssen, the pharmaceutical division of J&J, has a separate DICT committee and shared their best practices which read: "Plan early and with a focus and intention to have diverse enrollment, set the tone for diversity with your sites and study teams and monitor their progress, encourage sites to reach out to all potential patients, and do not underestimate the value of connections with communities."

▲ Pfizer shared their strategies, which are: "Embedding the importance of diversity in clinical trials, evolving how we partner with clinical trial sites, building trust and awareness in communities, and addressing practical barriers to participating in trials." ¹⁰

Pfizer also released a television commercial in April 2021 focused on Black community health inequities with a theme of increasing clinical trial participation.

▲ Roche, which combined pharmaceutical operations with **Genentech** in 2009, committed to advancing the following priorities: recruiting more representative populations into clinical research, enhancing personalized health care, and purpose-driven partnerships.¹¹

In March 2021, Genentech became a funding partner of the Society for Clinical Research Sites (SCRS) Diversity Program titled Site Awareness and Best Practices for Inclusion of Diverse Populations in Research. The program is aimed at developing a better understanding of the knowledge, expertise and best practices required for clinical research sites to meet the needs of an increasingly diverse population, and to provide knowledge and solutions to aid sites in more successfully including diverse populations in clinical research.

Then, in June 2021, Genentech created a new coalition of clinical research sites aimed at boosting diversity in oncology studies. The coalition includes an array of partners and sites around the United States, and each will look to better serve minorities in Genentech's oncology trials. The goal is to build a new clinical research ecosystem that actively includes diverse patient groups.¹¹

▲ Novartis' main strategy centers around building strategic partnerships, leveraging data and digital, and remodeling their process and tools.

They established a partnership involving historically Black colleges and universities and created a holistic commitment that will focus across four key areas: enabling the next generation of Black/African-American leaders, supporting the establishment of "Digitally Enabled Clinical Trial Centers of Excellence," managed and led by clinical researchers of color to increase diversity in clinical trials, supporting research and validation of existing data standards that drive diagnosis, clinical trial endpoints and population health policy, and establishing "Digitally

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DISPARITIES

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Enabled Research Centers" on the impact of the environment and climate change on health, with an emphasis on preventing the exacerbation of health disparities.¹²

▲ Merck, the fifth-largest pharmaceutical company, states, "The importance of including minority communities is critical across all levels of clinical research."

They created a cross-functional team with the intent to select trial sites with inclusion in mind, collaborate with trusted voices, outreach and provide education tailored to communities, create new enrollment standards within minority communities, and ongoing learning with subject matter experts. 13

CONCLUSION

The COVID-19 pandemic has brought to light the long-standing racial and ethnic disparities in clinical trials.

After examining the root causes of these disparities, the FDA put forth guidelines for pharmaceutical companies which summarized the current thinking on steps to broaden eligibility criteria in clinical trials through inclusive trial practices, trial designs, and methodological approaches.⁵ The guidance aims to provide recommendations for how sponsors can increase enrollment of underrepresented populations in their clinical trials.

In response, the top pharmaceutical companies released their own recommendations and put principles into

action to increase diversity in the future.

The question remains whether the approach from the pharmaceutical companies is working to fulfill these goals and if their strategies align with current research which has found successful outcomes.

This complex issue is compounded by the theory that each disease area and different malignancy may carry their own unique challenges and therefore require different approaches.

▲ Kashyap Patel, MD, BCMAS, is CEO of Carolina Blood and Cancer Care Associates in Rock Hill, South Carolina. Beth Winkley, MMS, PA-C is Medical Science Liaison – Solid Tumor Oncology at Janssen Pharmaceuticals, Charlotte, North Carolina. Emma Gillespie is an intern, Gabriel Hansen is a research associate and Hirangi Mukhi, BS, is Business Development Director at Carolina Blood and Cancer Care Associates in Rock Hill. South Carolina.

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The question remains whether the approach from the pharmaceutical companies is working to fulfill these goals and if their strategies align with current research which has found successful outcomes.

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DRIVEN TO FULFILL THE PROMISE OF BIOSIMILARS— THE PFIZER WAY

The Pfizer Promise is simple:

To help you provide patients with more treatment options while delivering the largest portfolio of potentially cost-saving biosimilars.¹⁻³



Breadth of offerings

Pfizer has the largest portfolio of oncology biosimilars on the market, including both cancer therapies and supportive care products, to give patients more treatment options.^{2,3}



Quality focused

Pfizer oncology biosimilars are all produced to meet the same high-quality standards as its biologics—using the same robust protocols for monitoring quality throughout every stage of the manufacturing process.⁴



Manufacturing and supply experience

Pfizer leverages more than 30 years of state-of-the-art manufacturing and supply-chain experience in biologics to reliably deliver biosimilars to patients.⁴

To learn more about Pfizer's oncology biosimilars, visit us online at PfizerBiosimilars.com

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PRACTICE LEADERS & INDUSTRY PARTNERS EFFECTIVELY ENGAGE AT NCODA INSTITUTE

ore than 170 oncology industry professionals from 70 different companies turned out for NCODA's third annual Oncology Institute, "Understanding the Challenges Oncology Patients and Practices Face Today," in Scottsdale, Arizona, on Aug. 25 and 26.

The event featured a welcome reception on night one, and a full day of presentations led by administrators, physicians, nurses, pharmacists and other professionals affiliated with NCODA on day two, all designed to facilitate a closer relationship between healthcare providers and their pharmaceutical industry partners.

The leadoff session, "Oncology 201: Business of Oncology and Treatment Education," was hosted by Ray Bailey, BPharm, RPh, Senior Vice President of Pharmacy Services | Florida Cancer Specialists & Research Institute, Austin Cox, PharmD, Medically Integrated Pharmacy Manager | Alabama Oncology, and Stacey McCullough PharmD, Senior Vice President of Pharmacy | Tennessee Oncology.

The session kicked off with a discussion of Pharmacy Benefit Managers (PBMs) and the often frustrating impact they have on a patient's prescription



Stacey McCullough

benefit as opposed to their medical benefit.

"When a physician prescribes an IV medication, they know they're going to walk into the treatment room and get their medication

there," McCullough explained. "When they prescribe an oral, we don't know what that patient's journey is going to be like. That's challenging for the physician and it's challenging for all our pharmacies."



NCODA's third annual Oncology Institute, held Aug. 25-26 in Scottsdale, Arizona, drew more than 170 oncology industry professionals from 70 different companies.



Ray Bailey

Bailey emphasized that PBMs allow no negotiation on the benefit side. "It's take it or leave it," Bailey said. "Your PBM says 'Here's your contract, here are your rates.' There's

no negotiations, versus the medical side. There, we do have engagement with our payers. On the pharmacy side, it's cut and dried. The PBM controls it all."

The situation can be further complicated if the patient's plan is out of network, and by payer plans that prohibit the medical practices from dispensing certain drugs. "We could be in network with that plan, but they've carved out specialty and certain drugs that they don't allow us to fill," Bailey said.

Such limitations often force practices to look at other strategies to help the patient.



Austin Cox

"We're constantly looking at alternative therapy," Cox noted. "We'll go some other route if it's efficacious. If we have no choice, we'll outsource. But when we send a patient outside of

our doors, care breaks down. You have treatment delays and it's just a disservice to our practice and to our patients."

Panelists agreed that establishing a closer relationship with a mail-order pharmacy was one option for dealing with PBM red tape.

"They're still our patients," Bailey said. "We have to step in and be advocates for our patients and make sure that just because their insurance says they have to go somewhere else (for prescriptions), we're still going to make sure they get

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O N C O L O G Y I N S T I T U T E

INSTITUTE

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access quickly and have good outcomes."

Enhancing the working relationship between manufacturers and practices was the focus of the panel discussion "How Can Industry Partners Be of Value to Practices?" hosted by Bret Tinney, Executive Director, Physician Networks and Strategic Accounts | BeiGene, Randy Erickson, RN, BSN, MBA, Chief Executive Officer | Utah Cancer Specialists, Christina Patterson, PA-C, Senior Advanced Practitioner and Dispensary Manager | Cancer Care Associates of York, and Lucius Daniel, PharmD, Lead Clinical Pharmacy Specialist | Karmanos Specialty Pharmacy.

From the manufacturers' perspective, Tinney noted that successful partnerships are focused on three main areas: 1. clinical education and market research, 2. patient support, and 3. market access and health economics and outcomes research (HEOR).

"With a new product or a new indication in this COVID world, how would you like to see pharmaceutical partners educate healthcare providers at your practice?" Tinney asked the panel.

Erickson said he believed a hybrid of virtual and in-person interaction was likely to be standard for some time to come. "I utilize virtual interactions, and I think that's here to stay," he said. "It allows you to cover a lot of space and be more effective."

Yet, despite "COVID fatigue," Erickson emphasized the importance of still meeting face-to-face. "For us, I still want to see people as much as possible," he said. "I think that is so important for [pharmaceutical partners] not to lose that personal contact. Yet it depends on

who you are talking to. For physicians, it's going to be different than for me as an administrator. And it's going to be different for our pharmacy team."



Randy Erickson

While access is still limited at Utah Cancer Specialists, the practice does allow pharmaceutical representatives to come in during physician meetings and talk about new indications for five or 10 minutes. Erickson said.

Erickson also encouraged pharmaceutical representatives to seek other avenues of engagement, including the practice's authorization, business, pharmacy and administrative teams.

Daniel, on the other hand, said his practice focuses on a single point of contact. He said he divides pharmaceutical relationships into four silos: 1. sales and marketing, 2. medical science and HEOR, 3. market access, and 4. patient services.

"When we get a new product list ... I anticipate what my providers will need," Daniel said. "I'll send a quick email out to the team leads and say ... 'These are some



Lucius Daniel

of the ideas I have from a key account perspective about how we may bring (this product) in? And then on its side-effect profile, I question how we are going to be supportive of the product throughout

its entire product life cycle, from launch all the way through educating our team and the patient."

"That's the approach I use in determining how to leverage our in-person and virtual time efficiently. I try to look at it from those four components how we, as the quarterback, can bring the pharmaceutical representatives in to help us and be efficient in the time we have."

Patterson said she also supports a single point of contact — typically herself — on both the clinical and dispensary sides. She said her focus is to make sure the appropriate people get the relevant details.

"I filter through to whom is appropriate and needs that information," Patterson explained. "Whether it's the



Christina Patterson

practitioners, who in our practice do all the education for the oral medications, or nursing, who do the infusion teaching. Then we make sure our dispensary team gets all

the information regarding copay assistance, vouchers and anything regarding authorization. And any of the side-effect management goes to the clinical team."

Tinney said pharmaceutical partners were eager to find other methods, in addition to Zoom conferences and virtual meetings, to engage with practices at all levels during the COVID environment.

"We in the industry rely on meetings like NCODA's Oncology Institute to engage at a very high level," Tinney said. "In an environment where a lot of these meetings have been shut down, we're looking for creative ways, partnerships and opportunities."

Daniel suggested that manufacturers and practices look at co-marketing opportunities, especially on particularly effective therapies.

Erickson suggested a collaboration on exploring what value pharmaceutical companies can bring to a practice. "We had one pharmaceutical company bring up something that we still use today – an engagement box, or patient experience box," he said. "It has things as simple as studies on painkillers in infusion rooms, and which work best and are most calming. It's something our practice still uses when it opens new clinics."

Other Oncology Institute sessions focused on "Evaluating Therapy Selections at the Practice," "Practice Leaders and Industry Partners Collaborating for Patient Care: Q&A on Identifying Challenges and Solutions," "Bills and Legislation Update: How Practices are Getting Involved," and "Addressing Healthcare Disparity: Looking Forward, Have We Done Enough?"

VIRGINIA CANCER INSTITUTE INITIATIVE UTILIZES TREATMENT SUPPORT KITS, APP & CURBSIDE PHARMACY TO BOOST ADHERENCE

mart phones may eventually turn out to be a smart way for oncologists to encourage compliance while helping monitor adherence among their oral chemotherapy patients.

In June 2020, Virginia Cancer Institute (VCI) launched a six-month initiative to improve oral therapy medication adherence and satisfaction among metastatic breast cancer patients.

The program grew out of a request for proposals by Pfizer, which was offering grants to practices pioneering methods to limit COVID-19 risk among cancer patients.

"We were one of the only practices in the United States that was awarded funding," said Jonathan Heller, MHS, PHR, CMPE, VCI's Chief Operating Officer. "We organized an adherence program for our breast cancer patients who were offered a complimentary app that they could use on their phone, iPad or mobile device. It allowed them to record symptom management as well as information about how they were progressing on their medication. The whole theory behind it was to increase communication between the patients and the providers."

In addition to a six-month subscription to the chemoWave app, participants also were given an NCODA Treatment Support Kit (TSK) loaded with a treatment calendar, dry skin creams, anti-diarrheal medication and other resources.

"We tried to provide things that we thought would help complement the patients' care," Heller explained. "Again, to try and help them stick with their oral medication compliance."

Participants were required to complete a weekly survey using the chemoWave app, the results of which were shared with the care team.

Patients also received a monthly call from a nurse navigator, plus took a



satisfaction survey every 90 days.

VCI also used part of its Pfizer grant to retool its oral pharmacy, Progressive Pharmacy Care, to offer patients curbside pickup of medications.

"We got the IT enhancement so the pharmacy team could bring everything out to the patient, who could then sign for it or pay if they had a copay, and then go on their way without having to come in," Heller said.

A total of 95 of VCI's metastatic breast cancer patients were invited into the program, of whom 43 agreed to receive the Treatment Support Kit and, of those, 12 enrolled in the chemoWave app.

Results overall were positive, with participants expressing satisfaction with the Treatment Support Kits, nurse navigator calls and VCI's outreach program. However, only 13 percent said the program helped them become more compliant in taking their medication.

Satisfaction with the app was mixed, with some patients requesting additional

instruction and a focus on physical functions they could perform rather than on those they couldn't. At the same time, most felt it helped them better connect with their care team and would recommend it to others. Others noted the app would have been more helpful if they had it at the beginning of their treatment journey.

Heller said VCI learned a lot of valuable lessons from the experience, including that:

▲ Metastatic cancer patients might not

be the ideal target population for introducing a new medication adherence app to their routine.



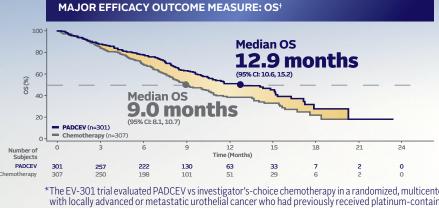
▲ App usage varied due to a patient's condition, such as treatment changes, hospital admissions or hospice admissions, and

▲ Hands-on app training is essential.

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IN POST-PLATINUM, POST-PD-(L)1 la/mUC PATIENTS

PADCEV® SIGNIFICANTLY IMPROVED OS vs CHEMOTHERAPY



30% reduction in the risk of death vs chemotherapy (N=608; HR=0.70; 95% Cl: 0.56, 0.89; P=0.0014)

*The EV-301 trial evaluated PADCEV vs investigator's-choice chemotherapy in a randomized, multicenter, phase 3 trial of 608 patients with locally advanced or metastatic urothelial cancer who had previously received platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor. Patients were randomized 1:1 to either 1.25 mg/kg of PADCEV via IV infusion over 30 minutes on days 1,8, and 15

of every 28-day cycle, or docetaxel at 75 mg/m², paclitaxel at 175 mg/m², or vinflunine at 320 mg/m² onday 1 of every 21-day cycle. For both arms, treatment continued until radiographic disease progression or unacceptable toxicity.

Based on log-rank test. Stratification factors were ECOG PS, region and liver metastasis.

> IMPORTANT SAFETY INFORMATION

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 is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (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.

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 55% of the 680 patients treated with PADCEV in clinical trials. Twenty-three percent (23%) of patients had maculo-papular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 13% of patients, including maculo-papular rash, rash erythematous, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmarplantar erythrodysesthesia. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=59), 24% of patients restarting at a reduced dose patients restarting at the same dose and 16% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 2.6% of patients. Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated. Withhold PADCEV and refer for specialized care for suspected SJS or TEN or for severe (Grade 3) skin reactions. Permanently discontinue PADCEV in patients with confirmed SJS or TEN, or for 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, 14% of the 680 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. The incidence of Grade 3-4

hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20.3). Hyperglycemia led to discontinuation of PADCEV in 0.6% of patients. 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 Severe, life-threatening or fatal pneumonitis occurred in patients treated with PADCEV. In clinical trials, 3.1% of the 680 patients treated with PADCEV had pneumonitis of any grade and 0.7% had Grade 3-4. In clinical trials, the median time to onset of pneumonitis was 2.9 months (range: 0.6 to 6). Monitor patients for signs and symptoms indicative of pneumonitis, 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 persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis.

Peripheral neuropathy (PN) occurred in 52% of the 680 patients treated with PADCEV in clinical trials, including 39% with sensory neuropathy, 7% with muscular weakness and 6% with motor neuropathy; 4% experienced Grade 3-4 reactions. PN occurred in patients treated with PADCEV with or without pre-existing PN. The median time to onset of Grade ≥2 PN was 4.6 months (range: 0.1 to 15.8) months). Neuropathy led to treatment discontinuation in 5% of patients. Monitor patients for symptoms of new or worsening peripheral neuropathy 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 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 34% of patients, and blurred vision occurred in 13% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19.1 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 680 patients, 1.6% 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

IN CISPLATIN-INELIGIBLE, POST-PD-(L)1 la/mUC PATIENTS In the EV-201‡ trial (Cohort 2) PADCEV DELIVERED CLINICALLY MEANINGFUL RESPONSE^{1,3} **MAJOR EFFICACY OUTCOME MEASURE:** CONFIRMED ORR BY BICR^{1,3,4} **ORR** CR: 22% **PR: 28**% (n=25/89) (n=20/89)(n=45/89; Major efficacy outcome measure: Median DOR^{§||} 95% CI: 39.8%, was 13.8 months with PADCEV (95% CI: 6.4, NE)1 61.3%) *The EV-201 trial (Cohort 2) was a single-arm, multicenter trial of 89 patients with locally advanced or metastatic urothelial cancer who had previously received a PD-1 or PD-L1 inhibitor and were cisplatin ineligible. Patients received 1.25 mg/kg of PADCEV via IV infusion over 30 minutes on days 1, 8, and 15 of every 28-day cycle and continued to receive treatment until disease progression or unacceptable toxicity. The major efficacy outcome measures, confirmed ORR and DOR, were assessed by BICR using RECIST v1.1 ORR consisted of confirmed CR and PR. CR was defined as the disappearance of all target and nontarget lesions. PR was defined as a ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Median duration of follow-up was 13,4 months.1,4, §Kaplan-Meier estimate of duration of response, defined as the time from first response to date of progression or death due to any cause, was assessed by BICR.^{4,6} Based on patients (n=45) with a response by BICR.

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%)
Rash, aspartate aminotransferase (AST) increased, glucose increased, creatinine increased, fatigue, PN, lymphocytes decreased, alopecia, decreased appetite, hemoglobin decreased, diarrhea, sodium decreased, nausea, pruritus, phosphate decreased, dysgeusia, alanine aminotransferase (ALT) increased, anemia, albumin decreased, neutrophils decreased, urate increased, lipase increased, platelets decreased, weight decreased and dry skin.

EV-301 Study: 296 patients previously treated with a PD-1/L1 inhibitor and platinum-based chemotherapy.
Serious adverse reactions occurred in 47% of patients treated with PADCEV;

Serious adverse reactions occurred in 4 /% of patients treated with PADCEV; the most common (≥2%) were urinary tract infection, acute kidney injury (7% each) and pneumonia (5%). Fatal adverse reactions occurred in 3% of patients, including multiorgan dysfunction (1.0%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis and pelvic abscess (0.3% each). Adverse reactions leading to discontinuation occurred in 17% of patients; the most common (≥2%) were PN (5%) and rash (4%). Adverse reactions leading to dose interruption occurred in 61% of patients; the most common (2.4%) were PN interruption occurred in 61% of patients; the most common (≥4%) were PN (23%), rash (11%) and fatigue (9%). Adverse reactions leading to dose reduction occurred in 34% of patients; the most common (≥2%) were PN (10%), rash (8%), decreased appetite and fatigue (3% each). Clinically relevant adverse reactions (<15%) include vomiting (14%), AST increased (12%), hyperglycemia (10%), ALT increased (9%), pneumonitis (3%) and infusion site extravasation (0.7%).

EV-201, Cohort 2 Study: 89 patients previously treated with a PD-1/L1 inhibitor and not eligible for platinum:

Serious adverse reactions occurred in 39% of patients treated with PADCEV; the most common (≥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 (1.1% each). Adverse reactions leading to discontinuation occurred in 20% of patients; the most common (≥2%) was PN (7%). Adverse reactions leading to dose interruption occurred in 60% of patients; the most common (≥3%) were PN (19%), rash (9%), fatigue (8%), diarrhea (5%), AST increased and hyperglycemia (3% each). Adverse reactions leading to dose reduction occurred in 49% of patients; the most common (≥3%) were PN (19%), rash (11%) and fatigue (7%). Clinically relevant adverse reactions (<15%) include vomiting (13%), AST increased (12%), lipase increased (11%), ALT increased (10%), pneumonitis (4%) and infusion site extravasation (1%)

DRUG INTERACTIONS

Effects of other drugs on PADCEV (Dual P-gp and Strong CYP3A4 Inhibitors) Concomitant use with a 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 at least 3 weeks after the last dose.

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

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

BICR=blinded independent central review; CI=confidence interval; CR=complete response; DOR=duration of response; HR=hazard ratio; IV=intravenous; Ia=locally advanced; mUC=metastatic urothelial cancer; NE=not evaluable; ORR=objective response rate; OS=overall survival; PD-(L)1=programmed death receptor-1 or programmed death-ligand 1; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

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3. Seagen Inc. and Astellas. PADCEV. Data on File. 4. Yu EV, Petrylak DP, O'Donnell PH, et al. Enfortumab vedotin after DP-1 or PD-1.1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2021;22(6):872-82. 5. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised ReCIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47. 6. Supplement to: Yu EV, Petrylak DP, O'Donnell PH, et al. Enfortumab vedotin after PD-1 or PD-1.1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2021;22(6):872-82.



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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® is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who:

- have previously received a programmed death receptor-1 (PD-1) or programmed deathligand 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

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, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Dose Modifications

Table 1. Dose Modifications

1330 2000						
Adverse Reaction	Severity*	Dose Modification*				
	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 3 skin reactions.				
Skin Reactions	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.				
	Grade 3 (severe) skin reactions	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.				
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	Grade 2	Withhold until Grade ≤ 1 for persistent or recurrent Grade 2 pneumonitis, 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.				
Trematologic toxicity	Grade 4	Withhold until Grade ≤ 1, then reduce dose by one dose level or discontinue treatment.				

^{*}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 55% of the 680 patients treated with PADCEV in clinical trials. Twenty-three percent (23%) of patients had maculopapular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 13% of patients, including maculo-papular rash, rash erythematous, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmar-plantar erythrodysesthesia. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=59), 24% of patients restarting at the same dose and 16% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 2.6% of patients.

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

Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for severe (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 \geq 8% were excluded from clinical trials. In clinical trials, 14% of the 680 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20.3 months). Hyperglycemia led to discontinuation of PADCEV in 0.6% of patients.

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.

Pneumonit

Severe, life-threatening or fatal pneumonitis occurred in patients treated with PADCEV. In clinical trials, 3.1% of the 680 patients treated with PADCEV had pneumonitis of any grade and 0.7% had Grade 3-4. In clinical trials, the median time to onset of pneumonitis was 2.9 months (range: 0.6 to 6 months).

Monitor patients for signs and symptoms indicative of pneumonitis 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 persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis.

Peripheral Neuropathy

Peripheral neuropathy occurred in 52% of the 680 patients treated with PADCEV in clinical trials including 39% with sensory neuropathy, 7% with muscular weakness and 6% with motor neuropathy; 4% 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 4.6 months (range: 0.1 to 15.8 months). Neuropathy led to treatment discontinuation in 5% of patients.

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 $Grade \ge 3$ peripheral

Ocular Disorders

neuropathy.

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV 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 34% of patients, and blurred vision occurred in 13% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19.1 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 680 patients, 1.6% 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-eifv to pregnant rats during the period of organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures approximately 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 Trial 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 as a single agent at 1.25 mg/kg in 680 patients in EV-301, EV-201, EV-101 (NCT02091999), and EV-102 (NCT03070990). Ocular disorders reflect 384 patients in EV-201, EV-101, and EV-102. Among 680 patients receiving PADCEV, 36% were exposed for ≥ 6 months, and 9% were exposed for ≥ 12 months. In this pooled population, the most common (≥ 20%) adverse reactions, including laboratory abnormalities, were rash, aspartate aminotransferase increased, glucose increased, creatinine increased, fatigue, peripheral neuropathy, lymphocytes decreased, alopecia, decreased appetite, hemoglobin decreased, diarrhea, sodium decreased, nausea, pruritus, phosphate decreased, dysgeusia, alanine aminotransferase increased, anemia, albumin decreased, neutrophils decreased, urate increased, lipase increased, platelets decreased, weight decreased and dry skin.

The data described in the following sections reflect exposure to PADCEV from an openlabel, randomized, study (EV-301); and Cohort 1 and Cohort 2 of an open-label, single arm, two cohort study (EV-201). Patients received PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Previously Treated Locally Advanced or Metastatic Urothelial Cancer

FV-301

The safety of PADCEV was evaluated 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-11 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 19.4 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 (1.0%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis and pelvic abscess (0.3% each).

Adverse reactions leading to discontinuation occurred in 17% of patients; the most common adverse reactions ($\geq 2\%$) 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 (\geq 2%) leading to dose reduction were peripheral neuropathy (10%), rash (8%), decreased appetite (3%) and fatigue (3%).

Table 3 summarizes the most common (≥ 15%) adverse reactions in EV-301.

Table 3. Adverse Reactions (≥ 15%) in Patients Treated with PADCEV in EV-301

	PADCEV n=296		Chemotherapy n=291			
Adverse Reaction	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 ²	50	9	40	7		
Pyrexia ³	22	2	14	0		
Nervous system disorders						
Peripheral neuropathy ⁴	50	5	34	3		
Dysgeusia⁵	26	0	8	0		
Metabolism and nutrition disorders						
Decreased appetite	41	5	27	2		

		CEV 296	Chemot n=2	
Adverse Reaction	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Gastrointestinal o	lisorders			
Diarrhea ⁶	35	4	23	2
Nausea	30	1	25	2
Constipation	28	1	25	2
Abdominal Pain ⁷	20	1	14	3
Musculoskeletal	and connective ti	ssue disorders		
Musculoskeletal Pain ⁸	25	2	35	5
Eye Disorders				
Dry eye ⁹	24	0.7	6	0.3
Blood and lympha	atic system disord	ers		
Anemia	20	6	30	12
Infections and inf	estations			
Urinary Tract Infection ¹⁰	17	6	13	3
Vascular disorde	rs			
Hemorrhage ¹¹	17	3	13	2
Investigations				
Weight decreased	16	0.3	7	0

Includes: blister, blood blister, conjunctivitis, dermatitis, dermatitis bullous, drug eruption, eczema, erythema, erythema multiforme, exfoliative rash, intertrigo, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculopapular, rash papular, rash pruritic, rash vesicular, skin irritation, skin exfoliation, stomatitis. Includes: fatique. asthenia

³Includes: pyrexia, hyperthermia, hyperpyrexia, body temperature increased

Includes: burning sensation, demyelinating polyneuropathy, dysesthesia, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy, peripheral sensory neuropathy, gait disturbance, polyneuropathy, sensory loss

⁵Includes: dysgeusia, ageusia, hypogeusia

⁶Includes: diarrhea, colitis, enterocolitis

⁷Includes: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, hepatic pain, abdominal tenderness, gastrointestinal pain

⁸Includes: myalgia, arthralgia, back pain, bone pain, pain in extremity, musculoskeletal pain, arthritis, neck pain, non-cardiac chest pain, musculoskeletal chest pain, spinal pain, musculoskeletal stiffness, musculoskeletal discomfort

⁹Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, Meibomian gland dysfunction, ocular discomfort, punctate keratitis

¹⁰Includes: urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal, streptococcal urinary tract infection, escherichia urinary tract infection, pyelonephritis acute, escherichia pyelonephritis, urinary tract infection fungal, cystitis, urinary tract infection staphylococcal, urinary tract infection pseudomonal

¹¹Includes: hematuria, rectal hemorrhage, gastrointestinal hemorrhage, epistaxis, upper gastrointestinal hemorrhage, tumor hemorrhage, hemoptysis, vaginal hemorrhage, anal hemorrhage, hemorrhage, to stroke, urethral hemorrhage, infusion site hemorrhage, conjunctival hemorrhage, hemorrhagic ascites, hemorrhoidal hemorrhage

Clinically relevant adverse reactions (< 15%) include vomiting (14%), aspartate aminotransferase increased (12%), hyperglycemia (10%), alanine aminotransferase increased (9%), dry eye (6%) and infusion site extravasation (0.7%).

EV-201, Cohort 2

The safety of PADCEV was evaluated 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 (1.1% each).

Adverse reactions leading to discontinuation occurred in 20% of patients; the most common adverse reaction ($\geq 2\%$) 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%), aspartate aminotransferase increased (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 4 summarizes the All Grades and Grade 3-4 adverse reactions reported in patients in EV-201, Cohort 2.

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

		CEV 89
	All Grades	Grades 3-4
Adverse Reaction	(%)	(%)
Skin and subcutaneous tissue disor	ders	
Rash ¹	66	17
Alopecia	53	0
Pruritus	35	3
Dry skin	19	1
Nervous system disorders		
Peripheral neuropathy ²	58	8
Dysgeusia ³	29	0
General disorders and administration	n site conditions	
Fatigue ⁴	48	11
Metabolism and nutrition disorders	•	
Decreased appetite	40	6
Hyperglycemia	16	9
Blood and lymphatic disorders	1	
Anemia	38	11
Gastrointestinal disorders		
Diarrhea ⁵	36	8
Nausea	30	1
Investigations		*
Weight decreased	35	1
Eye disorders	-	
Dry eye ⁶	30	0

Includes: blister, conjunctivitis, dermatitis bullous, dermatitis exfoliative generalized, eczema, erythema, erythema multiforme, intertrigo, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, stomatitis

²Includes: demyelinating polyneuropathy, gait disturbance, hypoesthesia, motor dysfunction, muscle atrophy, muscular weakness, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy, peripheral sensory neuropathy

³Includes: dysgeusia, ageusia, hypogeusia

Includes: fatigue, asthenia

⁵Includes: diarrhea, colitis, enterocolitis

⁶Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, Meibomian gland dysfunction, ocular discomfort, punctate keratitis, tear break up time decreased

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

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the trials described below with the incidence of antibodies in other trials or other enfortumab vedotin-ejfv products may be misleading.

Following administration of PADCEV 1.25 mg/kg; 16/590 (2.7%) patients tested positive for anti-therapeutic antibody (ATA) against enfortumab vedotin-ejfv at one or more post-baseline time points. Due to the limited number of patients with ATA against enfortumab vedotin-ejfv, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety or pharmacokinetics.

DRUG INTERACTIONS

Effects of Other Drugs on PADCEV

<u>Dual P-gp and Strong CYP3A4 Inhibitors</u>

Concomitant use with dual P-gp and strong CYP3A4 inhibitors may increase unconjugated 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 approximately 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 at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Preanancy testina

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 PADCEV treatment 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.

Infertilit

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 680 patients treated with PADCEV in clinical trials, 440 (65%) were 65 years or older and 168 (25%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients 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 \geq 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. No adjustment in the starting dose is required when administering PADCEV to patients with mild hepatic impairment (total bilirubin 1 to 1.5 \times ULN and AST any, or total bilirubin \leq ULN and AST > ULN).

Renal Impairment

No dose adjustment is required in patients with mild (CrCL > 60-90 mL/min), moderate (CrCL 30-60 mL/min) or severe (CrCL < 30 mL/min) renal impairment.

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081-0282-PM 07/21

OVERVIEW OF BTK INHIBITORS FOR B-CELL MALIGNANCIES

By Kirollos Hanna, PharmD, BCPS, BCOP, Jenny Nguyen, PharmD, & Sarah Tu, PharmD

-cell malignancies are a heterogeneous group of hematologic malignancies that include most non-Hodgkin's lymphomas (NHLs), and some lymphomas/leukemias such as mantle cell lymphoma



Kirollos Hanna



Jenny Nguyen



Sarah Tu

(MCL), Waldenström macroglobulinemia (WM), chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL).1

Bruton's Tyrosine Kinase (BTK) activity is known to play a significant role in survival and proliferation of leukemic B-cells as well as interactions between cells in the tumor microenvironment.2 BTK inhibitors (BTKi) have demonstrated promising anti-neoplastic activity in pre-clinical and clinical studies.2

Reversible BT-Ki's form transient inhibitor-protein complexes in equilibrium and subse-

quent concentration of these complexes is proportional to the concentration of free inhibitors in the cytoplasm.



Ibrutinib was the first-generation BTKi to change the landscape of B-cell malignancy treatment.

Thus, high levels of free inhibitors push the equilibrium to the inhibitor-protein complex orientation. Rapid metabolization causes equilibrium to reverse, resulting in inhibition failure due to decomposing inhibitor-protein complexes.

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

With an estimated incidence of 21,040 new cases in 2020, and 4,060 deaths, CLL remains one of the most common lymphoid malignancies in Western countries.3

The disease is more prevalent in males than females and extremely rare in children. CLL tends to increase with age, with the median age at diagnosis of 70 years old. These mature leukemia cells are often found in the peripheral blood, bone marrow, and lymphoid tissues.

Differentiating CLL from SLL is based upon location, with SLL primarily residing in the lymphoid tissue rather than the peripheral blood. However, the treatment for both CLL and SLL is the same.4

Clinical course and presentation

in CLL are highly variable and patients often present asymptomatic, requiring no treatment.

However, as lymphocytes accumulate and progress further, clinical features may include splenomegaly, hepatomegaly, or nontender lymphadenopathy. Although less frequently, patients may also present with B symptoms (fatigue, fever, night sweats, unintentional weight loss) or cytopenia (anemia, thrombocytopenia, neutropenia) due to bone marrow infiltration.5-7

Choice of therapy is dependent on variety of components including patient age, performance status, cytogenetics, prognostic factors and comorbidities. To stratify patients for management, two clinical staging systems, Rai and Binet, are used for CLL, and the Lugano Modification of Ann Arbor Staging System for SLL.4

Due to surmounting data showing positive results with novel oral therapies, treatment algorithms in CLL have shifted from traditional chemotherapy-based

CONTINUED ON NEXT PAGE

B-CELL MALIGNANCIES

BTK INHIBITORS

CONTINUED FROM PREVIOUS PAGE

regimens towards a targeted therapeutic approach. This is in part due to the discovery of B-cell receptor signaling playing a critical role in the development and expansion of CLL/SLL. Inhibition of BTK was sought as an innovative target following early findings of effective disease control in CLL models.⁸

CLL/SLL WITHOUT del(17P)/TP53

Ibrutinib was the first generation BTKi to change the landscape of B-cell malignancy treatment. In patient's without del(17p)/TP53 mutation, regardless of age or comorbidities, National Comprehensive Cancer Network (NCCN) treatment guidelines designate ibrutinib as a category 1 recommendation in both untreated and relapsed settings of CLL/SLL.9

The safety and efficacy of this monotherapy BTKi was confirmed in both phase III trials, RESONATE-2 and Alliance North American Intergroup Study (A041202).

In the first trial, a group of 269 patients (>65 years of age), were randomized to either first-line therapy of ibrutinib 420 mg continuous treatment or chlorambucil. Authors of the RESONATE-2 found higher overall response rate (ORR), (92% vs. 37%, P<.0001) as well as longer progression-free survival (PFS), (70% vs. 37%, P<.0001) in the ibrutinib arm versus chlorambucil arm, respectively.

Common grade >3 adverse events reported in the ibrutinib arm included neutropenia (13%), pneumonia (12%) and hypertension (8%).¹⁰

Furthermore, the ibrutinib group also improved PFS observed in highrisk CLL with del(11q) and unmutated IGHV. The benefit of ibrutinib was also replicated in the A041202 trial.

Patients > 65 years with untreated CLL that were assigned to either ibrutinib groups, monotherapy or with rituximab, both had superior PFS and ORR compared to bendamustine + rituximab (BR) arm.¹¹

Due to surmounting data showing positive results with novel oral therapies, treatment algorithms in CLL have shifted from traditional chemotherapy-based regimens towards a targeted therapeutic approach.

Combinations using ibrutinib also have established a role in the NCCN guidelines and are designated category 2b in those treatment naïve.⁹

For younger patients without del(17p)/TP53 mutation and unmutated IGHV, the E1912 study found ibrutinib + rituximab more effective compared to fludarabine + cyclophosphamide + rituximab (FCR). Whereas in elderly and comorbid patients without del(17p)/TP53, ibrutinib + obinutuzmab had better PFS than standard chemoimmunotherapy, chlorambucil + obinutuzumab.

In addition, regardless of age and comorbidities, ibrutinib is included in the relapsed or refractory (R/R) setting as a preferred category 1 recommendation in NCCN.⁹

Acalabrutinib is a second-generation BTKi that has shown promising results in both the frontline and R/R settings. Regardless of age or comorbidities, the treatment guidelines classify acalabrutinib + obinutuzumab in untreated patients, and monotherapy acalabrutinib in R/R as both preferred category 1 regimens.9 The combination of acalabrutinib + obinutuzumab was established in the ELEVATE-TN phase III study — where similar to the A041202 with ibrutinib, cohorts receiving a BTKi either monotherapy or in combination — found improved PFS compared to the chemoimmunotherapy arm.

The results included 2-year PFS rates for

the following: acalabrutinib + obinutuzumab (93%), acalabrutinib (87%), and clorambucil +obinutuzumab (47%).

The study was inadequately powered to determine differences in PFS between the two acalabrutinib arms. In terms of safety, the chemoimmunotherapy arm had higher incidence of neutropenia grade >3 (70%), followed by acalabrutinib + obinutuzumab (30%) and acalabrutinib (10%).¹⁴

Two trials have demonstrated the ongoing efficacy of acalabrutinib in the R/R setting.

In a phase II study of 134 patients, acalabrutinib led to a high ORR of 94% and PFS was not yet reached at follow-up of 42 months. ¹⁵ Furthermore, the AS-CEND trial highlighted acalabrutinib's superiority over chemoimmunotherapy agents, BR and idelalisib + rituximab (IdR) in R/R CLL. Acalabrutinib led to prolonging PFS that was not reached at 16 months compared to BR (17 months), and IdR (16 months) (P<.0001). ¹⁶

Recently, zanubrutinib, another second-generation BTKi, has been added to the NCCN guidelines as an option for patients who are intolerant of the other two BTKi's or if their use is contraindicated (category 2b). Furthermore, it is included as an alternative agent in the R/R setting regardless of age or comorbidities for those without del(17p)/TP53 mutation.⁹

CLL/SLL WITH del(17P)/TP53

The role of BTKi continues to show efficacy even in patients presenting with del(17p)/TP53.

In the RESONATE-2 study, patients with del(17p)/TP53 were excluded. However, 12 patients with TP53 mutation received ibrutinib and found to have 5-year PFS of 56% and median PFS not yet reached at six-year follow-up.¹⁰

The benefit of ibrutinib in treatment naïve with del(17p)/TP53 was also seen in the RESONATE-17, which showed a 5-year overall survival rate of 85% and PFS of 74% at median follow-up of 57 months.¹⁴

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BTK INHIBITORS

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Therefore, ibrutinib is considered a preferred first-line treatment in patients with this genetic aberration, in absence of a clinical trial. Furthermore, the same RESONATE-17 study demonstrated safety and efficacy of ibrutinib in R/R patients with del(17p)/TP53 (n=145) and considered a category 1 recommendation. ¹³

In the ELEVATE-TN trial mentioned above, PFS benefit was observed in all subgroups including patients with del(17p)/TP53 receiving acalabrutinib + obinutuzumab. ¹⁴ Patients with del(17p) and TP53 were represented in 9% and 11%, respectively, in the monotherapy acalabrutinib cohort, whereas the acalabrutinib + obinutuzumab arm represented 10% and 12%, respectively.

Based on these findings, acalabrutinib + obinutuzumab is a designated category 2A preferred regimen in treatment naïve.

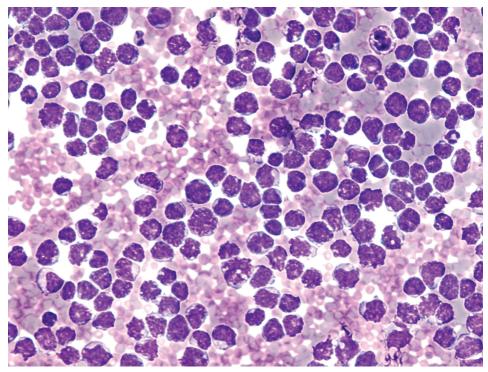
As patients progress into second-line and subsequent therapy, acalabrutinib remains an option as a category 1 preferred regimen. This is based on results of the ASCEND study demonstrating PFS benefit, with acalabrutinib, despite presence of del(17p)/TP53.¹⁶

Moreover, zanubrutinib is included as an option in R/R as well as first line treatment for patients with del(17p)/ TP53 who are intolerant of ibrutinib and acalabrutinib or use of either of those two agents are contraindicated.⁸

SAFETY IN BTK TRIALS

Several overlapping adverse events are noted in both acalabrutinb and ibrutinib trials. Grade >3 atrial fibrillation, hypertension, and bleeding were seen with acalabrutinib at 1%, 3% and 2%, respectively. 14,16 Similar grade >3 adverse events with ibrutinib included atrial fibrillation (6%), bleeding (4%), and hypertension (20%). 17-18

In regards to bleeding, it is important to balance the benefit and risks of concomitant use of acalabrutinib and ibrutinib with an anticoagulant or antiplatelet. Of note, warfarin use was excluded in the trials with these agents.



This pleural fluid cytology shows involvement by malignant cells of a mantle cell lymphoma in a pleomorphic variant.

Careful monitoring of signs of symptoms of bleeding is necessary upon initiation with acalabrutinib or ibrutinib therapy. Patients with existing or new hypertension, atrial fibrillation or other cardiac symptoms should be managed appropriately versus consideration of alternate therapies.

If BTKi treatment is switched, the decision to transition should be immediate to prevent further progression upon stopping BTKi.

MANTLE CELL LYMPHOMA

MCL is a rare and non-curable subtype of NHL resulting from malignant transformation of B-cells in the outer edge of the lymph node follicle (mantle zone). The majority of cases are associated with a chromosomal translocation t(11;14)(q13:q32) leading to overexpression of cyclin D121-24. MCL accounts for about 6% of NHL cases, is more common in men, Caucasians, and older adults (median age of 68 years old).²²

Patients usually present with swollen lymph nodes, fever, night sweats, weight loss and fatigue.

Various studies have demonstrated

use of BTKi in MCL. In a multicenter phase 2 study of ibrutinib in patients with R/R MCL, there was a 68% ORR, 21% complete response rate (CR) and 47% with partial response (PR).

Major adverse events included nausea, diarrhea and fatigue.²⁵

Another study found an 81% ORR for acalabrutinib with complete resolution in 40% and a median progression-free survival of 20 months.²⁶

Finally, a phase 2 trial among participants with various R/R B-cell malignancies was conducted for zanubrutinib and found an ORR of 84.7% in MCL patients.²⁷

While there is no standard of care, BTK inhibition has been effective for patients with advanced disease who have received at least one line of prior therapy. BTK retains MCL cells in lymphoid tissues, so BTK inhibition is known to induce migration of malignant cells into the peripheral blood.²³

For patients who experience a shorter than expected median PFS to front-line therapies, BTKi may be a potential

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B-CELL MALIGNANCIES

BTK INHIBITORS

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second-line agent.28

However, patients with durable responses to front-line therapy are likely to receive similar chemoimmunotherapy combinations in the second-line setting due to better outcomes.

MARGINAL ZONE LYMPHOMA

Marginal-zone lymphoma (MZL) is a slow-growing NHL that originates from memory B-cells present in the marginal zone of secondary lymphoid follicles. MZL cells are usually localized in the spleen and mucosa-associated lymphoid tissues (MALT).

MZL comprises about 5-17% of all NHLs with a median age of diagnosis of 60 years old and is more commonly observed in women than men.²⁹

The B cell receptor pathway is thought to be a key activation pathway associated with chronic inflammation in MZL, which makes BTK a potential target.²³

Data is limited with BTKi in MZL. In a phase 2 trial of R/R MZL (NCT01980628), ibrutinib demonstrated an ORR of 63%.

Grade 3 or higher adverse events included anemia, pneumonia and fatigue.³⁰

First-line treatment remains chemoimmunotherapy in this patient population, with BTKi listed as one of the preferred second-line agents.²⁸

WALDENSTRÖM MACROGLOBULINEMIA

Waldenström Macroglobulinemia (WM) is a rare incurable indolent B-cell malignancy characterized by IgM-secreting lymphoma cells in the bone marrow.^{23,31}

WM occurs in about three cases per million Americans or about 1,500 cases diagnosed yearly.³¹ WM is more common in Caucasians and men with a median age of 70 at diagnosis.²³

IgM paraprotein can cause vascular complications and neoplastic lymphoplasmacytic cell infiltration of the bone marrow, spleen, and lymph nodes. Patients may also present with weight loss,

fatigue, and bloody noses.

Poor prognostic factors include older age (age > 65 years), hemoglobin value < 10 g/dL, albumin level < 4 g/dL and elevated beta-2-microglobulin level.

In a phase 2 trial of R/R WM, ibrutinib demonstrated an ORR of 91% and a 73% response rate. Grade 2 adverse events included bleeding in 6% of patients (related to procedures or fish oil supplements) and reversible atrial fibrillation, which stopped with medication discontinuation (5%) (NCT01614821).

Combination therapy with rituximab has also demonstrated efficacy and has been incorporated into a category 1 preferred regimen per NCCN guidelines.²⁸

For MCL, MZL and WM, BTK inhibition can provide a potential treatment modality in either the second line or upfront settings, respectively.

Treatment should always be guided based individualized patient characteristics such as comorbidities, potential for adherence on oral therapy, anticipated toxicities and prior treatment exposure.

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N C O D A N E W S

NCODA EXPANDS EXECUTIVE COUNCIL WITH EIGHT NEW MEMBERS

NCODA recently expanded its Executive Council to include eight new members:

- ▲ Dallas Lawry, DNP, FNP-C, OCN, Oncology Nurse Practitioner at University of California - San Diego. Lawry was previously an oncology nurse at UCLA Medical Center - Santa Monica Hospital. She started her new role as an oncology NP this Fall at UC San Diego.
- Lucius Daniel, PharmD, is the Lead Clinical Pharmacy Specialist with Karmanos Specialty Pharmacy. Daniel has been a member of the Karmanos Cancer Center since March 2018, and has diverse pharmacy background with experience in medical affairs/market development in the pharmaceutical industry.
- ▲ Paul Chadwick, Chief Procurement Officer at Florida Cancer Specialists & Research Institute in Fort Myers, Florida. He is responsible for oversight of in-clinic IV drugs and the medically integrated oral pharmacy.
- ▲ Lucio Gordan, MD, President and Managing Physician of Florida Cancer Specialists & Research Institute, with a practice at the FCS Gainesville Cancer Center. As a cancer researcher and the recipient of research grants, he is actively engaged in clinical studies.
- ▲ Benjamin Lowentritt, MD, Director of Minimally

Invasive Surgery and Robotics and Director of the Prostate Cancer Care Program at Chesapeake Urology in Baltimore, Maryland.

- ▲ Stacey McCullough, PharmD, Senior Vice President of Pharmacy for Tennessee Oncology. She works with executive and clinical leadership in synchronizing business acuity to clinical excellence and developing strategies for system implementation across multiple clinical sites.
- Rajiv Panikkar, MD, Chair of the Geisinger Cancer Institute, where he leads 11 hematology/oncology, six radiation oncology, and four palliative medicine sites across Pennsylvania.
- ▲ Michelle Taymuree, PharmD, MBA, Oncology Manager of Pharmacy Services (system-wide) at Sutter Health. She is responsible for managing Clinical Pathways, authoring guidelines and policies, and developing pharmacy initiatives.

The Executive Council also includes:

Mary Anderson, BSN, RN, OCN, Oral Oncology Nurse Navigator | Norton Cancer Center; Robert **Ashford**, Director of Membership & Corporate Strategy | NCODA; Ray Bailey, BPharm, RPh, Senior Vice President of Pharmacy Services, Florida Cancer Specialists & Research Institute; Barry Brooks, MD, Medical Director of Oncolytics | McKesson Specialty Health;

Jonas Congelli, RPh, Chief of Pharmacy and Ancillary Services | Hematology Oncology Associates of CNY; **Austin Cox**, PharmD, Pharmacy Manager Alabama Oncology; Nancy Egerton, PharmD, Director of Pharmacy | New York Oncology Hematology; Randy Erickson, RN, BSN, MBA, CEO | Utah Cancer Specialists;

Linda Frisk, PharmD, Pharmacy Manager Ironwood Cancer and Research Centers; James Gilmore, PharmD, BCCCP, BCPS, Chief Pharmacy & Procurement Officer, AON; Kirollos Hanna, PharmD, BCPS, BCOP, Oncology Pharmacy Manager, Clinical Assistant Professor | M Health Fairview, Mayo Clinic College of Medicine; Jan Montgomery, PharmD, former Director of Pharmacy | South Carolina Oncology Associates;

Yen Nguyen, PharmD, Director of Pharmacy Oncology Consultants, PA; Robert Orzechowski, MBA, SHRM-SCP, COO | Lancaster Cancer Center; Michael **Reff**, RPh, MBA, Founder & Executive Director NCODA and Jim Schwartz, RPh, Past Executive Director of Pharmacy Operations | Texas Oncology.

"As NCODA grows, it is important that the organization has leaders with unique backgrounds and experiences so that we can continue to shape the cancer care landscape ... and do it in a way that is patient-centered and always collaborative," Reff noted.

BTK INHIBITORS

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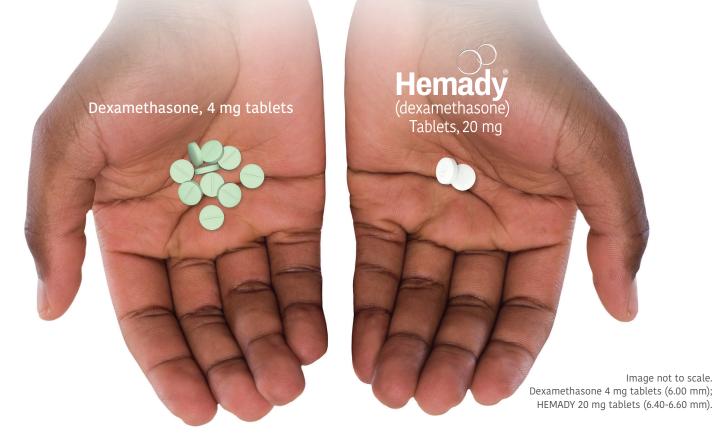
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Alterations in Cardiovascular/Renal Function: Alterations in cardiovascular and renal function can occur. Monitor for elevated blood pressure and sodium, and decreased potassium levels. Use with caution in patients with congestive heart failure and recent myocardial infarction.

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Behavioral and Mood Disturbances: Potentially severe psychiatric adverse reactions may occur with systemic corticosteroids, including HEMADY. Inform patients and caregivers of the potential for behavioral and mood changes and encourage them to seek medical attention if symptoms develop.

Kaposi's Sarcoma: Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Embryo-Fetal Toxicity: HEMADY can cause fetal harm when administered to pregnant women. Advise females of reproductive potential to use effective contraception during treatment and for one month after treatment with HEMADY. Refer to the prescribing information of the combination anti-myeloma product for additional Contraindications, Warnings and Precautions.

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TREATMENT UPDATES FOR RELAPSED & REFRACTORY MULTIPLE MYELOMA

IMMUNOTHERAPY, ANTIBODIES, NOVEL AGENTS AND BEYOND

By Lauren Held, PharmD, BCOP, & Shan Li O'Connor, PharmD, BCOP

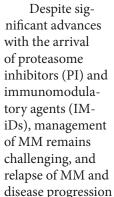
ultiple myeloma (MM) is a hematologic disorder characterized by a proliferation of malignant, monoclonal plasma cells in the bone marrow and/or extramedullary sites.

Over the past two decades, median survival of patients with MM has significantly



Lauren Held

improved, from three to four years to approximately seven to eight years with novel combination induction therapy followed by autologous stem cell transplantation.





is common even after achievement of a complete remission. 1,2

Relapsed/refractory MM (RRMM) is defined as a disease which becomes nonresponsive or progressive on therapy or within 60 days of the last treatment



in patients who had achieved a minimal response or better on prior therapy. RRMM often acquires additional mutation or genetic alterations that render the disease more resistant, leading to progressively shorter durations of remission or response to each salvage therapy.³

Apart from newer-generation PIs or IMiDs, drugs with novel mechanism of actions are also being explored in RRMM. Daratumumab, Selinexor and Belantamab mafodotin are recently FDA-approved agents for the treatment of RRMM. In addition, venetoclax, an oral tyrosine kinase inhibitor (TKI), has also shown to have activity in patients with RRMM who failed multiple prior therapies.

DARATUMUMAB

CD38 is a transmembrane glycoprotein expressed on the surface of hematopoietic cells and is overexpressed on MM cells. As a multi-function ectoenzyme, CD38 has several roles including receptor-mediated adhesion, signaling and modulation of cyclase and hydrolase activity.⁴

Daratumumab is a first-in-class human IgG1k monoclonal antibody that targets a unique epitope on the CD38 glycoprotein. Daratumumab induces cell death through various mechanisms including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and apoptosis via crosslinking. 5.6

Daratumumab may also modulate enzymatic activity, such as inhibiting the production of immunosuppressive adenosine and boosting intracellular nicotinamide adenine dinucleotide levels, resulting in cytotoxicity. While the direct on-tumor actions of daratumumab may produce rapid anti-myeloma responses, its immunomodulatory actions may contribute to durable responses and improved survival.⁷

The approval of daratumumab in 2015 has dramatically improved treatment outcomes either as monotherapy or in combination with PI and IMiDs.⁸

The synergism of daratumumab when combined with PI and IMiDs in

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LTIPLE M Y E L

MULTIPLE MYELOMA

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RRMM was demonstrated in two landmark trials.

In the POLLUX study, 569 patients with RRMM were assigned to receive either lenalidomide and dexamethasone alone (Rd) or with daratumumab (D-Rd). The 12-month progression free survival (PFS) in the daratumumab arm was 83.2% compared to 60.1% in the control group. The overall rate of response rate (ORR) of the D-Rd group was 92.9% versus 76.4% in the Rd group, and the proportion of those achieving a complete remission (CR) or better was 43.1% vs 19.2%, respectively.9 After a median follow-up of 44.3 months, daratumumab continued to offer a PFS benefit, greater overall responses as well as sustained minimal residual disease (MRD) negativity.10

Similarly, in the CASTOR trial, 499 patients with RRMM were randomly assigned to receive bortezomib and dexamethasone with (D-Vd) or without daratumumab (Vd). Daratumumab significantly improved the ORR and PFS across all subgroups. The D-Vd arm had a 61% lower risk for death or disease progression compared to the Vd arm.11 Due to daratumumab's unquestionable benefit, the study was stopped and patients in the Vd group had the option to receive daratumumab. After a median follow-up of 19.4 months, D-Vd arm continued to maintain significant benefit with respect to response rates and PFS.¹²

OTHER STUDIES

Most recently, daratumumab in combination with carfilzomib was studied in the CANDOR trial where 466 patients were randomized to receive either carfilzomib with daratumumab and dexamethasone (DKd) or carfilzomib and dexamethasone (Kd). After a median follow-up of 17 months, the median PFS was not reached in the KdD group vs 15.8 months in the Kd group. The frequency of adverse events leading to treatment discontinuation were similar in both groups.¹³ With approximately 11 months of additional follow-up, a 13.4 month improvement in median PFS was observed in patients treated with KdD (28.6 months) versus patients treated with Kd (15.2 months).14

Since its initial approval in 2015, daratumumab has been evaluated for its utility in frontline therapy. CASSIOPEIA trial was the first major phase III study that showed daratumumab's benefit when combined with traditional frontline induction/consolidation therapy prior to autologous stem cell transplant. The trial compared the combination of daratumumab with VTd (bortezomibthalidomide-dexamethasone) versus VTd alone as induction regimen in preparation of ASCT and for consolidation therapy. Patients who achieved a partial response (PR) or better were then further randomized to receive daratumumab maintenance versus observation until disease progression.

Patients in the daratumumab group maintained significantly better and deeper responses including stringent complete response (sCR), improved MRD negativity and PFS. This groundbreaking study led to FDA approval for daratumumab to be used as induction and consolidation for newly diagnosed MM patients who are transplant-eligible.15

Several other trials are currently ongoing to further investigate the role of frontline daratumumab in transplant-eligible candidates. In the phase I/II GRIF-FIN trial, 224 patients were randomly assigned to receive either D-VRd or VRd as induction/consolidation, followed by lenalidomide/daratumumab vs lenalidomide maintenance. Preliminary results show that daratumumab improved sCR rates (50% vs. 37%) except in patients with high-risk disease. Among patients who had achieved a CR, daratumumab group reported higher MRD negativity (59% vs. 24%).16

Another phase III study, PERSEUS is evaluating 690 patients in the same treatment arms for improved PFS rate between D-VRD and VRD group. Subcutaneous (SC) formulation of daratumumab is used in this study to limit

side effects and infusion times. The data from PERSEUS is not mature yet to be reported.17

INTRAVENOUS CONCERNS

Daratumumab was initially developed as an intravenous (IV) formulation. Administration of IV daratumumab takes about seven to eight hours for the first infusion and three to four hours thereafter.18 Recently, a rapid 90-minute infusion protocol has proven safe once patients tolerate the first two infusions.¹⁹ The long infusion time, particularly with initial daratumumab dose, makes it challenging to administer daratumumab IV in the community setting.

While the adverse event profile with IV daratumumab is modest — predominately consisting of grade 1 or 2 hematologic toxicity — upper respiratory tract infection, cough, fatigue, nausea and back pain, the risk of infusion-related reactions (IRRs) remains a challenge.9,11 Rates of IRRs vary from 28-50%, and are consistent in trials of daratumumab monotherapy and combination therapy.9-14 The risk of IRRs is highest during a patient's first daratumumab infusion and is relatively rare after the third infusion.

To mitigate the long infusion time, a SC formulation of daratumumab was approved for use in frontline setting for transplant-ineligible patients in combination with lenalidomide and dexamethasone or bortezomib, melphalan and prednisone; as well as in RRMM as monotherapy, or in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone in May 2020.20

SC daratumumab is given as a flat dose of 1800 mg/15ml administered over three to five minutes. Rates of IRRs were significantly lower in the SC daratumumab, only seen in 7.5% patients, with 50% of IRRs occurring within 3.3 hours of infusion.21 Based on its similar efficacy and reduced toxicity, SC daratumumab can help reduce dosing error, improve health-related quality of life and use of healthcare resources, as well as improve adaptation in the community setting.²²

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SELINEXOR

Exportin 1 (XPO1) functions as a nuclear exporter of tumor suppressor proteins with overexpression in myeloma cells leading to increased bone disease and shorter survival. Selinexor reversibly binds to a critical cysteine residue (cys-528) in the nuclear export sequence-binding groove of XPO1 and prevents transport proteins from the nucleus to the cytoplasm.²¹ Selinexor is a first-in-class oral small molecule inhibitor that selectively inhibits the nuclear export compound that blocks exportin 1 (XPO1) leading to accumulation of tumor suppressor proteins in the nucleus, inhibition of factor $\kappa\beta$, reduction of oncoprotein mRNA translation and apoptosis.^{23,24}

Selinexor was initially approved based on results of the phase 2b, multicenter, open-label STORM study that enrolled patients with measurable disease and had disease refractory to at least one immunomodulatory agent, one proteasome inhibitor, daratumumab, glucocorticoids and their most recent regimen. Selinexor 80 mg orally in combination with dexamethasone 20 mg was given on days 1 and 3 weekly. A total of 123 patients enrolled with 53% of patients having high-risk cytogenetics and a 6.6 year median duration of myeloma. Of the 123 patients enrolled, 118 (96%), discontinued treatment due to disease progression and adverse events being the most common.

Results showed a PR or better in 26% of patients with a median duration of response of 4.4 months. Median PFS was 3.7 months and median OS was 8.6 months. The most common toxicities included thrombocytopenia in 73% (grade 3 in 25% and grade 4 in 33%), fatigue in 73%, nausea in 72% and anemia in 67%.²⁵

Selinexor in combination with bortezomib and dexamethasone was further studied in the phase III BOSTON trial that enrolled 457 patients with myeloma previously treated with one to three lines of therapy including proteasome inhibitors. Patients were randomly allocated to receive

either Selinexor 100 mg orally once weekly, bortezomib 1.3 mg/m² once weekly and dexamethasone 20 mg twice (SVd) weekly or bortezomib and dexamethasone (Vd). Efficacy was measured by PFS and was 13.9 months and 9.5 months in the SVd and Vd arms, respectively.

Common toxicities in at least 20% of patients included nausea, fatigue, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, decreased weight, cataract and vomiting. ²⁶ Selinexor's significant safety profile often limits the use in clinical practice, however, recommendations have been published on toxicity management. ²⁷ Dose modifications may be required and expectations should be set when starting a patient on selinexor and advise patients to maintain adequate fluid and caloric intake throughout treatment. ²⁸

BELANTAMAB MAFODOTIN

B-cell maturation antigen (BCMA) is preferentially expressed by mature B lymphocytes and is essential for the survival of bone marrow plasma cells. Belantamab mafodotin is a humanized immunoglobulin G1 immunoconjugate that binds specifically to BCMA. Once bound to the cell surface, the active cytotoxic drug (cys-mcMMAF) is released inside the cell via proteolysis, resulting in cell killing through microtubule disruption leading to cell cycle arrest and apoptosis.²⁹

Approval of belantamab mafodotin was based on the multicenter, phase II DREAMM-2 clinical trial. A total of 97 patients with relapsed or refractory multiple myeloma progressing on at least three previous lines of therapy including autologous stem cell transplant were enrolled. Patients received either belantamab mafodotin 2.5 mg/kg or 3.4 mg/kg intravenously once every three weeks until disease progression or unacceptable toxicity.

Efficacy was based on ORR and response duration using the International Myeloma Working Group (IMWG) uniform response criteria. Patients receiving 2.5 mg/kg had an ORR of 31% with 73% of responders having response durations of greater than six months.

Toxicities occurring in greater than 20% of patients included keratopathy (76%), decreased visual acuity (55%), nausea (24%), blurred vision (27%), pyrexia (22%), infusion-related reactions (21%), and fatigue (20%).³⁰⁻³¹

Due to the ocular toxicity risks, belantamab mafodotin is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Requirements of the BLENREP REMS program include ophthalmic exams at baseline prior to each dose, and promptly for worsening symptoms. Patients should be instructed to use preservative-free lubricant eye drops at least four times a day starting with the first infusion, to avoid contact lenses unless directed by an ophthalmologist, and to use caution when driving or operating machinery.³²

VENETOCLAX

The BCL-2 family of antiapoptotic and proapoptotic proteins plays a critical role in regulating the intrinsic apoptosis pathway and cell survival. Overexpression of antiapoptotic proteins is heterogeneous in myeloma cells. Both MCL-1 and BCL-2 have been shown to be overexpressed in a subset of myeloma cells and have been implicated in mediating their survival.³³

Venetoclax is a first-in-class, potent, selective orally inhibitor of BCL-2. Selective BCL-2 targeting with venetoclax has shown promising antitumor activity in several hematologic malignancies, including chronic lymphocytic leukemia, acute myeloid leukemia, and non-Hodgkin's lymphoma. MM cells with a high dependency on BCL-2 protein for survival are particularly sensitive to venetoclax induced apoptosis.

Venetoclax monotherapy has demonstrated efficacy in the treatment of patients with RRMM, particularly those harboring the t (11;14) translocation.³⁷ Venetoclax-containing combination with bortezomib and dexamethasone was found to be of even higher efficacy.³⁸

BELLINI is a phase III, double-blind, placebo-controlled, multicenter trial investigating bortezomib/dexamethasone (Bd) plus venetoclax (VenBd) vs. Bd in patients

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with RRMM. Patients received 800 mg venetoclax or placebo tablets orally daily. Bortezomib 1.3mg/m² was given on days 1, 4, 8 and 11, and dexamethasone 20 mg was given on days 1, 2, 4, 5, 8, 9, 11 and 12 every 21 days for the first eight cycles. For cycle nine and beyond, bortezomib was given on days 1, 8, 15 and 22 and dexamethasone was given on days 1, 2, 8, 9, 15, 16, 22 and 23 of each 35-day cycle.³⁹

Eleven percent (11%) of the patients enrolled in the venetoclax arm harbored t(11;14), as compared with 15% in the placebo arm. At a median follow-up of 18.7 months, the ORR was 82% in the venetoclax arm compared with 68% in the placebo arm. Median PFS was 22.4 months with venetoclax versus 11.5 months in the placebo group. The proportion of patients who achieved a MRD negative response was also significantly higher in the venetoclax group than in the placebo group (45% vs. 0%).

The most common grade 3 or higher treatment-emergent adverse events were neutropenia, pneumonia, diarrhea and thrombocytopenia. Twenty-one percent (21%) of patients in the venetoclax group and 11% of patients in the placebo group died. Most treatment-emergent deaths in the venetoclaxgroup were associated with infection. The increased risk of infection-related deaths led to the implementation of antibiotic prophylaxis in the ongoing studies of venetoclax.³⁹

Venetoclax was also evaluated in a phase II dose escalation study in combination with carfilzomib, and dexamethasone in 42 patients with RRMM. The ORR was 78% with very good partial remission (VGPR) or better seen in 56% of the whole cohort. Interestingly, the ORR was 100% with VGPR or better of 88% in the among patients with t(11;14) with no new safety signals.⁴⁰

BCMA TARGETED CHIMERIC ANTIGEN RECEPTOR (CAR)-T CELLS

Currently, multiple BCMA-targeted therapeutics, including antibody drug

Recent drug development and approval has resulted in significant change in the management of MM.

Combination approach targeting MM cells as well as developing drugs with novel mechanisms of action have remarkably improved response.

conjugates (ADC), chimeric antigen receptor (CAR)-T cells and bispecific T cell engagers (BiTE), are all being studied and achieved responses in multiple myeloma.⁴¹

CAR-T cell therapy is a form of genetically modified autologous immunotherapy that combines target specificity of monoclonal antibodies and cytotoxicity of T cells. The treatment involves apheresis to harvest T lymphocytes, which are transduced with a gene that encodes a chimeric antigen receptor to direct cytotoxic T lymphocytes towards target cancer cells.

Currently, two CD19-engineered CAR-T cell products are FDA-approved for the treatment of advanced B cell malignancies. BCMA-targeted CAR-T products are currently being studied in clinical trials for the treatment of relapsed/refractory multiple myeloma with most of them showing high response rates in patients with high-risk cytogenetics and extra-medullary disease.⁴²

A common and unique toxicity associated with CAR-T cell therapy is neurotoxicity primarily manifested by cytokine release syndrome (CRS). Symptoms may be mild to life threatening and may manifest as confusion, altered level of consciousness, fever and encephalopathy.⁴²

In summary, recent drug development and approval has resulted in significant change in the management of MM. Combination approach targeting MM cells as well as developing drugs with novel mecha-

nisms of action have remarkably improved response. With ongoing research and development, the future landscape of multiple myeloma remains optimal for patients with RRMM.

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NCODA'S LEGISLATIVE & POLICY ADVISORY COMMITTEE:

A VOICE IN GOVERNMENT FOR CANCER PATIENTS & PRACTICES

By Kevin Scorsone

he NCODA Legislative & Policy Advisory Committee (LPAC) educates NCODA membership on legislative issues pertaining to oncology and cancer patients throughout the United States.

The committee, formed at the end of 2020, is chaired by Nancy Egerton, PharmD, BCOP, and includes Holly Books, BSN, RN, OCN, Barry Brooks, MD, MBA, Eric Dallara, RPh, Ben Jones, Jessica Nagro, MPA, and Wayne Ormsby, MD.

NCODA membership has responded in a positive way to committee statements and opinions on ideas and policies it feels will hinder the patient, physician, pharmacist and practice.

This summer, the committee hosted its first Legislative & Policy Roundtable, moderated by Brooks. Committee members Dallara, Jones and Nagro discussed the issues and advancements, and the changes needed in the oncology space in legislatures from coast to coast.

SCAN QR CODE TO LISTEN TO A
CLIP FROM THE LEGISLATIVE
& POLICY ADVISORY
COMMITTEE ROUNDTABLE



Maintaining a focus on legislative issues is important, and lobbying can help make a big difference.

NCODA President Jim Schwartz,

WEBINAR SERIES AND OTHER VIRTUAL INITIATIVES HELP NCODA ADVOCATE FOR MEDICALLY INTEGRATED ONCOLOGY

NCODA's virtual webinars provide members with invaluable information regarding new drugs that have had clinical and operational success at medically integrated practices across the country.

These webinars have helped NCODA to dramatically spread its reach, not only in terms of geography, but in participant diversity and disease state topics as well.

NCODA webinars have become a must-see program in the world of oncology. NCODA has increased Virtual Product Theater, Quarterly Clinical Corner and Special Webinar attendance

RPh, and member Debra Patt, MD, went before the Texas Legislature to be a voice for positive change for patients. Efforts like these can make a world of difference for both NCODA membership and cancer patients now and in the years to come.

During the 2021 NCODA Fall Summit in October, the committee will highlight its work in the session "State Legislation Successes: How Legislation and Policy Works for You, Your Patients and Practice."

NCODA encourages members to

by numbers we didn't think possible.

Our growing audience benefits both NCODA members and the patients they serve, because it increases their chances of finding new and comprehensive drugs that can help in the battle against cancer.

The National Monthly Webinar, held on the third Thursday of each month, has historically been NCODA's highest-attended webinar.

NCODA webinars would not be possible without NCODA staff, membership, dedicated speakers from various practices and our collaborative partners. They are truly a team effort.

participate in this session, as well as future LPAC virtual roundtables and in-person events starting in 2022. LPAC events are great opportunities to get questions answered and learn more about the legislative process, policy and how it affects all of us.

If you are interested in participating in the committee or have any questions, contact **Kevin.Scorsone@NCODA.org**.

▲ **Kevin Scorsone** is Associate Manager of Patient-Centered Initiatives and Legislative & Policy Liaison at NCODA.

During the 2021 NCODA Fall Summit in October, the committee will highlight its work in the session "State Legislation Successes: How Legislation and Policy Works for You, Your Patients and Practice."



FALL 2021 ONCOLYTICS TODAY | 35





ONUREG® is indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

*QUAZAR® AML-0011

The efficacy of ONUREG® was evaluated in QUAZAR® AML-001, a multicenter, randomized, double-blind, placebo-controlled, phase III study. Eligible patients were ages 55 years or older, had AML, and were within 4 months of achieving first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) with intensive induction chemotherapy. A total of 472 patients who completed induction with or without consolidation therapy were randomized 1:1 to receive ONUREG® 300 mg (n=238) or placebo (n=234) orally on Days 1 to 14 of each 28-day treatment cycle. Efficacy was established on the basis of overall survival (OS). The trial demonstrated a statistically significant improvement in OS for patients randomized to ONUREG® compared with placebo. In the trial, ONUREG® showed a median OS of 24.7 months (95% CI: 18.7, 30.5) vs 14.8 months (95% CI: 11.7, 17.6) for patients receiving placebo (HR 0.69 [95% CI: 0.55, 0.86; P=0.0009]).

 $AML, acute \ myeloid \ leukemia; \ CI, confidence \ interval; \ HR, hazard \ ratio.$

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ONUREG® is contraindicated in patients with known severe hypersensitivity to azacitidine or its components.

WARNINGS AND PRECAUTIONS

Risks of Substitution with Other Azacitidine Products

Due to substantial differences in the pharmacokinetic parameters, the recommended dose and schedule for ONUREG® are different from those for the intravenous or subcutaneous azacitidine products. Treatment of patients using intravenous or subcutaneous azacitidine at the recommended dosage of ONUREG® may result in a fatal adverse reaction. Treatment with ONUREG® at the doses recommended for intravenous or subcutaneous azacitidine may not be effective. Do not substitute ONUREG® for intravenous or subcutaneous azacitidine.

Myelosuppression

New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received ONUREG®. Febrile neutropenia occurred in 12%. A dose reduction was required for 7% and 2% of patients due to neutropenia and thrombocytopenia. Less than 1% of patients discontinued ONUREG® due to either neutropenia or thrombocytopenia. Monitor complete blood counts and modify the dosage as recommended. Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs.

Increased Early Mortality in Patients with Myelodysplastic Syndromes (MDS)

In AZA-MDS-003, 216 patients with red blood cell transfusiondependent anemia and thrombocytopenia due to MDS were randomized to ONUREG® or placebo. 107 received a median of 5 cycles of ONUREG® 300 mg daily for 21 days of a 28-day cycle.

ONUREG® provided ~10 months longer OS compared with placebo¹

24.7 MONTHS

with ONUREG®

(95% CI: 18.7, 30.5)



14.8 MONTHS

with placebo

(95% CI: 11.7, 17.6)

HR* 0.69 (95% CI: 0.55, 0.86; *P*=0.0009)

CL confidence interval.

*The HR is from a Cox proportional hazards model stratified by age (55 to 64 vs ≥65 years), cytogenetic risk category at time of induction therapy (intermediate risk vs poor risk), and received consolidation therapy (yes vs no).

Convenient, once-daily, oral dosing that patients can take at home¹



2 WEEKS ON WEEKS OFF

The recommended dosage of ONUREG® is one 300 mg tablet orally, once daily with or without food on Days 1-14 of each 28-day treatment cycle

- Patients should take an antiemetic 30 minutes prior to each dose of ONUREG® for the first 2 cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting
- Continue ONUREG® until disease progression or unacceptable toxicity
- Do not substitute ONUREG® for intravenous or subcutaneous azacitidine. The indications and dosing regimen for ONUREG® differ from that of intravenous or subcutaneous azacitidine
- If the absolute neutrophil count (ANC) is <0.5 Gi/L on Day 1 of a cycle, do not administer ONUREG®. Delay the start of the cycle until the ANC is \geq 0.5 Gi/L

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Enrollment was discontinued early due to a higher incidence of early fatal and/or serious adverse reactions in the ONUREG® arm compared with placebo. The most frequent fatal adverse reaction was sepsis. Safety and effectiveness of ONUREG® for MDS have not been established. Treatment of MDS with ONUREG® is not recommended outside of controlled trials.

Embryo-Fetal Toxicity

ONUREG® can cause fetal harm when administered to a pregnant woman. Azacitidine caused fetal death and anomalies in pregnant rats via a single intraperitoneal dose less than the recommended human daily dose of oral azacitidine on a mg/m² basis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONUREG® and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG® and for at least 3 months after the last dose.

ADVERSE REACTIONS

Serious adverse reactions occurred in 15% of patients who received ONUREG®. Serious adverse reactions in ≥2% included pneumonia (8%) and febrile neutropenia (7%). One fatal adverse reaction (sepsis) occurred in a patient who received ONUREG®.

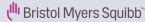
Most common (\geq 10%) adverse reactions with ONUREG® vs placebo were nausea (65%, 24%), vomiting (60%, 10%), diarrhea (50%, 21%), fatigue/asthenia (44%, 25%), constipation (39%, 24%), pneumonia (27%, 17%), abdominal pain (22%, 13%), arthralgia (14%, 10%), decreased appetite (13%, 6%), febrile neutropenia (12%, 8%), dizziness (11%, 9%), pain in extremity (11%, 5%).

LACTATION

There are no data regarding the presence of azacitidine in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with ONUREG® and for 1 week after the last dose.

Please see the Brief Summary of full Prescribing Information for ONUREG® on the following pages.

References: 1. ONUREG® [Prescribing Information]. Summit, NJ: Celgene Corporation; 2021. 2. U.S. Food and Drug Administration approves Onureg® (azacitidine tablets), a new oral therapy, as continued treatment for adults in first remission with acute myeloid leukemia [press release]. Bristol Myers Squibb website. https://news.bms.com/news/corporate-financial/2020/U.S.-Food-and-Drug-Administration-Approves-Onureg-azacitidine-tablets-a-New-Oral-Therapy-as-Continued-Treatment-for-Adults-in-First-Remission-with-Acute-Myeloid-Leukemia/default.aspx. Published September 1, 2020. Accessed August 18, 2021.



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08/21 2011-US-2100164



Learn more, sign up for updates, and find out how to access ONUREG® at

ONUREGpro.com/explore

$mode{ONUREG}^{\ensuremath{\mathbb{R}}}$ (azacitidine) tablets, for oral use

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

ONUREG (azacitidine) is indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

DOSAGE AND ADMINISTRATION

Important Administration Information

Do not substitute ONUREG for intravenous or subcutaneous azacitidine. The indications and dosing regimen for ONUREG differ from that of intravenous or subcutaneous azacitidine [see Warnings and Precautions].

Recommended Dosage

The recommended dosage of ONUREG is 300 mg orally once daily with or without food on Days 1 through 14 of each 28-day cycle. Continue ONUREG until disease progression or unacceptable toxicity.

Administer an antiemetic 30 minutes prior to each dose of ONUREG for the first 2 cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting.

If the absolute neutrophil count (ANC) is less than 0.5 Gi/L on Day 1 of a cycle, do not administer ONUREG. Delay the start of the cycle until the ANC is 0.5 Gi/L or more. Instruct patients on the following:

- · Swallow tablets whole. Do not cut, crush, or chew the tablets.
- Take a dose about the same time each day.
- If a dose of ONUREG is missed, or not taken at the usual time, take the dose as soon
 as possible on the same day, and resume the normal schedule the following day.
 Do not take 2 doses on the same day.
- If a dose is vomited, do not take another dose on the same day. Resume the normal schedule the following day.

ONUREG is a hazardous drug. Follow applicable special handling and disposal procedures.¹

Monitoring and Dosage Modifications for Adverse Reactions

Monitor complete blood count every other week for the first 2 cycles and prior to the start of each cycle thereafter. Increase monitoring to every other week for the 2 cycles after any dose reduction for myelosuppression.

The recommended dosage modifications for adverse reactions are provided in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Recommended Dosage Modification
Myelosuppression [see Warnings and Precautions]	Neutrophils less than 0.5 Gi/L on Cycle Day 1	Interrupt treatment. Resume at the same dose once neutrophils return to 0.5 Gi/L or higher.
	Neutrophils less than 1 Gi/L with fever at anytime	First Occurrence Interrupt treatment. Resume at the same dose once neutrophils return to 1 Gi/L or higher. Occurrence in 2 Consecutive Cycles Interrupt treatment. After neutrophils return to 1 Gi/L or higher, resume at reduced dose of 200 mg. If a patient continues to experience febrile neutropenia after dose reduction, reduce the treatment duration by 7 days. If febrile neutropenia reoccurs after dose and schedule reduction, discontinue ONUREG.
	Platelets less than 50 Gi/L with bleeding	First Occurrence Interrupt dose. Resume at the same dose once platelets return to 50 Gi/L or higher. Occurrence in 2 Consecutive Cycles Interrupt dose. After platelets return to 50 Gi/L or higher, resume at reduced dose of 200 mg. If a patient continues to experience thrombocytopenia with bleeding after dose reduction, reduce the treatment duration by 7 days. If thrombocytopenia with bleeding reoccurs after dose and schedule reduction, discontinue ONUREG.

(Continued)

Table 1: Recommended Dosage Modifications for Adverse Reactions (Continued)

Adverse Reaction	Severity	Recommended Dosage Modification	
Gastrointestinal Toxicity <i>[see</i> <i>Adverse Reactions]</i>	Grade 3 or 4 Nausea or Vomiting	Interrupt dose. Resume at the same dose one toxicity has resolved to Grade 1 or lower. If toxicity reoccurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. If a patient continues to experience the toxici after dose reduction, reduce the treatment duration by 7 days. If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG (azacitidine).	
	Grade 3 or 4 Diarrhea	Interrupt dose. Resume at the same dose once toxicity has resolved to Grade 1 or lower. If toxicity reoccurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG.	
Other Adverse Reactions [see Adverse Reactions]	Grade 3 or 4	Interrupt dose and provide medical support. Resume at the same dose once toxicity has resolved to Grade 1 or lower. If toxicity re-occurs, interrupt dose until resolved to Grade 1 or lower. Resume at reduced dose of 200 mg. If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. If the toxicity continues or reoccurs after dose and schedule reduction, discontinue ONUREG.	

CONTRAINDICATIONS

ONUREG is contraindicated in patients with known severe hypersensitivity to azacitidine or its components [see Adverse Reactions and Description (11) in full Prescribing Information].

WARNINGS AND PRECAUTIONS

Risks of Substitution with Other Azacitidine Products

Due to substantial differences in the pharmacokinetic parameters [see Clinical Pharmacology (12.3) in full Prescribing Information], the recommended dose and schedule for ONUREG are different from those for the intravenous or subcutaneous azacitidine products. Treatment of patients using intravenous or subcutaneous azacitidine at the recommended dosage of ONUREG may result in a fatal adverse reaction. Treatment of patients using ONUREG at the doses recommended for intravenous or subcutaneous azacitidine may not be effective.

Do not substitute ONUREG for intravenous or subcutaneous azacitidine [see Dosage and Administration].

Myelosuppression

New or worsening Grade 3 or 4 neutropenia and thrombocytopenia occurred in 49% and 22% of patients who received ONUREG, respectively. Febrile neutropenia occurred in 12%. A dose reduction was required for 7% and 2% of patients due to neutropenia and thrombocytopenia, respectively. Less than 1% of patients discontinued ONUREG due to either neutropenia or thrombocytopenia.

Monitor complete blood counts and modify the dosage as recommended [see Dosage and Administration]. Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs.

Increased Early Mortality in Patients with Myelodysplastic Syndromes

In AZA-MDS-003 (NCT01566695), 216 patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to myelodysplastic syndromes were randomized to ONUREG or placebo. One-hundred and seven patients received a median of 5 cycles of ONUREG 300 mg daily for 21 days of a 28-day cycle. Enrollment was discontinued early due to a higher incidence of early fatal and/or serious adverse reactions in patients who received ONUREG compared with placebo. The most frequent fatal adverse reaction was sepsis. The safety and effectiveness of ONUREG for treatment of myelodysplastic syndromes have not been established. Treatment of patients with myelodysplastic syndromes with ONUREG is not recommended outside of controlled trials.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ONUREG can cause fetal harm when administered to a pregnant woman. Azacitidine administered to pregnant rats via a single intraperitoneal dose less than the recommended human daily dose of oral azacitidine on a mo/m² basis caused fetal death and anomalies.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONUREG and for at

least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG (azacitidine) and for at least 3 months after the last dose [see Use in Specific Populations].

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

Myelosuppression [see Warnings and Precautions]

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.

Acute Myeloid Leukemia

The safety of ONUREG was evaluated in QUAZAR [see Clinical Studies (14) in full Prescribing Information]. Patients received ONUREG 300 mg (N=236) or placebo (N=233) orally once daily on Days 1 through 14 of each 28-day cycle. Among patients who received ONUREG, 71% were exposed for 6 months or longer, and 49% were exposed for greater than one year. The median duration of exposure to ONUREG was 11.6 months (range: 0.5 to 74.3 months) and the median number of cycles was 12 (range: 1 to 82 cycles).

Serious adverse reactions occurred in 15% of patients who received ONUREG. Serious adverse reactions in \geq 2% of patients who received ONUREG were pneumonia (8%) and febrile neutropenia (7%). One fatal adverse reaction (sepsis) occurred in a patient who received ONUREG.

Permanent discontinuation of ONUREG due to an adverse reaction occurred in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ONUREG in > 1% of patients included nausea (2.1%), diarrhea (1.7%), and vomiting (1.3%). Interruptions of ONUREG due to an adverse reaction occurred in 35% of patients. Adverse reactions which required an interruption of ONUREG in > 5% of patients included neutropenia (20%), thrombocytopenia (8%), and nausea (6%).

Dose reductions of ONUREG due to an adverse reaction occurred in 14% of patients. Adverse reactions which required a dose reduction in > 1% of patients included neutropenia (6%), diarrhea (3.4%), thrombocytopenia (1.7%), and nausea (1.7%).

The most common (≥ 10%) adverse reactions were nausea, vomiting, diarrhea, fatigue/asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness, and pain in extremity.

Table 2 summarizes the adverse reactions in QUAZAR.

Table 2: Adverse Reactions (≥ 5%) in Patients with AML Who Received ONUREG with a Difference Between Arms of > 2% Compared to Placebo in QUAZAR

Adverse Reaction		UREG =236)	Placebo (N=233)		
Auverse Reaction	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	
Gastrointestinal disorders					
Nausea	65	3	24	< 1	
Vomiting	60	3	10	0	
Diarrhea	50	5	21	1	
Constipation	39	1	24	0	
Abdominal pain ^a	22	2	13	< 1	
General disorders and admin	istration site	conditions			
Fatigue/astheniab	44	4	25	1	
Infections					
Pneumonia ^c	27	9	17	5	
Musculoskeletal and connec	tive tissue di	sorders			
Arthralgia	14	1	10	< 1	
Pain in extremity	11	< 1	5	0	
Metabolism and nutrition dis	orders				
Decreased appetite	13	1	6	1	
Blood and lymphatic disorde	rs				
Febrile neutropenia	12	11	8	8	
Nervous system disorders					
Dizziness	11	0	9	0	

 $^{^{\}rm a}$ Grouped term includes abdominal pain, abdominal pain upper, abdominal discomfort, and aastrointestinal pain.

Clinically relevant adverse reactions that did not meet criteria for inclusion in Table 2 were weight decreased (4%) in patients who received ONUREG (azacitidine).

Neutropenia, thrombocytopenia, and anemia of any grade occurred in 74%, 65%, and 25% of patients treated with ONUREG. Table 3 summarizes select Grades 3 or 4 hematological laboratory abnormalities in QUAZAR.

Table 3: Selected Hematological Laboratory Abnormalities That Worsened from Baseline in Patients Who Received ONUREG in QUAZAR

	ON	UREG	Placebo		
Laboratory Abnormality	Baseline Grade 0-2 N	Post-Baseline Grade 3 or 4 n (%)	Baseline Grade 0-2 N	Post-Baseline Grade 3 or 4 n (%)	
Neutropenia	223	109 (49)	217	50 (23)	
Thrombocytopenia	222	46 (21)	212	22 (10)	
Anemia	229	10 (4)	223	7 (3)	

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of intravenous or subcutaneous azacitidine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity reaction
- · Interstitial lung disease
- Tumor lysis syndrome
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Necrotizing fasciitis (including fatal cases)
- · Differentiation syndrome

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action [see Clinical Pharmacology (12.1) in full Prescribing Information] and findings in animals, ONUREG can cause fetal harm when administered to a pregnant woman. There are no available data on ONUREG use in pregnant women to evaluate for a drug-associated risk. Azacitidine was teratogenic and caused embryo-fetal lethality in animals at doses less than the recommended human daily dose of oral azacitidine on a mg/m² basis (see Data). Advise pregnant women of the potential risk to the fetus.

The estimated background of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No reproductive or developmental toxicity studies have been conducted with oral azacitidine.

Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single intraperitoneal injection of 6 mg/m² azacitidine (at doses less than the recommended human daily dose of oral azacitidine on a mg/m² basis) on gestation Day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation Day 15 at doses of approximately 3 to 12 mg/m² (at doses less than the recommended human daily dose of oral azacitidine on a mg/m² basis).

In rats, azacitidine was clearly embryotoxic when given an intraperitoneal injection on gestation Days 4 to 8 (postimplantation) at a dose of 6 mg/m² (at doses less than the recommended human daily dose on a mg/m² basis), although treatment in the preimplantation period (on gestation Days 1 to 3) had no adverse effect on the embryos. Azacitidine caused multiple fetal abnormalities in rats after a single intraperitoneal dose of 3 to 12 mg/m² (at doses less than the recommended human daily dose on a mg/m² basis) given on gestation Days 9, 10, 11, or 12. In this study, azacitidine caused fetal death when administered at 3 to 12 mg/m² on gestation Days 9 and 10; average live animals per litter was reduced to 9% of control at the highest dose on gestation Day 9. Fetal anomalies included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly), and others (micrognathia, gastroschisis, edema, and rib abnormalities).

Lactation

Risk Summary

There are no data regarding the presence of azacitidine in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with ONUREG and for 1 week after the last dose.

Females and Males of Reproductive Potential

ONUREG can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations].

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential before starting ONUREG.

^b Grouped term includes fatigue and asthenia.

^c Broad scope term includes influenza, pneumonia, respiratory tract infection, respiratory tract infection viral, bronchopulmonary aspergillosis, lung infection, Staphylococcal infection, atypical pneumonia, lower respiratory tract infection, lung abscess, Pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia fungal, Pseudomonas infection, hemoptysis, productive cough, pleural effusion, atelectasis, pleuritic pain, rales, Enterobacter test positive, and Hemophilus test positive.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with ONUREG (azacitidine) and for at least 6 months after the last dose.

Mala

Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG and for at least 3 months after the last dose.

Infertility

Based on animal data, ONUREG may impair male or female fertility [see Nonclinical Toxicology (13.1) in full Prescribing Information].

Pediatric Use

The safety and effectiveness of ONUREG in pediatric patients have not been established.

Geriatric Use

Of the 238 patients in QUAZAR who received ONUREG, 72% were 65 years of age or older, while 12% were 75 years of age or older. No overall differences in safety or effectiveness of ONUREG were observed between these patients and younger patients.

Renal Impairment

Monitor patients with severe renal impairment (creatinine clearance [CLcr] 15 to 29 mL/min calculated by Cockcroft-Gault formula) more frequently for adverse reactions and modify the ONUREG dosage for adverse reactions [see Dosage and Administration]

No dose adjustment of ONUREG is recommended for patients with mild to severe renal impairment (CLcr 15 to 89 mL/min) [see Clinical Pharmacology (12.3) in full Prescribing Information].

Hepatic Impairment

ONUREG has not been studied in patients with pre-existing severe hepatic impairment (total bilirubin $> 3 \times \text{ULN}$).

A recommended dosage of ONUREG has not been established for patients with moderate hepatic impairment (total bilirubin > 1.5 to $3 \times ULN$).

No dose adjustment of ONUREG is recommended for patients with mild hepatic impairment (total bilirubin \leq ULN and AST > ULN, or total bilirubin 1 to 1.5 \times ULN and any AST) [see Clinical Pharmacology (12.3) in full Prescribing Information].

PATIENT COUNSELING INFORMATION

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

Myelosuppression

Advise patients of the risk of myelosuppression with ONUREG and of the need to monitor complete blood counts before and during treatment [see Warnings and Precautions].

Gastrointestinal Toxicity

Advise patients of the risk of gastrointestinal toxicity with ONUREG (azacitidine) and of the potential need to use anti-emetic or anti-diarrheal medications during treatment [see Adverse Reactions].

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions, Use in Specific Populations].

Advise females of reproductive potential to use effective contraception during treatment with ONUREG and for at least 6 months after the last dose [see Use in Specific Populations].

Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG and for at least 3 months after the last dose [see Use in Specific Populations].

Lactation

Advise women not to breastfeed during treatment with ONUREG and for 1 week after the last dose [see Use in Specific Populations].

Administration

Advise patients to take ONUREG with or without food at about the same time each day and how to make up a missed or vomited dose. Advise patients to swallow tablets whole. Advise patients not to cut, crush, or chew the tablets [see Dosage and Administration].

Storage Instructions

Advise patients to keep ONUREG in the original container (bottles or blisters). If bottles are dispensed, advise patients to keep the container tightly closed with both desiccant canisters inside and to not eat the desiccant canisters [see How Supplied/Storage and Handling (16) in full Prescribing Information].

REFERENCES

"OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

Manufactured by: Celgene Corporation A Wholly Owned Subsidiary of Bristol Myers Squibb 86 Morris Avenue Summit, NJ 07901

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ONUPI.003 May 2021

2011-US-2100077 05/2021

راأا Bristol Myers Squibb

NCODA, THE MEDICALLY INTEGRATED TEAM & POSITIVE QUALITY INTERVENTION:

LEADING THE WAY TO BETTER PATIENT CARE

o promote higher quality patient care, NCODA created the NCODA Positive Quality Intervention (PQI), a peer-reviewed clinical guidance document for healthcare providers. PQIs provide quality standards and effective practices around a specific aspect of cancer care.

The goal of the PQI is to equip the entire multidisciplinary team with a sophisticated yet simple-to-use resource for managing patients receiving IV or oral oncolytics. The PQI in Action article explores how two medically integrated teams incorporate the PQI as part of their daily workflow and manage specific drug therapies.

The multidisciplinary teams at Seattle Cancer Care Alliance (SCCA) and Georgia Cancer Specialists (GCS) recently participated in the **Enfortumab** Vedotin (Padcev®) Management For Advanced Or Metastatic Urothelial Carcinoma POI in Action. Team members discussed the benefits of the multidisciplinary team, patient management on enfortumab vedotin and the value of NCODA's POI resource.

Enfortumab vedotin is a Nectin-4-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer 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.1

The enfortumab vedotin PQI principles include reviewing adverse events and suggested interventions, reviewing dose specific adjustments as required, and educating patients on potential toxicities.

Both SCCA and GCS utilize the team approach when treating patients.



The PQI in Action article incorporates the opinions of physicians, advanced practice providers, pharmacists, nurses and pharmacy technicians.

SCCA clinical oncology pharma-

cist Andrew Ruplin, PharmD, authored the Enfortumab Vedotin (Padcev®) Management For Advanced Or Metastatic Urothelial Carcinoma POI.

"I wanted to share the wealth of knowledge we've accumulated on this treatment as one of the original clinical trial sites," Ruplin said. "My colleague, Evan Yu, MD, was an author on the EV-201 study."

Ruplin said he marveled at the speed that updates and new developments for cancer treatments unfolded during the project.

"Though I wrote the original PQI a little over a year ago, I updated it three

times with new FDA approval information, published data including the phase 3 trial, and even then I realized during the PQI in Action webinar itself that the NCCN emetic risk category had changed," Ruplin said. "It really highlights the need for clinicians to stay abreast of the latest information in the ever-changing field of oncology."

Ruplin said he hopes his PQI in Action article can spur new ideas for both usage of enfortumab vedotin and, more broadly, cancer treatment at NCODA members' hospitals

and clinics.

Ruplin stressed that the PQI in Action was a group effort, and that his physician, nurse, pharma-



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cy technician and advanced practice provider colleagues were invaluable in describing specific interactions with patients on enfortumab vedotin.

▲ NCODA has openings to feature practices in 2021 and 2022 PQI in Action articles for both oral and IV therapies. If you are interested in participating, please contact **Ginger** Blackmon, PharmD, at Ginger.Blackmon@NCODA.org for more information.

REFERENCES

1. Padcev® (enfortumab vedotin- ejfv) [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc.; July 2021.

ACTIVE WEBINAR PARTICIPANTS WANTED!

2:00 to 3:00 p.m. Eastern Time | Every 3rd Thursday of the month

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THE PQI PODCAST OFFERS WEEKLY DISCUSSION **ABOUT ONCOLOGY TOPICS BY INDUSTRY EXPERTS**

he PQI Podcast is the latest addition to NCODA's growing suite of oncology education platforms.

THE

The podcast provides an overview of new Positive **Quality Intervention** (PQI) documents, as well as PQI in Action articles and other oncology topics.

Each week on The PQI Podcast, host Ginger Blackmon, PharmD — NCODA's Manager of Patient-Centered Communications chats with experts from the oncology community about clinical, operational and patient interest topics.

The podcast kicked off with the Rx to Go management team from Florida Cancer Specialists and Research Institute, including Ray Bailey, RPh, Kathy Hogan, RPh, and Natasha Khrystolubova, RPh, BPharm, BCOP. The team discussed the benefits of Medically

Integrated Pharmacy (MIP), patient-centered care and staff training, as well as recollected amusing stories from their early days in the pharmacy.

> Succeeding episodes have covered such topics as pharmacogenomics, breast cancer, women's health, equity in oncology, pharmacy students, the Oncology Pharmacy Technician Association and more.

Guests have ranged from John Marshall, MD, of Georgetown University and his wife Liza, a breast cancer survivor, to Saundra Pelletier, CEO of Evofem Biosciences.

Podcast participants have heard an important message from Carmen Guerra, MD, MSCE, FACP, Associate Director of Diversity and Outreach at the Abramson Cancer Center at the University of Pennsylvania.

Other guests have included influential pharmacists, such as Michael Schuh, PharmD, MBA, FAPhA of the Mayo

Clinic, and pharmacy technicians like OPTA leaders Taryn Newsome, CPhT, and Becki Tinder, CPhT.

This is just the beginning of NCODA's podcast journey. We hope you will join us along the way as we bring you messages from oncology centers across the country, inspirational stories of survival and conversations on how working together will only make us stronger in the fight against cancer. The heart of this podcast is our patients, and we hope you will join us each week as we move forward.

You can find the podcast on Apple and Spotify by searching The PQI Podcast. Don't forget to subscribe.

You can also find it on our website at NCODA.org and follow us on Instagram @thepqipodcast.

▲ Have a topic or speaker recommendation for The PQI Podcast? We would love to hear from our members. Email Ginger.Blackmon@NCODA.org.



NCODA'S POSITIVE QUALITY INTERVENTION IN ACTION

ZANUBRUTINIB (BRUKINSA®) PATIENT SELECTION AND MANAGEMENT IN MANTLE CELL LYMPHOMA





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WHEN HER2+ MBC PROGRESSES

PURSUE UNPRECEDENTED SURVIVAL

TUKYSA + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine¹

Reduced risk of disease progression or death by 46%

Median PFS: 7.8 months (95% CI: 7.5-9.6) vs 5.6 months (95% CI: 4.2-7.1); HR = 0.54 (95% CI: 0.42-0.71); *P* < 0.00001

Extended median OS by 4.5 months

Median OS: 21.9 months (95% CI: 18.3-31.0) vs 17.4 months (95% CI: 13.6-19.9); HR = 0.66 (95% CI: 0.50-0.87); P = 0.0048

The trial studied patients who had received prior trastuzumab, pertuzumab, and T-DM1 in the neoadjuvant, adjuvant, or metastatic setting.¹

TUKYSAhcp.com

Indication

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Select Safety Information

Warnings and Precautions

• Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.

If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; T-DM1 = ado-trastuzumab emtansine.

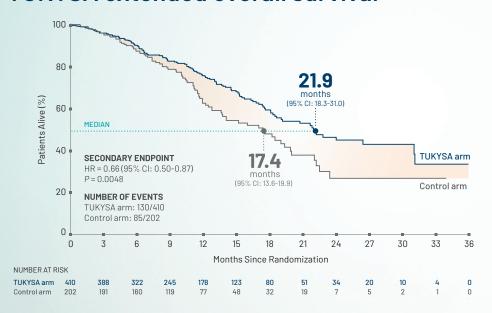




RAISING THE STANDARD FOR SURVIVAL

In combination with trastuzumab + capecitabine

TUKYSA extended overall survival*1





The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash¹

Important Safety Information Warnings and Precautions

- Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.
- If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.
- Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

• Embryo-Fetal Toxicity: TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in $\geq\!2\%$ of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in $\geq 1\%$ of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; those occurring in $\geq 2\%$ of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

In combination with trastuzumab + capecitabine

TUKYSA reduced the risk of disease progression or death

PRIMARY ENDPOINT*

PFS

46%

reduction in the risk of disease progression or death¹

- HR = 0.54 (95% CI: 0.42-0.71); P < 0.00001
- Median PFS: 7.8 months (95% CI: 7.5-9.6) in the TUKYSA arm vs 5.6 months (95% CI: 4.2-7.1) in the control arm

EXPLORATORY ANALYSIS*†

PFS AT 12 MONTHS

~3x as many patients were progression-free2

TUKYSA ARM

VS

12%

(33.1%; 95% CI: 26.6-39.7)

(12.3%; 95% CI: 6.0-20.9)

CONTROL ARM

*Study design: HER2CLIMB was a randomized (2:1), double-blind, placebo-controlled trial of 612 patients with HER2+ MBC who received TUKYSA + trastuzumab + capecitabine (TUKYSA arm; n = 410) or placebo + trastuzumab + capecitabine (control arm; n = 202). Primary endpoint was PFS (time from randomization to documented disease progression or death from any cause) in the first 480 randomized patients. Secondary endpoints assessed in all randomized patients included OS (time from randomization to death from any cause). PFS was evaluated in accordance with RECIST criteria, version 1.1, by means of BICR.¹

†This exploratory analysis is descriptive only. These are estimates and not exact numbers. HER2CLIMB was not powered to assess a statistical difference between treatment groups at this time point.

BICR = blind independent central review; CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; PPE = palmar-plantar erythrodysesthesia; RECIST = Response Evaluation Criteria in Solid Tumors.

Lab Abnormalities

In HER2CLIMB, Grade \geq 3 laboratory abnormalities reported in \geq 5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST.

The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

Drug Interactions

- Strong CYP3A/Moderate CYP2C8 Inducers: Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.
- Strong or Moderate CYP2C8 Inhibitors: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.
- CYP3A Substrates: Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.

• P-gp Substrates: Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

Use in Specific Populations

- Lactation: Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.
- Renal Impairment: Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.
- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. TUKYSA [Prescribing Information]. Bothell, WA: Seagen Inc. April 2020. **2.** Murthy RK, Loi S, Okines A, et al. Supplemental appendix for: Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020;382:597-609.





TUKYSA® (tucatinib) tablets, for oral use

Brief summary of Prescribing Information (PI). See full PI. Rx Only

INDICATIONS AND USAGE

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of TUKYSA is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity.

Advise patients to swallow TUKYSA tablets whole and not to chew, crush, or split prior to swallowing. Advise patients not to ingest tablet if it is broken, cracked, or not otherwise intact. Advise patients to take TUKYSA approximately 12 hours apart and at the same time each day with or without a meal. If the patient vomits or misses a dose of TUKYSA, instruct the patient to take the next dose at its usual scheduled time.

When given in combination with TUKYSA, the recommended dosage of capecitabine is 1000 mg/m² orally twice daily taken within 30 minutes after a meal. TUKYSA and capecitabine can be taken at the same time. Refer to the Full Prescribing Information for trastuzumab and capecitabine for additional information.

Dosage Modifications for Adverse Reactions

The recommended TUKYSA dose reductions and dosage modifications for adverse reactions are provided in Tables 1 and 2. Refer to the Full Prescribing Information for trastuzumab and capecitabine for information about dosage modifications for these drugs.

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

Dose Reduction	Recommended TUKYSA Dosage
First	250 mg orally twice daily
Second	200 mg orally twice daily
Third	150 mg orally twice daily

Permanently discontinue TUKYSA in patients unable to tolerate 150 mg orally twice daily.

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

Severity TUKYSA Dosage Modification				
Diarrhea ¹				
Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.			
Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.			
Grade 4	Permanently discontinue TUKYSA.			
Hepatotoxicity ^{1,2}				
Grade 2 bilirubin (>1.5 to $3 \times ULN$)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.			
Grade 3 ALT or AST (> 5 to $20 \times ULN$) OR Grade 3 bilirubin (> 3 to $10 \times ULN$)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.			
Grade 4 ALT or AST (> 20 × ULN) OR Grade 4 bilirubin (> 10 × ULN)	Permanently discontinue TUKYSA.			
ALT or AST > 3 × ULN AND Bilirubin > 2 × ULN	Permanently discontinue TUKYSA.			
Other adverse reactions ¹				
Grade 3	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.			
Grade 4	Permanently discontinue TUKYSA.			

Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03

Dosage Modifications for Severe Hepatic Impairment: For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 200 mg orally twice daily.

Dosage Modifications for Concomitant Use with Strong CYP2C8 Inhibitors: Avoid concomitant use of strong CYP2C8 inhibitors with TUKYSA. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 100 mg orally twice daily. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume the TUKYSA dose that was taken prior to initiating the inhibitor.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase > 5 × ULN, 6% had an AST increase > 5 × ULN, and 1.5% had a bilirubin increase > 3 × ULN (Grade \ge 3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy and contraception information.

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.

HER2-Positive Metastatic Breast Cancer (HER2CLIMB)

The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm.

Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in $\geq 2\%$ of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in \geq 1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in \geq 2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Table 3: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

Adverse Reaction	TUKYSA + Trastuzumab + Capecitabine (N = 404)			Placebo + Trastuzumab + Capecitabine (N = 197)		
		Grade (%)		Grade (%)		
	All	3	4	All	3	4
Gastrointestinal disor	ders					
Diarrhea	81	12	0.5	53	9	0
Nausea	58	3.7	0	44	3	0
Vomiting	36	3	0	25	3.6	0
Stomatitis ¹	32	2.5	0	21	0.5	0
Skin and subcutaneo	us tissue	disorders				
Palmar-plantar erythrodysesthesia syndrome	63	13	0	53	9	0
Rash ²	20	0.7	0	15	0.5	0
Hepatobiliary disorders						
Hepatotoxicity ³	42	9	0.2	24	3.6	0
Metabolism and nutrition disorders						
Decreased appetite	25	0.5	0	20	0	0

Abbreviations: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Adverse Reaction	TUKYSA + Trastuzumab + Capecitabine (N = 404)		Placebo + Trastuzumab + Capecitabine (N = 197)			
		Grade (%)		Grade (%)		
	All	3	4	All	3	4
Blood and lymphatic	system di	isorders				,
Anemia ⁴	21	3.7	0	13	2.5	0
Musculoskeletal and	connectiv	e tissue c	lisorders			
Arthralgia	15	0.5	0	4.6	0.5	0
Investigations		,				,
Creatinine increased ⁵	14	0	0	1.5	0	0
Weight decreased	13	1	0	6	0.5	0
Nervous System Disc	rders					
Peripheral neuropathy ⁶	13	0.5	0	7	1	0
Respiratory, thoracic	and medi	astinal di	sorders			
Epistaxis	12	0	0	5	0	0

- Stomatitis includes stomatitis, oropharyngeal pain, oropharyngeal discomfort, mouth ulceration, oral pain, lip ulceration, glossodynia, tongue blistering, lip blister, oral dysesthesia, tongue ulceration, and aphthous ulcer
- Rash includes rash maculo-papular, rash, dermatitis acneiform, erythema, rash macular, rash papular, rash pustular, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plantar erythema, skin toxicity, and dermatitis
- Hepatotoxicity includes hyperbilirubinemia, blood bilirubin increased, bilirubin conjugated increased, alanine aminotransferase increased, transaminases increased, hepatotoxicity, aspartate aminotransferase increased, liver function test increased, liver injury, and hepatocellular injury
- 4. Anemia includes anemia, hemoglobin decreased, and normocytic anemia
- 5. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function
- Peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Table 4: Laboratory Abnormalities ($\ge 20\%$) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of $\ge 5\%$ Compared to Placebo in HER2CLIMB

	TUKYSA + Tr + Capecitabi		Placebo + Tr + Capecitabi			
	All Grades %	Grades ≥3 %	All Grades %	Grades ≥3 %		
Hematology						
Decreased hemoglobin	59	3.3	51	1.5		
Chemistry	Chemistry					
Decreased phosphate	57	8	45	7		
Increased bilirubin	47	1.5	30	3.1		
Increased ALT	46	8	27	0.5		
Increased AST	43	6	25	1		
Decreased magnesium	40	0.8	25	0.5		
Decreased potassium ²	36	6	31	5		
Increased creatinine ³	33	0	6	0		
Decreased sodium ⁴	28	2.5	23	2		
Increased alkaline phosphatase	26	0.5	17	0		

- 1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NCI-CTCAE v.4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NCI CTCAE v5.0).
- 2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
- 3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
- 4. There is no definition for Grade 2 in CTCAE v.4.03.

Increased Creatinine: The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

DRUG INTERACTIONS

Effects of Other Drugs on TUKYSA

Strong CYP3A Inducers or Moderate CYP2C8 Inducers: Concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inducer decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inducer.

Strong or Moderate CYP2C8 Inhibitors: Concomitant use of TUKYSA with a strong CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

Effects of TUKYSA on Other Drugs

CYP3A Substrates: Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates,

where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

P-glycoprotein (P-gp) Substrates: Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy information. Based on findings in animals and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

Lactation

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information. There are no data on the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfed during treatment with TUKYSA and for at least 1 week after the last dose.

Females and Males of Reproductive Potential

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for contraception and infertility information.

<u>Pregnancy Testing</u>: Verify the pregnancy status of females of reproductive potential prior to initiating treatment with TUKYSA.

Contraception:

Females: Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

<u>Infertility:</u> Based on findings from animal studies, TUKYSA may impair male and female fertility.

Pediatric Use: The safety and effectiveness of TUKYSA in pediatric patients have not been established.

Geriatric Use: In HER2CLIMB, 82 patients who received TUKYSA were \geq 65 years, of whom 8 patients were \geq 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients \geq 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and \geq 65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients \geq 65 years compared to younger patients. There were too few patients \geq 75 years to assess differences in effectiveness or safety.

Renal Impairment: The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min estimated by Cockcroft-Gault Equation), because capecitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capecitabine for additional information in severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min).

Hepatic Impairment: Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Seagen®

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SUBCOMMITTEES HELP DRIVE REVIEW, MAINTENANCE, EDUCATIONAL SUPPORT & TRANSLATION OF OCE SHEETS

n an era where oral oncology treatment options make up a large portion of newly developed oncology agents, finding reliable and patient-friendly resources is essential for both healthcare providers and patients.

To simplify this pro-

cess, NCODA established

Education (OCE) commit-

the Oral Chemotherapy

tee in 2016. In collaboration with the Association of Community Cancer
Centers (ACCC), the Hematology/Oncology Pharmacy Association (HOPA), and the Oncology Nursing
Society (ONS), NCODA provides upto-date, drug-specific OCE sheets. These documents are used internationally and generate more than 34,000 page views

The OCE sheets contain accurate, easy-to-understand information. Each drug-specific OCE sheet includes:

- ▲ Information on the drug name;
- FDA-approved uses;

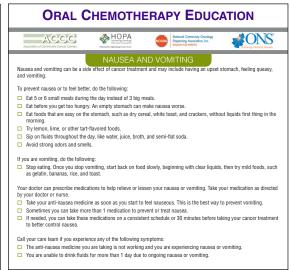
per month.

- ▲ Dose and schedule;
- ▲ Storage and handling;
- ▲ Body fluid/waste handling procedures;
- ▲ Drug and food interactions;
- Side effects and management;
- ▲ Pregnancy, sexual activity and contraception recommendations;
- ▲ Methods to obtain medication; and
- ▲ Additional resource instructions.

The OCE sheets aim to be as informative as possible, while still being concise resources for patients to utilize.

To accomplish this, the OCE sheets discuss side effects reported in approxi-





At left, an OCE sheet for Capecitabine. Above, a supplemental OCE sheet on Nausea and Vomiting.

mately 30% or greater of patients and any warnings or precautions.

To ensure the sheets are easy to understand for all patients, the goal is for them to be at an eighth-grade reading level or lower.

The OCE committee has expanded in recent years to provide more comprehensive educational materials for patients and healthcare providers. The committee is comprised of three distinct arms: OCE sheet development and maintenance, supplemental sheets and language support.

1. The OCE development and maintenance subcommittee is responsible for the initial review of OCE sheets and periodic audit reviews. Each OCE sheet goes through an extensive initial review to ensure the document contains accurate and patient-friendly educational information followed by ongoing reviews to ensure that they contain the most accurate, up-to-date information. This process includes all four guiding organizations – NCODA, ACCC, HOPA and ONS.

2. The OCE supplemental sheets subcommittee

is responsible for developing additional educational materials to support a patient's treatment journey. These include documents such as side effect management sheets, treatment calendar templates, safe handling documents, and more.

3. The OCE language support subcommittee

oversees translation initiatives. For the most effective education to occur, the availability of educational materials in the patient's preferred language is crucial. The subcommittee's most recent endeavor is translating OCE sheets into Spanish. Spanish versions of the most commonly used sheets are currently available on the OCE website. The committee is continuing to work on making more Spanish OCE sheets available.

All OCE sheets can be found online at **oralchemoedsheets.com**.

▲ The OCE committee is always looking for new members with innovative ideas to help deliver accurate, yet understandable information to patients. To get involved, contact **Marie Sirek**, PharmD, BCACP, at msirek@billingsclinic.org or **Julianne Darling**, PharmD, BCOP, at Julianne.Darling@NCODA.org.

48 ONCOLYTICS TODAY FALL 2021

MANAGING ADHERENCE IN ORAL CHEMOTHERAPY PATIENTS:

A TEAM-BASED APPROACH FOR OUTPATIENT CLINICS

By Shawn Costanzo, BSN, RN, OCN

hile oral anticancer therapies have been around since 1953, oral formulations are now being developed at a record pace, so much so that they have become the primary form of treatment for many cancers.

Oral therapies currently make up 25%-35% of oncology drugs in the drug pipeline, and that



number is anticipated to grow each year.

With this increase in development comes a challenge on how to manage these patients in the

Shawn Costanzo

outpatient clinic setting. It is imperative that patients adhere to their therapy to maximize effectiveness and create better outcomes.

I am the oral oncolytic nurse navigator for AdventHealth Hendersonville Cancer Services in Henderson, North Carolina.

In our clinics, I manage patients on oral anticancer treatment plans, assist with financial concerns, educate, and perform adherence and toxicity checks when a patient starts a new oral regimen. I follow patients weekly for the first month and monthly thereafter.

When a patient starts a new oral therapy, I rely on the clinic RNs to let me know how the patient is doing and if interventions are needed when they come in for an office visit or call the nurse triage line.

When I conducted a survey of nurses within our four clinics, an overwhelming 95% stated they were more familiar with IV treatments and lacked the knowledge on oral therapies; there-



Oral chemotherapy is a double-edged sword; while convenient for patients, it also can be confusing. Patient education and adherence monitoring now have become essential nursing responsibilities.

fore, many nurses do not feel prepared to educate patients.

EDUCATION IS CRITICAL

Education has become a critical issue. Traditionally, the physician goes over the treatment plan with the patient.

Because of the many new combination IV/oral treatment plans, it is now vital for infusion and clinic RNs to become knowledgeable about the side effects and toxicities that come with oral treatment plans so they can properly counsel patients and family members.

Many clinicians believe oral oncolytic drugs are less toxic than traditional IV therapy. However, oral therapies are associated with a wide variety of adverse events that can be life-threatening.¹

As nurses become educated on oral oncolytic drugs, they are more likely to assist patients with their adherence.

Taking medication at home can be very appealing to some patients. It gives them more flexibility with their schedule, eliminates transportation issues, avoids unnecessary venous access, allows

time for recreational travel and improves quality of life. With an oral treatment plan, patients no longer need to spend hours receiving infusions in the clinic.

But with these benefits also come barriers. Patients and clinicians face new challenges in managing their oral anticancer treatment in the home setting.

With traditional IV therapies, nurses and physicians oversee the entire administration process from beginning to end.

With oral treatments, we rely on the patient to administer at home correctly and safely. Patient adherence to their treatment plan is an area of concern for clinics due to the lack of staff who are knowledgeable in oral anticancer drugs and dedicated to managing oral oncolytic patients.²

FALLING THROUGH THE CRACKS

Clinic nurses are now challenged with the growing number of patients prescribed oral therapies and their need for specialized drug education.² Many clinics cannot afford an oral oncolytic nurse navigator, and therefore these

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NURSING

ADHERENCE

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patients can fall through the cracks.

Oral anticancer therapy is frequently not given the same focused attention to education and consent as the traditional IV therapy, which poses a risk to patient safety. Patients not properly adhering to therapy may experience disease progression and increased mortality rates.³

Some of the factors that determine non-adherence are little to no education, regimen complexity, side effects, toxicity, confusion and forgetfulness.⁴ Patients often will not report when they are having side effects and simply stop taking their oral chemotherapy.

Without close follow-up, the oncologist will not find out about the patient discontinuing use until they come in for a visit. Side effects such as nausea, fatigue and mouth sores are high on the list of reasons patients discontinue their therapy.⁵

The American Society of Clinical Oncology (ASCO) updated its safety standards in 2013 to include oral oncolytic drugs. ASCO guidelines outline the need for patient monitoring for adherence and toxicity.⁶

ANOTHER LAYER OF RESPONSIBILITY

Oncology nurses must become familiar with these oral anticancer therapies, which adds another layer of responsibility to their already busy plates. Even if the clinic has a dedicated oral oncolytic navigator, all nurses have a duty to make sure patients are adhering to their therapy.

Elizabeth Bettencourt, MSN, RN, OCN, an oral oncolytic nurse navigator at Palo Alto Medical Foundation in Sunnyvale, California, is the main point of contact for oral chemotherapy patients within her clinics.

Bettencourt provides the initial patient education and performs follow-up adherence checks within three to seven days of start date, weekly for three weeks and then monthly for another five months.

Registered nurses in the clinics

Adherence will always be a hurdle, but with an organized, team-based approach, clinics can better facilitate a comprehensive oral oncolytic plan.

are involved in other aspects of patient follow-up, such as virtual and in-person monitoring.

"Helping patients with adherence is always a challenge," Bettencourt notes.

"Use of Oral Chemotherapy Education (OCE) drug sheets and standardized education material helps both the patient and the care team."



Bettencourt also points out that the use of patient-specific instructions, calendars, smart device apps and more frequent follow-up assessments have helped keep patients on track and assisted clinic RNs in managing patient side effects.

NURSE EDUCATION PROGRAMS

Creating a good nursing education program can be challenging due to time constraints. Creating drug specific education sheets and drug infographics for nurses to reference can be helpful in quickly getting information disseminated.

Coordinating with nurse educators and drug representatives to schedule in-service training for frequently used drugs also can be very beneficial to nurses.

Many other resources are available online to assist patients with adherence.

The NCODA Nursing Committee, for example, is dedicated to promoting patient safety and providing resources to assist in support of patients taking oral anticancer drugs.

The committee has created several tools to assist with management of patients taking oral oncolytic drugs. NCODA members may access and download these resources at no cost.

Dealing with an oral anticancer treatment must be a team effort. It is essential that nurses, physicians, pharmacists and family members be involved in making sure the patient is safely adhering to their therapy and not having troublesome side effects.

Non-adherence can result in increased health costs and disease progression. Nurses are in a prime position to take a leadership role and support the patients receiving oral therapy to improve patient outcomes.²

Adherence will always be a hurdle, but with an organized and team-based approach, clinics can better facilitate a comprehensive oral oncolytic plan.

▲ **Shawn Costanzo**, BSN, RN, OCN, is the Oral Oncolytic Nurse Navigator for AdventHealth in Hendersonville, North Carolina.

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24-hour inhibition of BTK was maintained at 100% in PBMCs and 94% to 100% in lymph nodes when taken at the recommended total daily dose of 320 mg. The clinical significance of 100% inhibition has not been established.^{1,2}

STUDY 206 | PET-BASED¹

84% ORR (95% CI: 74, 91)

59% CR

19.5_m

(95% CI: 16.6, NE)

STUDY **003** | CT-BASED¹

84% orr

(95% CI: 67, 95)

22%

18.5_m

(95% CI: 12.6, NE)

Median follow-up time was 18.4 months for Study 206 and 18.8 months for Study 003³

BRUKINSA® (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

The most common adverse reactions (≥ 20%) included neutrophil count decreased, platelet count decreased, upper respiratory tract infection, white blood cell count decreased, hemoglobin decreased, rash, bruising, diarrhea, and cough.

The efficacy of BRUKINSA was IRC-assessed in 2 clinical trials that included a total of 118 adult patients with MCL who received at least 1 prior therapy. Tumor response was according to the 2014 Lugano classification for both studies, and the primary efficacy endpoint was ORR as assessed by an IRC. Study BGB-3111-206 (Study 206): N=86, Phase 2, open-label, global, multicenter, single-arm trial; PET scans were required for response assessment. Study BGB-3111-AU-003 (Study 003): N=32, Phase 1/2, open-label, global, multicenter, single-arm trial; PET scans were not required for response assessment and the majority of patients were assessed by CT scan. BTK=Bruton's tyrosine kinase; Cl=confidence interval; CR=complete response; CT=computed tomography; DOR=duration of response; IRC=independent review committee: NE=not estimable: ORR=overall response rate: PBMCs=peripheral blood mononuclear cells: PET=positron emission tomography.

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

ADVERSE REACTIONS

The most common adverse reactions in > 10% of patients who received BRUKINSA were decreased neutrophil count (53%), decreased platelet count (39%), upper respiratory tract infection (38%), decreased white blood cell count (30%), decreased hemoglobin (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), penumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an

adverse reaction leading to dose reduction (hepatitis B).

DRUG INTERACTIONS

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid coadministration with moderate or strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

References: 1. BRUKINSA [package insert]. BeiGene, Ltd; 2019. 2. Tam C, Trotman J, Opat S, et al. Phase I study of the selective BTK inhibitor canubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. Blood. 2019;134(11):851-869. 3. Data on file. BeiGene, Ltd. 2019.

Please see Brief Summary of full Prescribing Information on the following pages.



BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR BRUKINSA® (zanubrutinib)

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION 1 INDICATIONS AND USAGE

BRUKINSA is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia, and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%), and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

5.6 Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage [see Warnings and Precautions (5.1)]
- Infections [see Warnings and Precautions (5.2)]
- Cytopenias [see Warnings and Precautions (5.3)]
- Second Primary Malignancies [see Warnings and Precautions (5.4)]
- Cardiac Arrhythmias [see Warnings and Precautions (5.5)]

6.1 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 data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single agent at 160 mg twice daily in 524 patients in clinical trials BGB-3111-AU-003, BGB-3111-206, BGB-3111-205, BGB-3111-210, and BGB-3111-1002 and to BRUKINSA at 320 mg once daily in 105 patients in trials BGB-3111-AU-003 and BGB-3111-1002. Among 629 patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 61% were exposed for greater than one year.

In this pooled safety population, the most common adverse reactions in > 10% of patients who received BRUKINSA were neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory tract infection (38%), white blood cell count decreased (30%), hemoglobin decreased (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%).

Mantle Cell Lymphoma (MCL)

The safety of BRUKINSA was evaluated in 118 patients with MCL who received at least one prior therapy in two single-arm clinical trials, BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120] [see Clinical Studies (14.1)]. The median age of patients who received BRUKINSA in studies BGB-3111-206 and BGB-3111-AU-003 was 62 years (range: 34 to 86), 75% were male, 75% were Asian, 21% were White, and 94% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior lines of therapy (range: 1 to 4). The BGB-3111-206 trial required a platelet count $\geq 75 \times 10^9 / L$ and an absolute neutrophil count ≥ 1 x 10⁹/L independent of growth factor support, hepatic enzymes ≤ 2.5 x upper limit of normal, total bilirubin ≤ 1.5 x ULN. The BGB-3111-AU-003 trial required a platelet count $\geq 50 \times 10^9/L$ and an absolute neutrophil count $\geq 1 \times 10^9/L$ independent of growth factor support, hepatic enzymes ≤ 3 x upper limit of normal, total bilirubin \leq 1.5 x ULN. Both trials required a CLcr \geq 30 mL/min. Both trials excluded patients with prior allogeneic hematopoietic stem cell transplant, exposure to a BTK inhibitor, known infection with HIV, and serologic evidence of active hepatitis B or hepatitis C infection and patients requiring strong CYP3A inhibitors or strong CYP3A inducers. Patients received BRUKINSA 160 mg twice daily or 320 mg once daily. Among patients receiving BRUKINSA, 79% were exposed for 6 months or longer and 68% were exposed for greater than one year.

Fatal events within 30 days of the last dose of BRUKINSA occurred in 8 (7%) of 118 patients with MCL. Fatal cases included pneumonia in 2 patients and cerebral hemorrhage in one patient.

Serious adverse reactions were reported in 36 patients (31%). The most frequent serious adverse reactions that occurred were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Table 3 summarizes the adverse reactions in BGB-3111-206 and BGB-3111-AU-003.

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials

Body System	Adverse Reaction		f Patients 118)
		All Grades %	Grade 3 or Higher %
Blood and lymphatic system disorders	Neutropenia and Neutrophil count decreased	38	15
	Thrombocytopenia and Platelet count decreased	27	5
	Leukopenia and White blood count decreased		
	Anemia and Hemoglobin decreased	14	8
Infections and infestations	Upper respiratory tract infection¶	39	0
	Pneumonia§	15	10^
	Urinary tract infection	11	0.8
Skin and subcutaneous	Rash ^{II}	36	0
tissue disorders	Bruising*	14	0
Gastrointestinal	Diarrhea	23	0.8
disorders	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage [†]	11	3.4^

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving BRUKINSA in BGB-3111-206 and BGB-3111-AU-003 Trials (continued)

Musculoskeletal and connective tissue disorders	Musculoskeletal pain‡	14	3.4
Metabolism and nutrition disorders	Hypokalemia	14	1.7
Respiratory, thoracic and mediastinal disorders	Cough	12	0

- ^ Includes fatal adverse reaction
- * Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis
- † Hemorrhage includes all related terms containing hemorrhage, hematoma
- ‡ Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis
- § Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral
- II Rash includes all related terms containing rash
- ¶ Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral

Other clinically significant adverse reactions that occurred in < 10% of patients with mantle cell lymphoma include major hemorrhage (defined as \ge Grade 3 hemorrhage or CNS hemorrhage of any grade) (5%), hyperuricemia (6%) and headache (4.2%).

Table 4: Selected Laboratory Abnormalities* (> 20%) in Patients with MCL in Studies BGB-3111-206 and BGB-3111-AU-003

Laboratory Parameter	Percent of Pa	tients (N=118)
	All Grades (%)	Grade 3 or 4 (%)
Neutrophils decreased	45	20
Platelets decreased	40	7
Hemoglobin decreased	27	6
Lymphocytosis†	41	16
Chemistry abnormalities		
Blood uric acid increased	29	2.6
ALT increased	28	0.9
Bilirubin increased	24	0.9

^{*} Based on laboratory measurements.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 5: Drug Interactions that Affect Zanubrutinib

Moderate and Strong	Moderate and Strong CYP3A Inhibitors				
Clinical Impact	 Co-administration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC [see Clinical Pharmacology (12.3]] which may increase the risk of BRUKINSA toxicities. 				
Prevention or management	 Reduce BRUKINSA dosage when co-administered with moderate or strong CYP3A inhibitors [see Dosage and Administration (2.3)]. 				
Moderate and Strong	CYP3A Inducers				
Clinical Impact	Co-administration with a moderate or strong CYP3A inducer decreases zanubrutinib C _{max} and AUC [see Clinical Pharmacology (12.3)] which may reduce BRUKINSA efficacy.				
Prevention or management	 Avoid co-administration of BRUKINSA with moderate or strong CYP3A inducers [see Dosage and Administration (2.3)]. 				

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, BRUKINSA can cause fetal harm when administered to pregnant women. There are no available data on BRUKINSA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of zanubrutinib to pregnant rats during the period of organogenesis was associated with fetal heart malformation at approximately 5-fold human exposures (see Data). Women should be advised to avoid pregnancy while taking BRUKINSA. If BRUKINSA is used during pregnancy, or if the patient becomes pregnant while taking BRUKINSA, the patient should be apprised of the potential hazard to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Embryo-fetal development toxicity studies were conducted in both rats and rabbits. Zanubrutinib was administered orally to pregnant rats during the period of organogenesis at doses of 30, 75, and 150 mg/kg/day. Malformations in the heart (2- or 3-chambered hearts) were noted at all dose levels in the absence of maternal toxicity. The dose of 30 mg/kg/day is approximately 5 times the exposure (AUC) in patients receiving the recommended dose of 160 mg twice daily.

Administration of zanubrutinib to pregnant rabbits during the period of organogenesis at 30, 70, and 150 mg/kg/day resulted in post-implantation loss at the highest dose. The dose of 150 mg/kg is approximately 32 times the exposure (AUC) in patients at the recommended dose and was associated with maternal toxicity.

In a pre- and post-natal developmental toxicity study, zanubrutinib was administered orally to rats at doses of 30, 75, and 150 mg/kg/day from implantation through weaning. The offspring from the middle and high dose groups had decreased body weights preweaning, and all dose groups had adverse ocular findings (e.g. cataract, protruding eye). The dose of 30 mg/kg/day is approximately 5 times the AUC in patients receiving the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of zanubrutinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from BRUKINSA in a breastfed child, advise lactating women not to breastfeed during treatment with BRUKINSA and for at least two weeks following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BRUKINSA therapy.

Contraception

Females

BRUKINSA can cause embryo-fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for at least 1 week following the last dose of BRUKINSA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

Advise men to avoid fathering a child while receiving BRUKINSA and for at least 1 week following the last dose of BRUKINSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 641 patients in clinical studies with BRUKINSA, 49% were \geq 65 years of age, while 16% were \geq 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

8.6 Renal Impairment

No dosage modification is recommended in patients with mild to moderate renal impairment (CLcr \geq 30 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients with severe renal impairment (CLcr < 30 mL/min) or on dialysis [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

Dosage modification of BRUKINSA is recommended in patients with severe hepatic impairment [see Dosage and Administration (2.2)]. The safety of BRUKINSA has not been evaluated in patients with severe hepatic impairment. No dosage modification is recommended in patients with mild to moderate hepatic impairment. Monitor for BRUKINSA adverse reactions in patients with hepatic impairment [see Clinical Pharmacology (12.3)].

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[†] Asymptomatic lymphocytosis is a known effect of BTK inhibition.

BREAKING THROUGH FOR BETTER PATIENT CARE

NCODA PARTNERS WITH PRIME THERAPEUTICS TO OFFER ACCREDITATION FOR ITS NEW MIP PROGRAM

ince 2016, "Going Beyond the First Fill" has been NCODA's credo and the primary focus of its Mission to create a patient-centered, safe, high-quality, comprehensive program to meet the needs of the oncology community.

And now, thanks to a unique opportunity that combines the scope and influence of Prime Therapeutics' radically different pharmacy benefit manager (PBM) program with the focus and efficacy of NCODA's radically different pharmacy accreditation program, the world of oral oncolytics is about to enter a whole new era.

Prime Therapeutics recently launched IntegratedRx™ Oncology — a PBM program that allows practices to keep oral oncolytic prescriptions in-house rather than send them out to centralized mail-order pharmacies. Members can receive their medicine through their clinic's integrated pharmacy, where the provider and pharmacist are part of the same team, allowing for direct lines of communication.

CONTINUED ON NEXT PAGE

NCODA LAUNCHES NEW COE ACCREDITATION PROGRAM CREATED SPECIFICALLY FOR MIP ONCOLOGY PRACTICES

or more than six years, NCODA has addressed the growing need for Medically Integrated Pharmacies (MIP) to enhance care of cancer patients receiving oral and IV therapy by improving operations at the pharmacy level.

Now, thanks to the establishment of the Patient-Centered Standards for Medically Integrated Dispensing: ASCO/NCODA Standards in December 2019, NCODA is about to take its Mission to the next level.

On Aug. 10, 2021, NCODA announced the creation of the NCODA Center of Excellence (CoE) Medically Integrated Pharmacy (MIP) Accreditation Program.

The program, based on compliance with the ASCO/NCODA Standards, focuses on enhanced patient care and quality of services.

Leading the program is Elizabeth Bell, NCODA's newly named Director of Medically Integrated Pharmacy Accreditation.

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C O V E R S T O R Y

PARTNERSHIP

CONTINUED FROM PREVIOUS PAGE

Prime's goal is end-to-end coordination across the entire treatment pathway, helping improve adherence, shortening time to dispense, and creating a better member and provider experience from the first fill through the last fill.

The partnership model makes Prime Therapeutics the only large PBM that doesn't require patients to use a mail-order pharmacy. It will enable patients to receive cancer medications up to two days faster than traditional PBM models.

Prime believes IntegratedRx™ will result in significant savings for plan sponsors through lower medication costs and waste reduction through better integration.

Prime's regional Blue Plan clients nationwide will have the option to join IntegratedRx™ Onclology beginning in January 2022. Between 300 and 600 oncology practices will be eligible to participate in the program.

At present, around a dozen plans



Joe Leach

have committed to joining IntegratedRx[™].

"Most of our health plans have been very enthusiastic." said Joe Leach, MD, Senior Vice President and Chief Medical Offi-

cer at Minnesota-based Prime Therapeutics. "We expect very broad participation once we roll Integrated Rx^{TM} Oncology out to scale."

ACCREDITATION OPTIONS

Pharmacy accreditation is a key aspect of IntegratedRx™ Oncology, and that's where the new NCODA Center of Excellence (CoE) Medically Integrated Pharmacy (MIP) Accreditation Program comes in

Participants in IntegratedRx™ Oncology must receive accreditation through either NCODA CoE MIP, URAC or Accreditation Commission for Health Care (ACHC) within one year. But while URAC and ACHC accreditations focus primarily on large mail-order pharmacies, NCODA CoE is specifically designed for MIP practices.

It's a pivotal moment for both NCODA and Prime Therapeutics.

"This collaboration with Prime Therapeutics allows us to scale the concept of putting medically integrated pharmacy at the top," said Michael Reff, RPh, MBA,



Michael Reff

Founder & Executive Director of NCODA.

"I think it's going to be a great partnership," Leach agreed. "The timing is perfect. NCODA is rolling out a product that

we need and we're rolling out a network that will help raise awareness of the accreditation process that NCODA is building. I'm excited to see what we can do together."

DEVELOPMENT BEGAN IN 2020

How this moment evolved is a story in itself.

For Prime, the journey began about a year and a half ago, when Leach and Chief Innovation Officer Jarrod Henshaw began brainstorming for a way to set the company apart from other PBMs.

"The industry trend for PBMs has been to drive as many prescriptions as they can to their own mail-order pharmacies," Leach explained. This centralized strategy has become a detriment for integrated practices, preventing them from utilizing their own pharmacies to their full benefit.

Leach, who still practices at Minnesota Oncology, an MIP practice, knows this firsthand. "We have a very high-functioning integrated pharmacy, yet we struggle to fill prescriptions because we are not included in the networks for the majority of large payers," he said.

Yet, even more troubling, Leach

stressed, mail-order pharmacies simply aren't able to provide patient centered-care in the same way

"One of the things that makes Prime different from other large PBMs is that we don't own a mail-order pharmacy, so we don't have that incentive," Leach said. "We talked about all of the clinical benefits of integrating a pharmacy and clinical practice. We thought it would be an opportunity to improve clinical care for our oncology patients by exploring a different model."

Mark Alwardt, McKesson's Vice President of Medically Integrated Dispensing, was a key partner in the project.



Mark Alwardt

"We had several measures that covered everything from patient satisfaction to adherence," Alwardt said. "In all of them, Prime found it to be a viable model."

According to Prime, pilot practices experienced better pharmacy average wholesale price (AWP) discounts, lower per member per month (PMPM) costs, improved adherence, improved time-to-medication, improved patient satisfaction and a more intimate patient experience by keeping prescriptions in-house.

Alwardt, who has an extensive background in healthcare on both the provider and payer side, is a firm believer in keeping care at the practice.

"This is a profound moment," he said.
"This is, quite literally, a first in healthcare.
I've been associated with networks of all sorts for more than 16 years, and there has never been one that centers on medically integrated dispensing as its core pharmacy."

Prime began working with pharmaceutical distributor McKesson in October 2020 to develop the model. A working pilot was ready by February 2021 and then tested at three McKesson-affiliated practices in Minnesota,

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Florida and Oregon.

COMPASS ONCOLOGY

Compass Oncology, a provider network with five locations near Portland, Oregon, and Vancouver, Washington, was one of the sites chosen for Prime's pilot program.

Cisco Jorgensen, PharmD, BCPS, is Pharmacy Manager for the Compass



Cisco Jorgensen

Oncology Retail Pharmacy. Jorgensen characterized his operation as "a fairly small pharmacy" that fills about 700 prescriptions per month for approximately 35 providers. However, the major-

ity of the prescriptions are oral oncolytics, rather than supportive care, he said.

He estimates that 50 percent of Compass Oncology's prescriptions are in-house, with the remainder sent out to mail-order pharmacies due to insurance requirements.

Approximately 40 patients were impacted by the pilot program, he said. Patients became eligible for the pilot based on an existing Prime Therapeutics' BIN/PCN combination. The goal was to enhance the experience of the patient and provider, improve outcomes and reduce overall cost.

Under the pilot, Jorgensen noted that he experienced better outcomes in many areas. For instance, he said, the pilot enabled a "tenfold improvement" in prior authorization determination times compared to their mail-order pharmacy counterparts.

Jorgensen emphasized the frustration three of his patients underwent dealing with mail-order pharmacies, including terrible phone support, apathy towards financial toxicity, lack of education, lost prescriptions and missed deliveries.

"You can prescribe the best medications to your patient, but if it is not convenient and affordable, it's not going to work," he said. "By communicating with our providers, nursing staff and patients each

step along the way, we ensure we get the best outcomes and patient experience."

The Prime program also confirmed what Compass already knew about the patient value of MIP and keeping prescriptions in-house, he added.

"Our patients trust us. Their providers and care team are here. They appreciate the convenience of receiving all of their services, including pharmacy, in one location," Jorgensen said. The practice also benefited, he said, in time savings and revenue.

"Patient satisfaction is vitally important and we know that this is reduced by the delays and problems our patients experience. Our goal is to reduce this burden by working on their behalf. We assist with prior authorizations, financial assistance, patient education and refill management. The MIP model supports this; by taking care of our patients, we are able to build our business."

REGENCE

Regence is a nonprofit independent licensee of the Blue Cross and Blue Shield Association operating health plans in



Marion Couch

Oregon, Idaho, Utah and Washington

Marion Couch, MD, PhD, MBA, FACS, is Senior Vice President of Health Care Services & Chief Medical Officer of Regence.

"We're focused

on member experience, simplicity and partnerships," Couch said. "This program with Prime and the cancer centers really hits on that."

The program assures a tight connection with the cancer center and is "incredibly more convenient" for the patient," she said, adding that at the same time it also empowers the pharmacist.

"The pharmacist has access to the electronic medical record (EMR). They can educate. They can be more involved. They're part of the team," Couch said. "It's also more convenient for the member — they don't have to go to a mail-order pharmacy or mail-order — they can get it right there.

And when you are struggling with cancer, that simplicity matters."

Regence has been involved in the pilot program for several months, and while it's still too early to analyze performance data, Couch said feedback from both patients and cancer centers has been positive. The program appears to show great promise, she said.

"Because we're a Blue plan, we very much believe in partnership, and that's something we're doubling down on now. We want to support our provider partners," Couch said. "The great thing about this program is that it's a formal pilot that can be scaled ... the ability to scale a defined program is something that we are really excited about."

NCODA ENTERS THE PICTURE

NCODA eventually became part of that partnership. It was pulled into the program's development in Fall 2020, after Henshaw contacted Lisa Harrison, RPh, President, Specialty Distribution at AmerisourceBergen, a group purchasing organization (GPO), for her expertise in

> medically integrated pharmacy.



Lisa Harrison

"Prime was interested in thinking through what a medically integrated dispensing network would look like, and over many months we

discussed how we could put that network together," Harrison said.

As a true believer in MIP, the moment and its potential were not lost on her.

"This is huge," Harrison said. "It's market-changing. It could change the paradigm, and that's what we need to not only be successful for our providers, but also for our patients."

Through her discussion with Prime, Harrison told Henshaw about NCODA and the recently established Patient-Centered **Standards for Medically Integrated Dispensing:** ASCO/NCODA Standards.

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More importantly, Harrison introduced Henshaw to Reff.

As someone who has toiled for close on five years to convince payers about the efficacy and benefits of MIP, Reff knew exactly what challenges Prime was facing.

"Prime had to convince the plans that this wasn't just a financially driven strategy for the doctors," Reff explained. "It wanted a standard, demonstrating quality and value, showing that the practice is actually doing what they say they are doing, not haphazardly filling prescriptions just to support their bottom line."

"And that's where NCODA accreditation comes in. Our CoE MIP program means practices will have better patient adherence, less waste, fewer unaddressed side effects and fewer costs. We're going to standardize and measure better customer service."

Practices participating in the IntegratedRx™ Oncology program will be required to acquire one of three pharmacy accreditations within one year. The NCODA CoE MIP Accreditation will be one of the options.

Given its focus and minimal cost, NCODA believes its program will be a popular option.

"URAC and ACHC are more focused



Jonas Congelli

on the business side," explained Jonas Congelli, RPh, Chief of Pharmacy and Ancillary Services at Hematology Oncology Associates of Central New York, and a member of the Executive Ac-

creditation Council supporting the NCO-DA CoE MIP Accreditation Program.

"While that's important, the very first four standards have nothing to do with actually touching a patient. At times I feel like we're just doing things to satisfy the accreditation that have nothing to do in effecting good patient care. But now,

BY KEEPING PATIENT PRESCRIPTIONS IN-HOUSE, MIP **ACCREDITATION WILL YIELD A TREASURE TROVE OF DATA**

While the goals of improved patient care, less waste and better outcomes are paramount in the MIP practice, one other benefit holds the key to the future evolution of oncology: access to clean, tangible data.

By keeping prescriptions in-house, the medically integrated team can intimately direct, monitor and share patient care. Utilizing the ASCO/ NCODA Standards, the MIP practice will be able to accurately track and record patient adherence, side effects, speed to therapy and other metrics tied to oral oncolytic treatment.

Data is king, and nowhere is its importance better understood Lucio Gordan than at Florida Cancer Specialists & Research Institute (FCS). With nearly 100 clinical sites, 250 oncologists and approximately 4,200 employees, FCS is the largest provider of cancer care services in Florida and one of the largest privately owned practices in the country.

"Data is important because if we don't

measure what we're doing, we can't really prove that we're doing it," said Lucio Gordan, MD, FCS President and Managing Physician, and a member of the Executive Accreditation Council for the NCODA Center of Excellence Medically Integrated Pharmacy Accredita-

tion program. "Data allows us to self-correct, it helps us get to the next level."

FCS sees about 75,000 new patients each year and hosts large number of clinical trials. In doing so, it collects a lot of data — including procedures, around two million returns per year.

"Clearly having more regional perspective data on the patient (is important), especially if we're able to organize this data upfront

when a patient starts on a new therapy," Gordan said. "When we can put in the side-effect profile, the laboratory data and the financial toxicity each into a discrete box, it creates a very powerful story."

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we're going to have an accreditation that's meaningful to patient care."

For many MIP practices, the accreditation program will be an opportunity to confirm what they already know — and practice — regarding value-based patient care, according to Elizabeth Bell, NCODA's newly named Director of Medically Integrated Pharmacy Accreditation.

"The practices are going to show us that they are patient-centered, that they are ensuring the safety and the quality of services, and that they have processes and programs in place to bring down the cost of therapy," Bell explained.

GROWING INTEREST IN THE PROGRAM

Practices are getting excited as word gets around about the NCODA/Prime partnership.

Alabama Oncology (AO) — where Austin Cox, PharmD, is Pharmacy Manager — is one such practice. And Cox, a member of the NCODA CoE Accreditation Working Group couldn't be happier.

"When I heard that the first PBM that was on board was Prime, I was just



Austin Cox

chomping at the bit to get involved," Cox said.

"Prime is the most impactful PBM in our network. We contracted with Prime through our local Blue Cross Blue Shield plan,

which represents 90% commercial market share in the state of Alabama. So, they literally have a ton of leverage over us. I'm very excited that Prime is partnering with NCODA."

Alabama Oncology has been an MIP since 2016. And while it is ACHC and URAC accredited, Cox said the model doesn't necessarily create the efficiencies the practice needs for AO's integrated care practice.

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ACCREDITATION

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In addition, an Executive Accreditation Council and an Accreditation Working Group will provide guidance, insight and support for the new CoE MIP Accred-

itation Program.



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Bell joined NCODA with more than 20 years of experience in healthcare accreditation, compliance and management.

Bell has extensive experience with

accreditation programs. She has managed quality and accreditation departments, developed healthcare quality initiatives and led statewide compliance audit teams. Most recently, she served as the vice president of consulting services for a healthcare accreditation consulting company.

"The NCODA CoE MIP Accreditation Program is extremely patient-centered and does not include many of the administrative requirements found in other pharmacy accreditation programs," Bell said. "It's designed to improve patient outcomes, increase access to medications and ensure the safety of patients taking oral oncolytics. It was built to be meaningful and to bring value to MIP practices that go through the accreditation process."

Currently, three NCODA member practices were selected for the pilot program, which is projected to be completed before the end of 2021.

UNIQUE IN MANY WAYS

What sets the program apart is its commitment to the following **CoE MIP Tenets:** Patient-Centered, Always Collaborative, Quality & Value, Robust, Independent, Innovative and Budget-Neutral.

It's designed to hit the **Quadruple Aim** of better outcomes, improved patient experience, improved clinician experience and lower (healthcare) costs.

Key accreditation focus areas include adherence, safety, cost and waste reduction,

EXECUTIVE ACCREDITATION COUNCIL AND ACCREDITATION WORKING GROUP TO OVERSEE NEW NCODA ACCREDITATION PROGRAM

Two boards will help support NCODA's Center of Excellence Medically Integrated Pharmacy Accreditation Program: the Executive Accreditation Council and the Accreditation Working Group.

The Executive Accreditation Council will serve to provide guidance on the CoE MIP accreditation program, insight on the current/ future oncology ecosystem and network and program support.

Executive Accreditation Council members include Gury Doshi, MD | Texas Oncology; Lucio Gordan, MD | Florida Cancer Specialists & Research Institute; Michele Galioto | ONS; Brian Morrissey, MBA | Pfizer; Stacey McCullough, PharmD | Tennessee Oncology; Jonas Congelli, RPh | HOACNY; Luis Raez, MD | Memorial Healthcare System; and other leaders to be determined.

The Accreditation Working Group will serve to provide guidance and assistance in the development and revision of accreditation tools and resources.

Working group members include Kara Sammons (Co-Chair), MS, PharmReg, CPhT | Rx To Go / Florida Cancer Specialists & Research Institute; Ryan Scott (Co-Chair), PharmD, MBA, MHA, CSP | Intermountain Specialty Pharmacy; Tiffany Mitchem, PharmD | Southern Cancer Center & Coastal Pharmacy; Kristina Hazard, PharmD, BCOP | Kaiser Permanente; Stephanie Parker, PharmD | Illinois CancerCare; Kyle Kitchen, PharmD | Utah Cancer Specialists; Hind Hamid, PharmD, BCOP | DCH Regional Medical Center; Brittney Carden, PharmD Mitchell Cancer Institute; Joy Pratt, PharmD | Tennessee Cancer Specialists; Ernestine Wigelsworth, PharmD | Cancer Specialists of North Florida; Chris Sellers, RPh | Texas Oncology; Jenelle Griffiths, PharmD, CPh, CSP | Baptist Health South Florida Specialty Pharmacy; Jonathan Heller, MHS, PHR, CMPE, DLM (ASCP) Virginia Cancer Institute; Austin Cox, PharmD | Alabama Oncology; Meg Butler, PharmD | Clearview Cancer Institute; and Christie C. Smith, PharmD, MBA | AmerisourceBergen.

education, speed to therapy, patient satisfaction and financial assistance.

The program is unique in several ways, Bell noted.

First, it's the only oncology accreditation focused on medically integrated pharmacy. Existing pharmacy accreditation programs — URAC and ACHC — focus primarily on the needs of mail-order pharmacies. For MIP practices, such standards are not always relevant or supportive of patient care.

The pharmaceutical distributor McKesson currently has 175 MIP practices in its network, according to Mark Alwardt, Vice President of Medically Integrated Dispensing. Of those, he estimates that only "a single digit percentage" are accredited with either URAC or ACHC.

"Typically, the existing accreditations have not been an exact fit for integrated pharmacies," Alwardt said. "Some of the measurements and quality criteria don't quite fit that type of model."

Second is the cost factor. Up until now, pharmacy accreditation has been

an expensive proposition, costing tens of thousands of dollars, especially for larger practices. This is not so with NCODA CoE MIP accreditation.

"This program is designed to be budget-neutral for NCODA," Bell said. "It's not meant to generate a profit, so it will be much less expensive than the existing pharmacy accreditations out there today."

Finally, NCODA's CoE MIP Accreditation Program is designed to not only confirm that practices have met the Patient-Centered Standards for Medically Integrated Dispensing: ASCO/NCODA Standards, but to assist in that achievement.

To that end, NCODA's full toolbox of initiatives, including Oral Chemotherapy Education (OCE) sheets, Positive Quality Interventions (PQI), Patient Satisfaction Surveys (PSS) and other tools, are available to help participants attain accreditation.

"The most exciting thing is that this accreditation is patient-centered and more applicable for the medically integrated pharmacy community," said Austin Cox,

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PharmD, a member of the NCODA Executive Council. "It will allow us to more accurately measure factors such as medication adherence, which is much needed for our patient population."

GENERATING A LOT OF INTEREST

Seeds for the establishment of the CoE MIP program were first planted at the conclusion of the 2021 NCODA Spring Forum by NCODA President Jim Schwartz, RPh. Since then, NCODA has had several practices express interest in CoE MIP accreditation as soon as the program goes live.

One such program is American Oncology Network, LLC (AON), a multi-state accreditated practice considering additional accreditation for its large integrated pharmacy.

"Accreditations are very important. They allow pharmacies to validate



James Gilmore

the quality and compliance of all their programs and to differentiate that model above everybody else in the marketplace," said James Gilmore, PharmD, AON's Chief Pharmacy

and Procurement Officer.

"Payers really recognize that we're operating at a higher level of service with better patient outcomes. All those things lead back to our ability to gain access to contracts with certain PBMs and allow us to keep more prescriptions in house. Plus it really helps us provide better

service to the patient."

Clearly, MIP accreditation is an idea that's time has come, especially in the wake of the December 2019 publication of the ASCO/NCODA Standards which, in turn, helped establish the blueprints of the accreditation.

"Because of those established standards, we're not reinventing the wheel. We're giving medically integrated pharmacies a program tailored to their needs, a program designed to help them reach and maintain the highest level of patient care," said Michael Reff, RPh, MBA, NCODA Founder & Executive Director.

For more information on the NCODA Center of Excellence Medically Integrated Pharmacy Accreditation Program, contact **Elizabeth.Bell@NCODA.org**.

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Many components, such as investment in phone data collection, are geared more for mail-order pharmacies, he said.

"Sometimes you're just spinning your wheels and doing busy work that's really not impacting your patients or your practice in a positive way," Cox said.

Monitoring phone metrics, for instance, is unnecessary at practices like AO since it already answers phones on time using dedicated customer service staff within its MIP model, he said.

THE PROGRAM "SELLS REALLY WELL"

Since Prime is owned by a number of Blue Cross Blue Shield plans, Leach was particularly well-positioned to help promote Integrated Rx^{m} on the payer side.

"It sells really well," Leach noted. "I remember I was presenting it to one of our Blue clients and their comment was, 'What's the downside here? It seems like everyone comes out ahead in this.' It's true. It's good for providers. It's good for patients. And frankly it's good for plans because of the favorable cost of goods that providers are able to obtain."

Eventually, Prime plans to roll out Integrated Rx^{∞} to a much larger network, including health systems.

Networks aside, however, in the end it's all about patient care.

"My most important focus is how we can improve the experience for the patient while making life less difficult for doctors who are just trying to do the right thing," Leach said.

It's a philosophy that directly reflects the NCODA Mission, and the realization of the **Beyond The First Fill** initiative that Reff started in 2015 when he first collaborated with a regional plan in Syracuse, New York.

Taking matters into his own hands, Reff advocated for the unique value proposition of MIP services, which resulted in several NCODA member practices gaining the ability to go **Beyond The First Fill** with their regional plans.

"By putting the patient first and being collaborative," Reff said, "We're changing the world!"

For more information on IntegratedRx™ Oncology, go to www.primetherapeutics.com or follow @Prime_PBM on Twitter.

DATA

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Todd Schonherz, Chief Executive Officer at American Oncology Network (AON), sums that story up in one word: "completeness,"



Todd Schonherz

both for the patient and for the practice.

"When prescriptions are filled outside of our pharmacy, we're left in the dark as to what's going

on," Schonherz said.

"If you're going to be at an organization that's going to move toward value-based or risk-based agreements, having the ability to directly and precisely monitor what's going on is incredibly important."

FALL 2021



Injection for IV use 500 mg/25 mL, 100 mg/5 mL

INDICATION

SARCLISA (isatuximab-irfc) is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor.

SARCLISA is indicated, in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

IMPORTANT SAFETY INFORMATION CONTRAINDICATIONS

SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

WARNINGS AND PRECAUTIONS Infusion-Related Reactions

Serious infusion-related reactions (IRRs), including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms include cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling.

Based on ICARIA-MM, IRRs occurred in 38% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases.

In IKEMA, infusion-related reactions occurred in 46% of patients treated with SARCLISA, carfilzomib, and dexamethasone (Isa-Kd). In the Isa-Kd arm, the infusion-related reactions occurred on the infusion day in 99% of episodes. In patients treated with Isa-Kd, 95% of those experiencing an infusion-related reaction experienced it during the first cycle of treatment. All infusion-related reactions resolved: within the same day in 74% of episodes, and the day after in 24% of episodes.

The most common symptoms (≥5%) of an infusion-related reaction in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients. To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H₂ antagonists, diphenhydramine or equivalent, and dexamethasone.

Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade ≥2 reactions, interrupt SARCLISA infusion and provide appropriate medical management. For patients with grade 2 or grade 3 reactions, if symptoms improve to grade ≤1, restart SARCLISA infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased

incrementally. In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if an anaphylactic reaction or life-threatening (grade 4) IRR occurs and institute appropriate management.

Neutropenia

SARCLISA may cause neutropenia.

In patients treated with Isa-Pd, neutropenia occurred in 96% of patients and grade 3-4 neutropenia occurred in 85% of patients. Neutropenic complications occurred in 30% of patients, including febrile neutropenia (12%) and neutropenic infections (25%), defined as infection with concurrent grade ≥3 neutropenia. The most frequent neutropenic infections included infections of the upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3-4 neutropenia in 19% of patients (grade 3 in 18% and grade 4 in 1.7%). Neutropenic complications occurred in 2.8% of patients, including febrile neutropenia (1.1%) and neutropenic infections (1.7%).

Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia, delay SARCLISA dose until neutrophil count recovery to at least 1.0×10^{9} /L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

Second Primary Malignancies

The incidence of second primary malignancies is increased in patients treated with SARCLISA-containing regimens. The overall incidence of second primary malignancies in all the SARCLISA-exposed patients was 3.6%.

In ICARIA-MM, second primary malignancies occurred in 3.9% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm.

In IKEMA, second primary malignancies occurred in 7% of patients in the Isa-Kd arm and in 4.9% of patients in the Kd arm.

The most common (≥1%) second primary malignancies in ICARIA-MM and IKEMA (N=329) included skin cancers (4% with SARCLISA-containing regimens and 1.5% with comparative regimens) and solid tumors other than skin cancer (1.8% with SARCLISA-containing regimens and 1.5% with comparative regimens). All patients with skin cancer continued treatment after resection of the skin cancer.

To see the data and for full Prescribing Information, visit sarclisahcp.com

Monitor patients for the development of second primary malignancies.

Laboratory Test Interference

Interference with Serological Testing (Indirect Antiglobulin

SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false-positive indirect antiglobulin test (indirect Coombs test). The indirect antiglobulin test was positive during Isa-Pd treatment in 68% of the tested patients, and during Isa-Kd treatment in 63% of patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment.

Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and that SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol-treated RBCs. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices.

Interference with Serum Protein Electrophoresis and

Immunofixation Tests
SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity

Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS

In combination with pomalidomide and dexamethasone: The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, pneumonia, and diarrhea. The most common hematology laboratory abnormalities (≥80%) were decreased hemoglobin, decreased neutrophils, decreased lymphocytes, and decreased platelets.

In combination with carfilzomib and dexamethasone: The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, fatigue, hypertension, diarrhea, pneumonia, dyspnea, insomnia, bronchitis, cough, and back pain. The most common hematology laboratory abnormalities (≥80%) were decreased hemoglobin, decreased lymphocytes, and decreased

Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions in >5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections [3%]).

Serious adverse reactions occurred in 59% of patients receiving Isa-Kd. The most frequent serious adverse reactions in >5% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the Isa-Kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients).

USE IN SPECIAL POPULATIONS

Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with Pd, advise lactating women not to breastfeed during treatment with SARCLISA.

Please see Brief Summary of the Prescribing Information on the following pages.



Rx Only

(isatuximab-irfc) injection, for intravenous use

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

SARCLISA is indicated

- . in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor
- in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosage

Administer pre-infusion medications [see Dosage and Administration (2.2)].

· SARCLISA should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions if they occur [see Warnings and Precautions (5.1)].

The recommended dose of SARCLISA is 10 mg/kg actual body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone, according to the schedule in Table 1 [see Clinical Studies (14) in the full prescribing information].

Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone or in Combination with Carfilzomib and Dexamethasone

Cycle	Dosing schedule
Cycle 1	Days 1, 8, 15, and 22 (weekly)
Cycle 2 and beyond	Days 1, 15 (every 2 weeks)

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.

SARCLISA is used in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone. For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies (14) in the full prescribing information and manufacturer's prescribing information.

Missed SARCLISA Doses

If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

2.2 Recommended Premedications

Administer the following premedications prior to SARCLISA infusion to reduce the risk and severity of infusion-related reactions [see Warnings and Precautions (5.1)]:

- When administered in combination with SARCLISA and pomalidomide: Dexamethasone 40 mg orally or intravenously (or 20 mg orally or intravenously for patients ≥75 years of age). When administered in combination with SARCLISA and carfilzomib: Dexamethasone 20 mg (intravenously on the days of SARCLISA and/or carfilzomib infusions, orally on day 22 in cycle 2 and beyond, and orally on day 23 in all cycles).

 • Acetaminophen 650 mg to 1,000 mg orally (or equivalent).
- H2 antagonists
- Diphenhydramine 25 mg to 50 mg orally or intravenously (or equivalent). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (orally or intravenously) corresponds to the dose to be administered before infusion as part of the premedication and part of the backbone treatment. Administer dexamethasone before SARCLISA and pomalidomide and before SARCLISA and carfilzomib administration.

Administer the recommended premedication agents 15 to 60 minutes prior to starting a SARCLISA infusion.

Dose Modifications

No dose reduction of SARCLISA is recommended. Dose delay may be required to allow recovery of blood counts in the event of hematological toxicity [see Warnings and Precautions (5.2, 5.4)]. For information concerning drugs given in combination with SARCLISA, see manufacturer's prescribing information.

2.4 Preparation

Prepare the solution for infusion using aseptic technique as follows: Calculate the dose (mg) of required SARCLISA based on actual patient weight (measured prior to each cycle to have the administered dose adjusted accordingly) [see Dosage and Administration (2.1)]. More than one SARCLISA vial may be necessary to obtain the required dose

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Remove the volume of diluent from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP diluent bag that is equal to the required volume of SARCLISA
- Withdraw the necessary volume of SARCLISA injection from the vial and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

 The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP),
- polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate
- Gently homogenize the diluted solution by inverting the bag. Do not shake.

2.5 Administration

- Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadiene (PBD), or polyurethane [PU]) with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).
- . The infusion solution should be administered for a period of time that will depend on the infusion rate (see Table 2). Use prepared SARCLISA infusion solution within 48 hours when stored refrigerated at 2°C-8°C, followed by 8 hours (including the infusion time) at room temperature.
- Do not administer SARCLISA infusion solution concomitantly in the same intravenous line with other agents.

 On the days where both SARCLISA and carfilzomib are administered, administer dexamethasone first, followed by SARCLISA infusion, then followed by carfilzomib infusion.

Following dilution, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 2. Incremental escalation of the infusion rate should be considered only in the absence of infusion-related reactions [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)1.

Table 2: Infusion Rates of SARCLISA Administration

	Dilution Volume	Initial Rate	Absence of Infusion- Related Reaction	Rate Increment	Maximum Rate
First infusion	250 mL	25 mL/ hour	For 60 minutes	25 mL/hour every 30 minutes	150 mL/ hour
Second infusion	250 mL	50 mL/ hour	For 30 minutes	50 mL/hour for 30 minutes then increase by 100 mL/hour	200 mL/ hour
Subsequent infusions	250 mL	200 mL/ hour	-	-	200 mL/ hour

CONTRAINDICATIONS

SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients [see Warnings and Precautions (5.1)].

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

Serious infusion-related reactions including life-threatening anaphylactic reactions have occurred with SARCLISA treatment. Severe signs and symptoms included cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angioedema, and swelling.

Based on ICARIA-MM, infusion-related reactions occurred in 38% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd) [see Adverse Reactions (6.1)]. All infusion-related reactions started during the first SARCLISA infusion and resolved on the same day in 98% of the cases.

In IKEMA, infusion-related reactions occurred in 46% of patients treated with SARCLISA, carfilzomib, and dexamethasone (Isa-Kd). In the Isa-Kd arm, the infusion-related reactions occurred on the infusion day in 99% of episodes. In patients treated with Isa-Kd, 95% of those experiencing an infusion-related reaction experienced it during the first cycle of treatment. All infusion-related reactions resolved: within the same day in 74% of episodes, and the day after in 24% of episodes [see Adverse Reactions (6.1)].

The most common symptoms (≥5%) of an infusion-related reaction in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients.

To decrease the risk and severity of infusion-related reactions, premedicate patients prior to SARCLISA infusion with acetaminophen, H2 antagonists, diphenhydramine, or equivalent, and dexamethasone [see Dosage and Administration (2.2)].

Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade ≥2 reactions, interrupt SARCLISA infusion and provide appropriate medical management. patients with grade 2 or grade 3 reactions, if symptoms improve to grade ≤1, restart SARCLISA infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown in Table 2 [see Dosage and Administration (2.5)]. In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if an anaphylactic reaction or life-threatening (grade 4) infusion-related reaction occurs and institute appropriate management.

5.2 Neutropenia

SARCLISA may cause neutropenia.

In patients treated with Isa-Pd, neutropenia occurred in 96% of patients and grade 3–4 neutropenia occurred in 85% of patients. Neutropenic complications occurred in 30% of patients, including febrile neutropenia (12%) and neutropenic infections (25%), defined as infection with concurrent grade ≥3 neutropenia. The most frequent neutropenic infections included infections of the property of the pr of the upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%) [see Adverse Reactions (6.1)].

In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3-4 neutropenia in 19% of patients (grade 3 in 18% and grade 4 in 1.7%). Neutropenic complications occurred in 2.8% of patients, including febrile neutropenia (1.1%) and neutropenic infections (1.7%) [see Adverse Reactions (6.1)]. Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia delay SARCLISA dose until neutrophil count recovery to at least 1.0×10^9 /L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

5.3 Second Primary Malignancies

The incidence of second primary malignancies is increased in patients treated with SARCLISAcontaining regimens. The overall incidence of second primary malignancies in all the SARCLISA-exposed patients was 3.6%

In ICARIA-MM, second primary malignancies occurred in 3.9% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm.

In IKEMA, second primary malignancies occurred in 7% of patients in the Isa-Kd arm and in 4.9% of patients in the Kd arm.

The most common (≥1%) second primary malignancies in ICARIA-MM and IKEMA (N=329) included skin cancers (4% with SARCLISA-containing regimens and 1.5% with comparative

(isatuximab-irfc) injection, for intravenous use

regimens) and solid tumors other than skin cancer (1.8% with SARCLISA-containing regimens and 1.5% with comparative regimens). All patients with skin cancer continued treatment after resection of the skin cancer.

Monitor patients for the development of second primary malignancies.

5.4 Laboratory Test Interference

Interference with Serological Testing (Indirect Antiglobulin Test)

SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). The indirect antiglobulin test was positive during Isa-Pd treatment in 68% of the tested patients, and during Isa-Kd treatment in 63% of patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without

patients with a positive indirect antigodumin test, blood translusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment. Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol-treated RBCs. If an emergency transfusion is required, non-cross-matched ABO/RhD-compat-ible RBCs can be given as per local blood bank practices [see Drug Interactions (7.1)].

Interference with Serum Protein Electrophoresis and Immunofixation Tests

SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein [see Drug Interactions (7.1)].

5.5 Embryo-Fetal Toxicity

Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose [see Use in Specific Populations (8.1, 8.3)]. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions from SARCLISA are also described in other sections of the labeling:

- Infusion-Related Reactions [see Warnings and Precautions (5.1)]
- Neutropenia [see Warnings and Precautions (5.2)]
- Second Primary Malignancies [see Warnings and Precautions (5.3)]

6.1 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.

Multiple Myeloma

Combination treatment with pomalidomide and dexamethasone (Isa-Pd)

The safety of SARCLISA was evaluated in ICARIA-MM, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients received SARCLISA 10 mg/kg in patients with previously freated multiple hydronia. Patients received SAROLISA 10 highsy intravenously, weekly in the first cycle and every two weeks thereafter, in combination with pomalidomide and dexamethasone (Ba-Pd) (n=152) or pomalidomide and dexamethasone (Pd) (n=149) [see Clinical Studies (14) in the full prescribing information]. Among patients receiving Isa-Pd, 66% were exposed to SARCLISA for 6 months or longer and 24% were exposed for greater than 12 months or longer.

Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions in >5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections [3%]).

Permanent treatment discontinuation due to an adverse reaction (grades 1-4) occurred in 7% of patients who received Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (2.6%). SARCLISA alone was discontinued in 3% of patients due to infusion-related reactions.

Dosage interruptions due to an adverse reaction occurred in 31% of patients who received SARCLISA. The most frequent adverse reaction requiring dosage interruption was infusionrelated reaction (28%).

The most common adverse reactions (≥20%) were upper respiratory tract infection, infusionrelated reactions, pneumonia, and diarrhea.

Table 3 summarizes the adverse reactions in ICARIA-MM.

Table 3: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Pomalidomide, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in ICARIA-MM Trial

Adverse Reactions	SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd)				malidomide methasone	
		(N=152)			(N=149)	
	All Grade 3 Grade 4 (%)			All Grades (%)	Grade 3 (%)	Grade 4 (%)
General disorders and administration site conditions						
Infusion-related reaction*	38	1.3	1.3	0	0	0
Infections	Infections					
Upper respiratory tract infection [†]	57	9	0	42	3.4	0
Pneumonia [‡]	31	22	3.3	23	16	2.7

Table 3: Adverse Reactions (≥10%) in Patients Receiving SARCLISA Pomalidomide, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in ICARIA-MM Trial (continued)

Adverse Reactions	SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd)			Pomalidomide + Dexamethasone (Pd)		
		(N=152)		(N=149)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Blood and lymphatic system disorders						
Febrile neutropenia	12	11	1.3	2	1.3	0.7
Respiratory, thoracio	and medi	astinal disc	orders			
Dyspnea [§]	17	5	0	12	1.3	0
Gastrointestinal disc	Gastrointestinal disorders					
Diarrhea	26	2	0	19	0.7	0
Nausea	15	0	0	9	0	0
Vomiting	12	1.3	0	3.4	0	0

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*Infusion-related reaction includes infusion-related reaction, cytokine release syndrome, and drug hypersensitivity.

†Upper respiratory tract infection includes bronchiolitis, bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, nasopharyngitis, parainfluenzae virus infection, pharyngitis, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tracheitis, upper respiratory tract infection, and upper respiratory tract infection

‡Pneumonia includes atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenzal, pneumonia pneumococcal, pneumonia streptococ-cal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal, and pneumocystis jirovecii pneumonia.

§Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.

Table 4 summarizes the hematology laboratory abnormalities in ICARIA-MM.

Table 4: Hematology Laboratory Abnormalities During the Treatment Period in Patients Receiving Isa-Pd versus Pd in ICARIA-MM

Laboratory Parameter	SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd)				malidomide methasone	
		(N=152)			(N=149)	
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hemoglobin decreased	99	32	0	97	28	0
Neutrophils decreased	96	24	61	92	38	31
Lymphocytes decreased	92	42	13	92	35	8
Platelets decreased	84	14	16	79	9	15

The denominator used to calculate the percentages was based on the safety population.

Combination treatment with carfilzomib and dexamethasone (Isa-Kd)

The safety of SARCLISA was evaluated in IKEMA, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients received SARCLISA 10 mg/kg patients with previously treated multiple inyeloma. Patients received SARCLISA 10 mg/kg intravenously weekly in the first cycle, and every two weeks thereafter, in combination with carfilzomib and dexamethasone (Isa-Kd) (n=177) or carfilzomib and dexamethasone (Kd) (n=122) [see Clinical Studies (14) in the full prescribing information]. Among patients receiving Isa-Kd, 68% were exposed to SARCLISA for 12 months or longer and 51% were exposed for greater than 18 months.

Serious adverse reactions occurred in 59% of patients receiving Isa-Kd. The most frequent serious adverse reactions in >5% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the Isa-Kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients)

Permanent treatment discontinuation due to an adverse reaction (grades 1–4) occurred in 8% of patients who received Isa-Kd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Kd were infections (2.8%). SARCLISA alone was discontinued in 0.6% of patients due to infusion-related reactions.

Dosage interruptions due to an adverse reaction occurred in 33% of patients who received SARČLISA. The most frequent adverse reaction requiring dosage interruption was infusionrelated reaction (30%).

The most common adverse reactions (≥20%) were upper respiratory tract infection, infusionrelated reactions, fatigue, hypertension, diarrhea, pneumonia, dyspnea, insomnia, bronchitis, cough, and back pain.

Table 5: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Carfilzomib, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in IKEMA

Adverse Reactions	SARCLISA + Carfilzomib + Dexamethasone (Isa-Kd) (N=177)				arfilzomib nethason (N=122)	
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
General disorders a	nd administration	site cond	litions			
Infusion-related reaction*	46	0.6	0	3.3	0	0
Infections		•				
Upper respiratory tract infection [†]	67	9	0	57	7	0
Pneumonia [‡]	36	19	3.4	30	15	2.5
Bronchitis§	24	2.3	0	13	0.8	0
Vascular disorders		•	•			
Hypertension [¶]	37	20	0.6	32	18	1.6
Respiratory, thoracio	and mediastinal	disorders	3			
Dyspnea#	29	5	0	24	0.8	0
Cough ^b	23	0	0	15	0	0
Gastrointestinal disorders						
Diarrhea	36	2.8	0	29	2.5	0
Vomiting	15	1.1	0	9	0.8	0
General disorders a	nd administration	site cond	litions			
Fatigue ⁶	42	5	0	32	3.3	0

^{*}Infusion-related reaction includes infusion-related reaction, cytokine release syndrome, and hypersensitivity.

†Upper respiratory tract infection includes acute sinusitis, chronic sinusitis, H1N1 influenza, H3N2 influenza, influenza, laryngitis, laryngitis viral, nasal herpes, nasopharyngitis, pharyngitis, pharyngotonsillitis, respiratory syncytial virus infection, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, tracheitis, upper respiratory tract infection, viral rhinitis, respiratory tract infection, respiratory tract infection viral, influenza like illness, parainfluenzae virus infection, respiratory tract infection bacterial, and viral upper respiratory tract infection.

‡Pneumonia includes atypical pneumonia, lower respiratory tract infection viral, pneumocystis jirovecii pneumonia, pneumonia, pneumonia influenzal, pneumonia legionella, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, pulmonary sepsis, and pulmonary tuberculosis.

§Bronchitis includes bronchitis, bronchitis viral, respiratory syncytial virus bronchitis, bronchitis chronic, and tracheobronchitis.

¶Hypertension includes hypertension, blood pressure increased, and hypertensive crisis. #Dyspnea includes dyspnea and dyspnea exertional.

PCough includes cough, productive cough, and allergic cough.

BFatigue includes fatigue and asthenia.

Table 6 summarizes the hematology laboratory abnormalities in IKEMA.

Table 6: Hematology Laboratory Abnormalities During the Treatment Period in Patients Receiving Isa-Kd versus Kd in IKEMA

Laboratory Parameter	SARCLISA + Carfilzomib + Dexamethasone (Isa-Kd)				arfilzomib methasone	
		(N=177)			(N=122)	
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hemoglobin decreased	99	22	0	99	20	0
Lymphocytes decreased	94	52	17	95	43	14
Platelets decreased	94	19	11	88	16	8
Neutrophils decreased	55	18	1.7	43	7	0.8

The denominator used to calculate the percentage was based on the safety population.

Description of Selected Adverse Reactions

Infusion-related reactions

In ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 58 patients (38%) treated with SARCLISA. All patients who experienced infusion-

related reactions experienced them during the 1st infusion of SARCLISA, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 3.9%, grade 2 in 32%, grade 3 in 1.3%, and grade 4 in 1.3% of the patients. Signs and symptoms of grade 3 or 4 infusion-related reactions included dyspnea, hypertension, and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 30%. The median time to infusion interruption was 55 minutes. SARCLISA was discontinued in 2.6% of patients due to infusion-related reactions.

In IKEMA, infusion-related reactions were reported in 81 patients (46%) treated with Isa-Kd. Grade 1 infusion-related reactions were reported in 14%, grade 2 in 32%, and grade 3 in 0.6% of the patients treated with Isa-Kd. Signs and symptoms of grade 3 infusion-related reactions included dyspnea and hypertension. SARCLISA was discontinued in 0.6% of patients due to infusion-related reactions [see Warnings and Precautions (5.1)].

In a separate study (TCD14079 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all grade 2) were reported in 40% of patients, at the first administration, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

In ICARIA-MM, the incidence of grade 3 or higher infections was 43% in the Isa-Pd group. Pneumonia was the most common severe infection with grade 3 reported in 22% of patients in the Isa-Pd group compared to 16% in the Pd group, and grade 4 in 3.3% of patients in the Isa-Pd group compared to 2.7% in the Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in the Isa-Pd group compared to 5.4% in the Pd group. Fatal infections occurred in 3.3% of patients in the Isa-Pd group and in 4% in the Pd

In IKEMA, the incidence of grade 3 or higher infections was 38% in the Isa-Kd group. Pneumonia was the most common severe infection with grade 3 in 19% of patients in the Isa-Kd group compared to 15% in the Kd group, and grade 4 in 3.4% of patients in the Isa-Kd group compared to 2.5% in the Kd group. Treatment was discontinued due to infection in 2.8% of patients in the Isa-Kd group compared to 4.9% in the Kd group. Fatal infections occurred in 2.3% of patients in the Isa-Kd group and 0.8% in the Kd group.

Cardiac failure

In IKEMA, cardiac failure (including cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular failure, and pulmonary edema) was reported in 7.3% of patients with the Isa-Kd group (grade ≥3 in 4%) and in 6.6% of patients with the Kd group (grade ≥3 in 4.1%). Serious cardiac failure was observed in 4% of patients in the Isa-Kd group and in 3.3% of patients in the Kd group. See the current prescribing information for carfilzomib for more information.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other isatuximab-irfc products may be misleading.

In ICARIA-MM and IKEMA, no patients tested positive for antidrug antibodies (ADA). Therefore, the neutralizing ADA status was not determined. Overall, across 9 clinical studies in multiple myeloma (MM) with SARCLISA single-agent and combination therapies including ICARIA-MM and IKEMA (N=1018), the incidence of treatment emergent ADAs was 1.9%. No clinically significant differences in the pharmacokinetics, safety, or efficacy of isatuximab-irfc were observed in patients with ADAs.

DRUG INTERACTIONS

7.1 **Laboratory Test Interference**

Interference with Serological Testing

SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches in patients treated with SARCLISA [see Warnings and Precautions (5.4)].

Interference with Serum Protein Electrophoresis and Immunofixation Tests

SARCLISA may be incidentally detected by serum protein electrophoresis and immunofixation assays used for the monitoring of M-protein and may interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria [see Warnings and Precautions (5.4)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

SARCLISA can cause fetal harm when administered to a pregnant woman. The assessment of isatuximab-irfc-associated risks is based on the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on SARCLIŠA use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction toxicity studies have not been conducted with isatuximab-irfc. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of SARCLISA and pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy. Pomalidomide is only available through a REMS program.

(isatuximab-irfc) injection, for intravenous use

Clinical Considerations

Fetal/neonatal reactions

Immunoglobulin G1 monoclonal antibodies are known to cross the placenta. Based on its mechanism of action, SARCLISA may cause depletion of fetal CD38-positive immune cells and decreased bone density. Defer administration of live vaccines to neonates and infants exposed to SARCLISA in utero until a hematology evaluation is completed.

Data

Animal data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density which recovered 5 months after birth. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

8.2 Lactation

Risk Summary

There are no available data on the presence of isatuximab-irfc in human milk, milk production, or the effects on the breastfed child. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to SARCLISA are unknown. Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide and dexamethasone, advise lactating women not to breastfeed during treatment with SARCLISA. Refer to pomalidomide prescribing information for additional information.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

With the combination of SARCLISA with pomalidomide, refer to the pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential. Contraception

Females

SARCLISA can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise female patients of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of SARCLISA. Additionally, refer to the pomalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential.

Males

Refer to the pomalidomide prescribing information.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of SARCLISA, 56% (586 patients) were 65 and over, while 16% (163 patients) were 75 and over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years and over and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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Revised: March 2021

WHILE THERE'S NO MAGIC PATH TO A SUCCESSFUL CAREER, LEADERS SHARE A FEW BASIC TRUTHS WORTH KNOWING

harmacy students must rigorously prepare themselves for their future roles in the healthcare industry, yet some of the most important career information they'll need moving forward isn't accessible in a college course or even an internship.

While knowledge can be found in a book, wisdom comes with life experience, which is why NCODA hosted the Student Track "Exploring Careers for Students Within Oncology" during the 2021 Spring Forum.

Moderator Jason Darmanin, past National President of the NCODA Professional Student Organization, led an informative question-and-answer session with three women who have experienced nearly all aspects of pharmacy in their storied careers:

▲ Shana Gunderson Hua, PharmD, Medical Affairs Executive Director – Mega National Accounts | Genentech;

▲ Brooke Patterson, PharmD, BCACP, Director, Global Compound Market Access Leader, Vaccines | Janssen Pharmaceuticals, Inc.; and

▲ Roula Qaqish, PharmD, Vice President of U.S. Medical Affairs | AbbVie.

"My career journey has not been a straight line,"
Gunderson Hua said, noting she taught in academia, worked in the AIDS Ward at Cook County Hospital in Chicago, provided everything from research to network contracting to strategic business development for large companies like Walgreens, started her own consulting company and more, before transitioning into oncology and her current role at Genentech.

"Take some calculated risks in your career," Gunderson Hua urged students. "Each day, challenge yourself to do something hard and remember it's OK if what you had planned didn't work out because you will learn more from that experience."

It's also important to remember that healthcare is a "team sport" and that interacting with colleagues is essential, Gunderson Hua said. "Everyone has something to offer, and you will have more success and provide better solutions. Most importantly, you will have more fun and laughs along the way."

Patterson's career took her from a residency in Atlanta, where she helped develop treatments for HIV patients, to a professorship at the University of Missouri | Kansas City School of Pharmacy and the Kansas City Free Health Clinic, where she again managed HIV patients. After about a decade,



Shana Gunderson Hua



Brooke Patterson



Roula Qaqish

she joined Janssen and eventually migrated into oncology.

"One of the beauties of working for a company as large as J&J is that I was able to explore another area of interest and passion, which was oncology," Patterson said, noting that both of her parents are cancer survivors. However, her interest was less in the "slash-and-burn" way of treatment and more into targeted therapies that harness the patient's immune system.

"All that knowledge I had from HIV was really helpful because the immune system is the immune system," Patterson said. "It's just harnessing or changing it in different ways."

She encouraged students to maintain a thirst for science, and to keep an open mind. "If you would have told me 15 years ago that I'd be working in oncology, I would have told you no way," she said. "But I absolutely love it. I got here because I wanted to be here."

Qaqish noted her career path has been fairly straightforward; she's been at AbbVie for nearly 20 years. She urged students to avoid the belief that the grass is always greener on the other side, and to understand that "the only thing you can change is yourself."

"As leaders, we are the ones who are tapped for leading change or advocating new heights or elevating teams and big names and big topics and big words that we use in pharma," Qaqish said. "Yet it's meaningless if we are not willing to accept that in some instances — and there's

plenty of those — our realities are things you cannot change.

"For me, accepting the things that I cannot change and having the courage to change the things that I can and the wisdom to know the difference is absolutely important in times when things can be challenging. It's an important lens in a filter that comes, sadly, with age, so don't expect to have it today. It's something that requires internal thirst and strength to get."

Finally, all three presenters emphasized the importance of maintaining a good balance between work and personal life:

Gunderson Hua: "It's not just work; you have to have a life. Sometimes you have to reach out and ask for help."

Patterson: "I think that the analogy of helping yourself first when the oxygen masks start dropping down in the airplane and then helping the people beside you is really true."

Qaqish: "You're no good to anyone if you're not good to yourself. We need to pace ourselves in a way that we can be good to others. It's a matter of discipline to take care of yourself."

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Being a part of the NCODA Professional Student Organization (PSO) community is such a remarkable experience. Together, we keep each other updated and informed on current clinical oncology practices, while also providing opportunities that aid in developing leadership skills."

> - Jonathan Rivera PharmD Candidate | Class of 2023 University of North Texas Health Science Center

ABOUT PSO

Our focus is to offer an international community for healthcare students with a passion in the oncology and pharmaceutical industries. The NCODA Professional Student Organization (PSO)

was established for students interested in oncology pharmacy, association management, and industry leadership.

SO BENEFI

- First professional student organization for students interested in oncology/association management/industry leadership
- Opportunities to attend NCODA international meetings and present
- International public speaking opportunities
- Create educational materials that will help cancer patients
- International publishing opportunities (ForumRewind & Oncolytics Today)
- Increased networking opportunities with oncology clinical, industry professionals, and key opinion leaders
- Access to over 30+ hours of oncology video education (Student Educational Talks)
- Oncology clinical practice experience and mentorship
- Other Student Opportunities:
 - 1-year post-graduate oncology fellowships
 - International elective APPE rotation in oncology







FOR MORE INFORMATION OR TO SUGGEST NEW CHAPTERS Email Austin Starkey at Austin.Starkey@NCODA.org Scan to visit, or check out www.NCODA.org/professional-student-organizations



More than 200 pharmacy students attended the inaugural NCODA Professional Student Organization Meeting in Detroit on Sept. 16-17.

MORE THAN 30 PHARMACY SCHOOLS COMMIT TO START NEW CHAPTERS AT INAUGURAL PSO EVENT

Sessions at the PSO meeting included:

- Business of Oncology 101, presented by Mark Alwardt, Vice President of Medically Integrated Dispensing at McKesson, Sonia Oskouei, PharmD, Vice President of Biosimilars at Cardinal Health and Lisa Harrison, RPh, President and General Manager of Oncology Supply at AmerisourceBergen;
- Pharmacogenomics: Paving the Way for Targeted Therapies, Holli Dilks, PhD, Senior Director of Clinical Development and Medical Affairs at Foundation Medicine, Michael J. Schuh, PharmD, MBA, FAPhA, Assistant Professor of Pharmacy at the Mayo Clinic in Florida and Sherif El-Refai, PharmD, PhD, MBA, Associate Director for Medical Affairs at Tempus Labs:
- Working Within a Medically Integrated Dispensing Team, Mary Anderson, BSN, RN, OCN, Oral Oncology Nurse Navigator at Norton Cancer Institute, Michelle Taymuree, PharmD, MBA, Oncology Manager at Sutter Health, Rebecca Garland, RPhT, Pharmacy Adherence Manager at Florida Cancer Specialists and Research Institute and Elisabeth Heath, MD, FACP, Associate Center Director at Karmanos Cancer Institute;
- Navigating Career Paths in Oncology,
 Alisha Ahmed, PharmD, MBA, RPh, Market
 Development Manager at Seagen, Christie Baker,
 PharmD, Pharmacy Manager at Texas Oncology
 and Sydney Schultz, PharmD, PGY2 Oncology
 Resident at the Mayo Clinic; and
- Oncology's Innovative Frontier, Marty Whalen, MBA, Vice President of Hematology at Bristol Myers Squibb, Kent Barnes, Vice President of Sales & Marketing at Seagen and Janet Loesberg, PharmD, Senior Vice President of Medical Affairs at Blueprint Medicines.

ore than 200 pharmacy students from over 100 unique schools across the US and Canada attended the 2021 NCODA Professional Student Organization (PSO) Meeting, participating both live and virtually at the first annual event. The theme of the meeting was "An Oncology Student Pharmacist's Career Journey."

Students from more than 30 pharmacy schools committed to start new Professional Student Organization (PSO) chapters during the group's sold-out meeting on Sept. 17 in Detroit. These schools will join the 33 established chapters across North America.

The University of Toronto was named PSO Chapter of the Year during an awards ceremony hosted by Michael Reff, RPh, MBA, Founder & Executive Director of NCODA, and Madison Motzner, NCODA PSO National President from Washington State University College of Pharmacy and Pharmaceutical Sciences.

The all-day conference, preceded by a welcome reception at the Henry Ford Museum on Sept. 16, featured speakers from across the oncology spectrum, including pharmacists, providers, nurses, practice leaders, academic representatives, industry professionals and NCODA staff.

Tim Whitten, BPharm, MBA, President and CEO of Taiho Oncology, a pharmaceutical company focused on developing cancer treatments, presented the morning keynote session, "Pharmaceutical Excellence in Leadership for Students."



Doha Anwar, 2024 PharmD Candidate from The University of Alberta (Canada), pins the NCODA Professional Student Organization map to signify her commitment to start a PSO chapter at her school.

Whitten talked about the life lessons he learned growing up in a poor, but hard-working lower-middle class family. He encouraged students to lead a purposed-filled life, especially one that helps the less fortunate. "It comes from having the right role model," he said. "I watched my parents and that's the way I got my purpose."

Lori Pierce, MD, Chair of the Board of the American Society of Clinical Oncology (ASCO), presented on "The Future of Oncology" in the afternoon.

Conference sessions focused on many different aspects of oncology pharmacy, giving students a unique opportunity to gain insight from more than two dozen experienced professionals.

During the leadership workshop "Residency/Fellowship Preparation," Kristen Felthousen, MS, Program Manager at the University of

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PROFESSIONAL STUDENT ORGANIZATION



Students attending the NCODA PSO Meeting speak with Isabel Houlzet (right), PharmD, BCPS, BCOP, Clinical Pharmacy Specialist at Miami Cancer Institute (MCI) - Baptist Health South Florida, about MCI's PGY2 Oncology Residency program.

PS₀

CONTINUED FROM PREVIOUS PAGE

Southern California School of Pharmacy, and Julianne Darling, PharmD, BCOP, Manager of Clinical Initiatives at NCODA, offered extensive and specific tips for the post-collegiate interview process.

Felthousen emphasized that students remember they are entering a pharmacy "practice." "You're practicing, just like a medical practice," she said. "It's experiential education because you are learning. It's not that you know everything. And admitting that you don't is incredibly valuable."

Several PSO members told the audience about their experience with PSO and NCODA.

Alanda Barash, a 2022 PharmD Candidate at Washington State University and NCODA National Executive Board (NEB) Vice President, helped current NEB National President Motzner form a chapter there in 2019.

"NCODA was just starting the chapter when I found out that my mom was diagnosed with cancer," Barash said, also noting that her mother-in-law is a cancer survivor. "Oncology is really personal to me. All the resources NCODA provided just kept me wanting to learn more and continue to be involved."

My-Lien Au, a 2022 PharmD candidate at the University of North Texas Health Science Center, also was a founding member at her school.

"My story is a little bit different; as an undergrad I was diagnosed with diffuse large B-cell lymphoma," Au said. "And then I kind of figured oncology was where I wanted to be, and it was only further solidified during my expe-



The NCODA PSO National Executive Board includes (from left) Jonathan Rivera, President-Elect, Madison Motzner, President, Alanda Barash, Vice President of Communications, Diane Hobbs, Vice President of International Meetings, and My-Lien Au, Vice President of Community Service.

riences at pharmacy school. I was able to learn about oncology medications and be a part of my own NEB team, and really be an advocate."

NEB President-Elect Jonathan Rivera, a 2023 PharmD Candidate at the University of North Texas Health Science Center, encouraged meeting participants to consider starting their own PSO chapters.

"There's a lot of benefits that come with joining," Rivera said. "We are the first professional organization for students interested in oncology as well as association management and industry leadership." Also, membership is complimentary, which is a significant benefit for students, he added.

"It's a wonderful experience for students, with opportunities to attend NCODA conferences like this, as well as the Spring Forum and Fall Summit," he said.

Comments from students who attended NCODA's inaugural PSO meeting:

"I was able to network with key leaders in both industry and hospital oncology pharmacy. I was presented with the opportunity to learn about current best practices in oncology and other sectors, learn about fellowship and residency programs, and network with key leaders." Read more at https://lnkd.in/diMjumS9.

— Greta Johnson, 2024 PharmD Candidate, Northeastern University Bouvé College of Health Sciences

"The past two days were definitely something to remember! The sessions on living a purpose-filled life, Business 101 of Oncology and interviewing tips — while having the opportunity to network — were just a few of my token moments!"

— Chinenye Agim, 2022 PharmD Candidate, University of South Carolina College of Pharmacy

"What an INCREDIBLE first annual Professional Student Organization meeting made possible by NCODA! I met a LOT of other pharmacy students from all over the country ... I'm still pinching myself and I can't stop smiline!"

— Erika Quedding, 2024 PharmD Candidate, Northeast Ohio Medical University

"Thank you to the entire NCODA team and students for this wonderful experience. It was one of the best experiences I've ever had!"

— Nihar Sajja, 2023 PharmD Candidate, Medical College of Wisconsin

"I gained priceless knowledge about the world of oncology from influential professionals in the field. I am grateful for the experience to gain a deeper understanding and appreciation of oncology."

— Taylor Certain, 2022 PharmD Candidate, Florida A&M University

"This was an amazing opportunity to hear from some of the leading stakeholders in oncology today. Can't wait for next year!"

— Mattie Kilpatrick, 2023 PharmD Candidate, Auburn University Harrison School of Pharmacy

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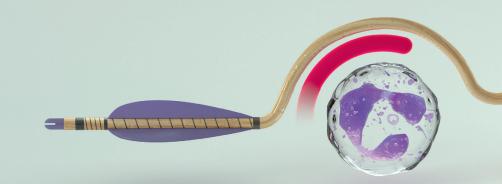
To decrease the incidence of chemotherapy-induced myelosuppression in patients when administered prior to a platinum/ etoposide-containing regimen or topotecan-containing regimen

FOR EXTENSIVE-STAGE SMALL CELL LUNG CANCER (ES-SCLC)

SPARE THE MARROW.

COSELA HELPS PROTECT AGAINST MYELOSUPPRESSION,

COSELA™ (trilaciclib) helps protect hematopoietic stem and progenitor cells (HSPCs), the source of blood cell lineages



PROACTIVELY HELP PROTECT AGAINST MULTIPLE MYELOSUPPRESSIVE CONSEQUENCES WITH THE FIRST AND ONLY MYELOPROTECTION THERAPY

The Pivotal Study (Study 1) compared an etoposide/carboplatin + atezolizumab (E/P/A) regimen with COSELA vs without COSELA*

VISIT **COSELA.COM** FOR MORE DETAILS

INDICATION

COSELA is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

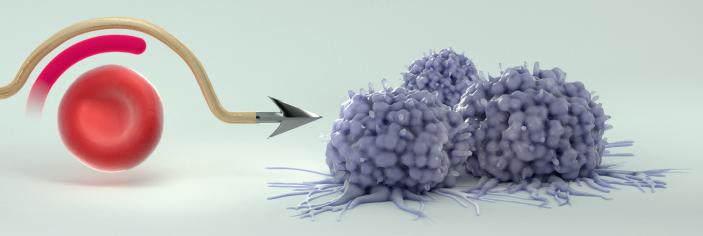
*COSELA was evaluated in 3 randomized, double-blind, placebo-controlled clinical studies. The Pivotal Study (Study 1) evaluated COSELA or placebo administered prior to treatment with E/P/A in 107 patients with newly diagnosed ES-SCLC not previously treated with chemotherapy. In this study, COSELA significantly reduced the primary endpoints of incidence (adjusted relative risk [aRR] 0.038 [95% CI, 0.008, 0.195], P<0.0001) and duration in Cycle 1 (mean difference -3.6 [95% CI, -4.9, -2.3], P<0.0001) of severe neutropenia and significantly decreased the rate of all-cause chemotherapy dose reductions (aRR 0.242 [95% CI, 0.079, 0.742). The incidence of Grade 3/4 anemia was 19% and 28% (aRR 0.663 [95% CI, 0.336, 1.310]) and RBC transfusions on/after 5 weeks were 13% and 21% (aRR 0.642 [95% CI, 0.294, 1.404) with and without COSELA, respectively.



Reference: COSELA (trilaciclib). Prescribing Information. G1 Therapeutics, Inc; 02/2021. G1 Therapeutics™ and the G1 Therapeutics logo, COSELA™ and the COSELA logo are trademarks of G1 Therapeutics, Inc.

SPEAR THE TUMOR.

WHILE CHEMOTHERAPY TARGETS CANCER CELLS



SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATION

 COSELA is contraindicated in patients with a history of serious hypersensitivity reactions to trilaciclib.

WARNINGS AND PRECAUTIONS

Injection-Site Reactions, Including Phlebitis and Thrombophlebitis

COSELA administration can cause injection-site reactions, including phlebitis and thrombophlebitis, which occurred in 56 (21%) of 272 patients receiving COSELA in clinical trials, including Grade 2 (10%) and Grade 3 (0.4%) adverse reactions. Monitor patients for signs and symptoms of injection-site reactions, including infusion-site pain and erythema during infusion. For mild (Grade 1) to moderate (Grade 2) injection-site reactions, flush line/cannula with at least 20 mL of sterile 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after end of infusion. For severe (Grade 3) or life-threatening (Grade 4) injection-site reactions, stop infusion and permanently discontinue COSELA. Injection-site reactions led to discontinuation of treatment in 3 (1%) of the 272 patients.

Acute Drug Hypersensitivity Reactions

 COSELA administration can cause acute drug hypersensitivity reactions, which occurred in 16 (6%) of 272 patients receiving COSELA in clinical trials, including Grade 2 reactions (2%). Monitor patients for signs and symptoms of acute drug hypersensitivity reactions. For moderate (Grade 2) acute drug hypersensitivity reactions, stop infusion and hold COSELA until the adverse reaction recovers to Grade ≤1. For severe (Grade 3) or life-threatening (Grade 4) acute drug hypersensitivity reactions, stop infusion and permanently discontinue COSELA.

Interstitial Lung Disease/Pneumonitis

• Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinases (CDK)4/6 inhibitors, including COSELA, with which it occurred in 1(0.4%) of 272 patients receiving COSELA in clinical trials. Monitor patients for pulmonary symptoms of ILD/pneumonitis. For recurrent moderate (Grade 2) ILD/pneumonitis, and severe (Grade 3) or life-threatening (Grade 4) ILD/pneumonitis, permanently discontinue COSELA.

Embryo-Fetal Toxicity

 Based on its mechanism of action, COSELA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should use an effective method of contraception during treatment with COSELA and for at least 3 weeks after the final dose.

ADVERSE REACTIONS

 The most common adverse reactions (≥10%) were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increased, headache, and pneumonia.

To report suspected adverse reactions, contact G1 Therapeutics at 1-800-790-G1TX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This information is not comprehensive. Please see the Brief Summary of Prescribing Information on the adjacent page.



COSELA™ (trilaciclib) for injection, for intravenous use

Initial U.S. Approval: 2021

BRIFF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

COSELA is indicated to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

DOSAGE AND ADMINISTRATION

Recommended Dosage: The recommended dose of COSELA is 240 mg/m² per dose. Administer as a 30-minute intravenous influsion completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered. The interval between doses of COSELA on sequential days should not be greater than 28 hours.

Missed Treatment Session(s): If the COSELA dose is missed, discontinue chemotherapy on the day the COSELA dose was missed. Consider resuming both COSELA and chemotherapy on the next scheduled day for chemotherapy.

Discontinuation of Treatment: If COSELA is discontinued, wait 96 hours from the last dose of COSELA before resumption of chemotherapy only.

Dose Modification for Adverse Reactions: Withhold, discontinue, or alter the administration of COSELA to manage adverse reactions as described in Table 1.

Table 1: Recommended Actions for Adverse Reactions

Adverse Reaction	Severity Grade*	Recommended Action
	Grade 1: Tenderness with or without symptoms (e.g., warmth, erythema, itching)	Interrupt or slow infusion of COSELA. If 0.9% Sodium Chloride Injection, USP is being used as a diluent/flush, consider changing to 5% Dextrose Injection, USP as appropriate for subsequent infusions.
Injection site reactions including phlebitis and thrombophlebitis	Grade 2: Pain; lipodystrophy; edema; phlebitis	Interrupt infusion of COSELA. If pain not severe, follow instructions for Grade 1. Otherwise, stop infusion in extremity and rotate site of infusion to site in alternative extremity. If 0.9% Sodium Chloride Injection, USP is being used as a diluent/flush, consider changing to 5% Dextrose Injection, USP as appropriate for subsequent influsions. Central access may also be considered.
	Grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated. Grade 4: Life-threatening consequences; urgent interventions indicated.	Stop infusion and permanently discontinue COSELA.
	Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting Activities of Daily Living (ADL).	Stop infusion and hold COSELA until recovery to Grade ≤1 or baseline, then consider resuming COSELA. If Grade 2 recurs, permanently discontinue COSELA.
Acute drug hypersensitivity reactions	Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. OR Grade 4: Life-threatening consequences; urgent	Permanently discontinue COSELA.
	intervention indicated.	Held COCE A set lessons to Conde of an heading
	Grade 2 (symptomatic)	Hold COSELA until recovery to Grade ≤1 or baseline, then consider resuming COSELA. If Grade 2 recurs, permanently discontinue COSELA.
Interstitial lung disease/ pneumonitis	Grades 3: Severe symptoms; limiting self-care ADL; oxygen indicated. OR Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Permanently discontinue COSELA.
Other toxicities	Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.	Hold COSELA until recovery to Grade ≤1 or baseline, then consider resuming COSELA. If Grade 3 recurs, permanently discontinue COSELA.
	Grade 4: Life-threatening consequences; urgent intervention indicated.	Permanently discontinue COSELA.

*National Cancer Institute - Common Terminology for Adverse Events (NCI-CTCAE) Version 4.03x

CONTRAINDICATIONS

COSELA is contraindicated in patients with a history of serious hypersensitivity reactions to trilaciclib. Reactions have included anaphylaxis. WARNINGS AND PRECAUTIONS

Injection-Site Reactions, Including Phlebitis and Thrombophlebitis: COSELA administration can cause injection-site reactions including philebitis and thrombophilebitis, Injection-site reactions including philebitis and thrombophilebitis. Injection-site reactions including philebitis and thrombophilebitis and thrombophileb to diser from start or CSELA was 1 oays (arigher 1 oays) and the line preceding used in CSELA was 1 day (1 to 15). The resolved cases), lijection-site reactions including philebitis and thrombophlebitis resolved in 49 (88%) of the 56 patients and led to discontinuation of treatment in 3 (1%) of the 272 patients. Monitor patients for signs and symptoms of injection-site reactions, philebitis, and thrombophlebitis, including infusion-site pain and erythema during infusion. For mild (Grade 1) to moderate (Grade 2) injection-site reactions, that line/cannuls with at least 2 On Lof sterile 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after end of infusion. For severe (Grade 3) or life-threatening (Grade 4) injection-site reactions, stop infusion and permanently discontinue COSELA.

Acute Drug Hypersensitivity Reaction: COSELA administration can cause acute drug hypersensitivity reactions, including facial Added that proper sharing reactions, including that added and urticaria. Adulted drug hypersensitivity reactions occurred in 16 (6%) of 272 patients receiving OSSEA in clinical trials, including Grade 2 reactions (2%). One patient experienced a Grade 2 anaphylactic reaction 4 days after receiving COSELA, which resolved with epinephrine, and treatment with COSELA was continued. The median time to onset from start of COSELA was 77 days (range 2 to 256) and from the preceding dose of COSELA was 1 day (range 1 to 28). The median duration was 6 days (range 1 to 69 for the resolved cases). Acute drug hypersensitivity reactions resolved in 12 (75%) of the 16 patients. Monitor patients for signs and symptoms of acute drug hypersensitivity reactions including facial, eye, and tongue edema, urticaria, pruritus, and anaphilyatic reactions. For moderate (Grade 2) acute drug hypersensitivity reactions, stop infusion and hold COSELA until the adverse reaction recovers to Grade ≤1. For severe (Grade 3) or life-threatening (Grade 4) acute drug hypersensitivity reactions, stop infusion and permanently discontinue COSELA.

permanently discontinue COSELA.

Interstitial Lung Disease/Pneumonitis: Severe, life-threatening, or fatal interstitial ung Disease (ILD) and/or pneumonitis can occur in patients treated with cyclin-dependent kinases (CDK)4/6 inhibitors, the same drug class as COSELA ILD/pneumonitis occurred in 1 (0.4%) of 272 patients receiving COSELA in clinical trials. The adverse reaction was Grade 3 and reported 2 months after discontinuing COSELA, in a patient receiving a confounding medication. The adverse reaction did not resolve. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis such as cough, dyspnea, and hypoxal. For recurrent moderate (Grade 3) ILD/pneumonitis, permanently discontinue COSELA For severe (Grade 3) or life-threatening (Grade 4) ILD/pneumonitis, permanently discontinue COSELA Sased on its mechanism of action, COSELA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should use an effective method of contraception during treatment with COSELA and for at least 3 weeks after the final dose.

ANYERSE FEATURMS

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the label:

Injection-Site Reactions, including phlebitis and thrombophlebitis; Acute Drug Hypersensitivity Reactions; ILD/Pneumonitis

Injection-Site Reactions, including phlebits and thrombophlebits, Acute Drug Hypersensitivity Reactions; ILD/Pheumonitis

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The safety of COSELA was evaluated in Studies 1, 2, and 3. Patients received COSELA 240 mg/m² by 30-minute intravenous initiosin prior to chemotherapy on each chemotherapy day. The data described in this sectived in COSELA 240 mg/m² by 30-minute intravenous initiosin prior to chemotherapy on each chemotherapy day. The data described in this sectived in COSELA among 240 patients (122 patients in the trilacicib group and 118 patients in the placebo group) being treated for extensive stage-small cell lung cancer (ES-SCLC) in 3 randomized, double-blind, placebo-controlled trials: 32 patients with treatment naive ES-SCLC received carboplatin (AUC 5 Day 1) + etoposide (100 mg/m² Days 1-3) every 21 days; 32 repatients with previously treated ES-SCLC received topotecan (1.5 mg/m² Days 1-5) every 21 days.

Study 1: COSELA Prior to Etoposide, Carboplatin, and Atezolizumab (EP/A): Patients with newly diagnosed ES-SCLC not

Baded ES-SCLE GENERAL Prior to Etoposide, Carboplatin, and Atezolizumab (EIP/A): Patients with newly diagnosed ES-SCLC not previously treated with chemotherapy: Study 1 (G1T28-05; NCT03041311) was an international, randomized (1:1), double-blind, placebo-controlled study of C0SELA or placebo administered prior to treatment with etoposide, carboplatin, and atezolizumab (EP/A) for patients with newly diagnosed ES-SCLC not previously treated with chemotherapy. The data presented was the first of patients who received study treatment. Eighty-five percent of patients receiving COSELA and 91% receiving placebo completed valued of Ed-Valued of Ed-Valued

Study 2: COSELA Prior to Etoposide and Carboplatin (E/P): Patients with newly diagnosed ES-SCLC not previously treated with chemotherapy: Study 2 (61728-02; NCT02499770) was an international, randomized (1:1), double-blind, placebo-controlled study of COSELA or placebo administered prior to treatment with etoposide and carboplatin (E/P) for patients with newly diagnosed ES-SCLC not previously treated with chemotherapy. The data presented below are for the 75 patients who received study treatment. Seventy-six

percent of patients in the COSELA group and 87% of patients in the placebo group completed at least 4 cycles of therapy. The median

percent or patients in the USELA group and 37% of patients in the placebo group completed at least 4 cycles of therapy. The median duration of treatment was 6 cycles in each treatment group.

Study 3: COSELA Prior to Topotecan: Patients with ES-SCLC previously treated with chemotherapy: Study 3 (G1T28-03; NCTI02514447) was an international, randomized (2:1), double-blind, placebo-controlled study of COSELA or placebo administered prior to treatment with topotecan for patients with ES-SCLC previously treated with chemotherapy. The data presented below are for the 60 patients who received study treatment with the 1.5 mg/m² dose of topotecan. Thirty-eight percent of patients receiving COSELA and 29% of patients receiving placebo completed 5 or more cycles of therapy. The median duration of treatment was 3 cycles in each treatment was 10 cycles in each

Integrated Safety Analysis: The adverse reaction summary presented in Table 3 are pooled safety results from Studies 1, 2, and 3. The patients included in the pooling are those randomized patients that received at least 1 dose of COSELA (122 patients) or placebo (118 patients). Seventy-one percent of patients receiving COSELA and 78% of patients receiving placebo completed at least 4 cycles of therapy. The median duration of treatment was the same (4 cycles) for patients receiving COSELA and placebo.

Serious adverse reactions occurred in 30% of patients receiving COSELA Serious adverse reactions reported in >3% of patients who received COSELA included respiratory failure, hemorrhage, and thrombosis.

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received COSELA Adverse reactions leading to permanent discontinuation of any study treatment for patients receiving COSELA included pneumonia (2%), asthenia (2%), injection-site reaction, thrombocytopenia, cerebrovascular accident, ischemic stroke, infusion-related reaction, respiratory failure, and myositis (-1% each). Fatal adverse reactions were observed in 5% of patients receiving COSELA. Fatal adverse reactions for patients receiving COSELA included pneumonia (2%), respiratory failure (2%), acute respiratory failure (<1%), hemoptysis (<1%), and cerebrovascular accident (<1%). Infusion interruptions due to an adverse reaction occurred in 4.1% of patients who received COSELA.

The most common adverse reactions (≥10%) were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increased, headache, and pneumonia. The most frequently reported Grade ≥3 adverse reaction (≥5%) in patients receiving COSELA occurring at the same or higher incidence than in patients receiving placebo was hypophosphatemia.

The most common adverse reactions reported in at least 5% of patients receiving COSELA with a ≥2% higher incidence compared to patients receiving placebo are shown in Table 3.

Table 3: Adverse Reactions in ≥5% Patients with SCLC Receiving COSELA (with ≥2% Higher Incidence

Adverse Reaction	COSELA	(N=122)	Placebo	(N=118)
	All Grades ^a (%)	Grade ≥3 (%)	All Grades ^a (%)	Grade ≥3 (%)
Fatigue	34	3	27	2
Hypocalcemia ^b	24	<1	21	<1
Hypokalemia ^c	22	6	18	3
Hypophosphatemia ^d	21	7	16	2
Aspartate aminotransferase increased ^e	17	<1	14	<1
Headache	13	0	9	0
Pneumonia	10	7	8	7
Rash	9	<1	6	0
Infusion-related reaction	8	0	2	0
Edema peripheral	7	0	4	<1
Abdominal pain upper	7	0	3	0
Thrombosis	7	3	2	2
Hyperglycemia	6	2	3	0

"Graded per NCI CTCAE v4.03x "Hypocalcemia=calcium decreased (lab) or treatment-emergent adverse event (TEAE) preferred term 'Hypocalcemia

"Hypokalemia phosasium decreased (lab) or TEAE preferred terms 'Hypokalemia,' 'Blood potassium decreased'
"Hypophosphatemia=phosphate decreased (lab) or TEAE preferred terms 'Hypophosphatemia,' 'Blood phosphorus decreased'
"Appartate aminotransferase increased aspartate aminotransferase increased (lab) or TEAE preferred terms 'Hypophosphatemia,' 'Blood phosphorus decreased'
"Appartate aminotransferase increased aspartate aminotransferase increased (lab) or TEAE preferred term 'Blood aspartate aminotransferase increased

Grade 3/4 hematological adverse reactions occurring in patients treated with COSELA and placebo included neutropenia (32% and 69%), febrile neutropenia (3% and 9%), anemia (16% and 34%), thrombocytopenia (18% and 33%), leukopenia (4% and 17%), and lymphopenia (<1% and <1%), respectively.

DRUG INTERACTIONS

Effect of COSELA on Other Drugs, Certain OCT2, MATE1, and MATE 2K Substrate: COSELA is an inhibitor of OCT2, MATE1, and MATE-2K. Co-administration of COSELA may increase the concentration or net accumulation of OCT2, MATE1, and MATE-2K substrates in the kidney (e.g., dofetilide, dalfampridine, and cisplatin). Refer to the prescribing information for these concomitant medications for

assessing the benefit and risk of concomitant use of COSELA. Table 4: Potentially Significant Drug Interactions with COSELA.

Drugs	Recommendations	Comments
Dofetilide	The potential benefits of taking COSELA concurrently with dofetilide should be considered against the risk of QT interval prolongation.	Increased dofetilide blood levels may occur in patients who are also receiving COSELA. Increased plasma concentrations of dofetilide may cause serious ventricular arrhythmias associated with Ω T interval prolongation, including torsade de pointes.
Dalfampridine	The potential benefits of taking COSELA concurrently with dalfampridine should be considered against the risk of seizures in these patients.	Increased dalfampridine blood levels may occur in patients who are also receiving COSELA. Elevated levels of dalfampridine increase the risk of seizure.
Cisplatin	Closely monitor for nephrotoxicity.	Concurrent treatment with COSELA may increase the exposure and alter the net accumulation of cisplatin in the kidney, which may associate with dose-related nephrotoxicity.

LISE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Based on the mechanism of action, COSELA can cause fetal harm when administered to a pregnant woman. There are no available human or animal data on COSELA use to evaluate for a drug-associated risk of major birth defects, miscarniage or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarniage for the indicated population is unknown. All pregnancies have a background risk of the defect, loss, or other adverse outcomes. However, the background risk of major birth defects is 2% to 4% and of miscarniage is 15% to 20% of

outer awerse outcomes, nowever, the background risk of high or thin delects is 2% to 4% and or imiscarriage is 13% to 20% or clinically recognized pregnancies in the United States general population.

Lactation: <u>Bisk Summary</u>: There are no data on the presence of trilacibils in either human or animal milk, the effects on the breastfed child or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children, advise lactating women to not breastfeed while taking COSELA and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

<u>Pregnancy Testing</u>: Based on its mechanism of action, COSELA can cause fetal harm if administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to initiating COSELA.

Contraception: COSELA can cause fetal harm when administered to pregnant women. Advise female patients of reproductive potential to use effective contraception during treatment with COSELA and for at least 3 weeks after the final dose.

<u>Infertility</u>: No studies have been performed in humans to evaluate the effects of COSELA on fertility in either sex. Based on animal toxicology studies, COSELA may impair fertility in females of reproductive potential.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: In the pooled efficacy dataset from Studies 1, 2 and 3, 46% of 123 patients randomized to COSELA were ≥65 years of age, and 49% of 119 patients randomized to placebo were ≥65 years of age. No overall differences in safety or effectiveness of COSELA were observed between these patients and younger patients.

Hepatic Impairment: Use of COSELA is not recommended in patients with moderate or severe hepatic impairment. No dosage

adjustment is recommended for patients with mild hepatic impairment (total bilirubin < upper limit of normal [ULN] and asparates aminotransferase [AST] > ULN, or total bilirubin >1.0 to 1.5 × ULN, irrespective of AST). The pharmacokinetics of CÓSELA have not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN, irrespective of AST).

PATIENT COUNSELING INFORMATION

Injection Site Reactions. Including Phlebitis and Thrombophlebitis: Inform patients of the signs and symptoms of injection-site reactions, including phlebitis and thrombophlebitis. Advise patients to contact their healthcare provider immediately for signs and symptoms of injection-site reactions, including phlebitis and thrombophlebitis.

Acute Drug Hypersensitivity Reactions: Advise patients to contact their healthcare provider immediately for signs and symptoms of acute drug hypersensitivity reactions, including facial, eye, and tongue edema, urticaria, pruritis, and anaphylactic reactions.

Interstitial Lung Disease/Pneumonitis: Advise patients to immediately report new or worsening respiratory symptoms.

Embryo-Fetal Toxicity: Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider

of a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatm COSELA and for at least 3 weeks after the final dose.

Lactation: Advise women not to breastfeed during treatment with COSELA and for at least 3 weeks after the final dose of COSELA. Drug Interactions: Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products.

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DESPITE CHALLENGING TIMES, NCODA DOUBLES DOWN ON ITS ADVANCED PHARMACY PRACTICE EXPERIENC

By Christine Pujol, PharmD, MBA

ver the course of the 2020-'21 school year, NCODA continued to provide a high-quality Advanced Pharmacy Practice Experience (APPE) for pharmacy students across North America.

While many rotation sites had to



Christine Pujol

cancel student rotations due to lack of accommodations, NCODA stepped up and took in twice the number of students as the previous year.

NCODA continues to provide both in-person and

virtual rotations to fourth-year pharmacy students. It currently offers its elective APPE rotation to 17 schools across the U.S. and Canada.

NCODA's APPE rotation offers a unique experience to all students interested in oncology and association management. Students partaking in NCODA's APPE rotation are able to

NCODA APPE AFFILIATIONS

- 1. Albany College of Pharmacy and Health Sciences
- 2. Binghamton University
- 3. Keck Graduate Institute
- 4. Mercer University
- 5. Midwestern University
- 6. Regis University
- 7. Shenandoah University
- 8. St. John Fisher College
- 9. Texas Tech University
- 10. The Ohio State University
- 11. University of Arizona
- 12. University of Charleston School of Pharmacy
- 13. University of Kansas
- 14. University of Minnesota
- 15. University of Rhode Island
- 16. University of South Florida
- 17. University of Toronto

interact with all members of the medically integrated oncology team, and complete meaningful projects. We participate in journal clubs, topic discussions and oncology research, as well as present on a variety of different topics.

NCODA's APPE program truly pro-

vides students with a unique and tailored experience. While students may typically have a general understanding of oncology medications, this rotation helps to solidify their knowledge to better prepare them to help cancer patients upon graduation.

The rotation provided me with many opportunities to grow professionally by sharpening my skills in presenting, researching and writing, all while learning the unique aspects of association management. I learned about oncology medications, cost avoidance, interprofessional teamwork and quality improvement, among many other skills.

I also gained an appreciation for all the stakeholders involved in oncology, from pharmacies and clinics to insurance and pharmaceutical companies.

My preceptors were phenomenal, and they genuinely cared about my APPE experience. I loved this rotation so much that I shared it with my classmates. I highly recommend it!

▲ **Christine Pujol**, PharmD, MBA, is a 2021 graduate of the Bernard J. Dunn School of Pharmacy | Shenandoah University in Winchester, Virginia, and a former NCODA APPE student.

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- Regis University
- St. John Fisher College

- Shenandoah University
- The Ohio State University
- The University of Rhode Island
- University of Arizona



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OPTA EVOLVING AS PHARMACY TECHS CONTINUE TO TAKE ON MORE CLINICAL RESPONSIBILITIES

By Taryn Newsome, CPhT

he evolving role of the pharmacy technician continues to set high standards within the Medically Integrated Pharmacy.

Oncology pharmacy technicians work with all aspects of the medically integrated team to ensure that patients receive their therapies safely and effectively. Their role continues to evolve as



Taryn Newsome

they take on more clinical responsibilities. NCODA created the Oncology Pharmacy Technician Association (OPTA) to facilitate this evolution.

I am extremely honored to be the

Oncology Pharmacy Technician Association Coordinator for NCODA. My goal is to reach every pharmacy technician that I possibly can who desires an advancement in their role.

Before I joined the NCODA team, OPTA accompanied me throughout my pharmacy technician career and changed my perception of what a pharmacy technicians could achieve. I was able to connect and build relationships with pharmacy technicians throughout the country who were experiencing the same things I was experiencing. I gained a stronger confidence in my role as well as gained a passion to achieve and learn more.

OPTA recognizes the importance of increasing skill sets to provide better patient care and offers several opportunities for oncology pharmacy technicians to accomplish this goal.

OPTA'S MONTHLY MEETING

OPTA members gather virtually for an informative and interactive meet-

ing on the second Wednesday of each month. These meetings are designed to expand knowledge specific to the oncology pharmacy tech role. Participants can learn from their peers, experience different perspectives and broaden their way of thinking. Each meeting offers a variety of information:

Drug Update: OPTA updates members on new drug approvals and drug

indications. Sessions are presented by an Advanced Pharmacy Practice Experience (APPE) pharmacy student on rotation with NCODA. The student also writes an article for the OPTA newsletter. Updates include the disease state, indications, dosing, risk factors, symptoms, possible adverse reactions, patient monitoring and more.



OPTA relaunched its newsletter in May.

Technician in Focus: In this segment, an OPTA member discusses the work they perform within the practice and shares the pharmacy processes they utilize to improve patient care. Specific job duties and the tech role within the pharmacy is also highlighted.

Hot Topic Discussion: This segment is a roundtable discussion lead by OPTA leaders with the goal of increasing member involvement. OPTA members have an opportunity to have an open discussion on specific pharmacy topics.

NCODA and OPTA Updates: Updates are provided at every meeting to ensure OPTA members are kept informed of important news and initiatives. This segment also highlights member resources, such as NCODA's Financial Assistance tool, free Continuing Education locator and Oral

Chemotherapy Education (OCE) sheets.

OPTAReview

OPTAReview is a virtual newsletter that encompasses essential and informative news for oncology pharmacy technicians. Members receive a copy via email at the beginning of each month. The newsletter was completely revamped earlier this year and relaunched in May.

New content was added, along with QR codes to allow members quick access to NCODA resources. Each month's newsletter includes:

- ▲ A welcome message authored by an OPTA leader;
- ▲ A profile of an OPTA leader, including a photo, short biography and personal information to help members get to know one another on a more intimate level:
- ▲ A Technician in Focus profile similar to the OPTA leader article; and
- ▲ A drug update focused on new FDAapproved products and new indications.

NCODA recognizes the significant role of the oncology pharmacy technician in the medically integrated practice and the many career opportunities for pharmacy technicians nationwide. Pharmacy technicians who demonstrate a higher level of learning and professionalism are better able to advance both patient care and their own careers. OPTA provides a platform to expand and develop these leadership skills.

▲ **Taryn Newsome**, CPhT, is the Oncology Pharmacy Technician Association Coordinator at NCODA.

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Study design: ELITEK was studied in a multicenter, randomized, open-label, 3-arm, phase 3 study in 275 patients with leukemia, lymphoma, and solid tumor malignancies at risk for hyperuricemia and TLS. Patients were randomized 1:1:1 to 1 of 3 arms. Patients in Arm A received ELITEK 0.2 mg/kg/d for 5 days (n=92). Patients in Arm B received ELITEK 0.2 mg/kg/d from Day 1 through Day 3, followed by oral allopurinol 300 mg/d from Day 3 through Day 5 (overlap on Day 3: ELITEK 0.2 mg/kg/d and allopurinol 300 mg/d administered approximately 12 hours apart) (n=92). Patients in Arm C received oral allopurinol 300 mg/d for 5 days (n=91). Anticancer therapy was initiated 4 to 24 hours after the first antihyperuricemic dose in each arm. The primary endpoint of this study was the uric acid response rate, defined as the proportion of patients with plasma uric acid levels ≤7.5 mg/dL from Day 3 to Day 7, after initiation of antihyperuricemic treatment.^{1,2}

ELITEK is indicated for the initial management of plasma uric acid levels in patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid. ELITEK is indicated only for a single course of treatment.

Important Safety Information

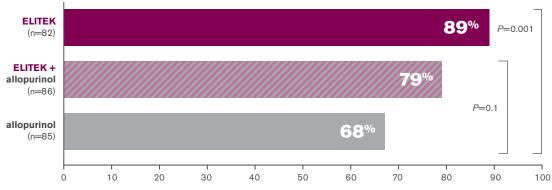
WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS, METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS

- Hypersensitivity Reactions: ELITEK can cause serious and fatal hypersensitivity reactions including anaphylaxis. Immediately and permanently discontinue ELITEK in patients who experience a serious hypersensitivity reaction.
- Hemolysis: Do not administer ELITEK to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue ELITEK in patients developing hemolysis.
 Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting ELITEK.
- Methemoglobinemia: ELITEK can result in methemoglobinemia in some patients. Immediately and permanently discontinue ELITEK in patients developing methemoglobinemia.
- Interference with Uric Acid Measurements: ELITEK enzymatically degrades uric acid in blood samples left at room temperature. Collect blood samples in prechilled tubes containing heparin and immediately immerse and maintain sample in an ice water bath. Assay plasma samples within 4 hours of collection.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNING, on the following pages.

ELITEK GIVEN PROPHYLACTICALLY MAINTAINED NORMAL URIC ACID LEVELS IN SIGNIFICANTLY MORE HIGH-RISK ADULT PATIENTS VS ALLOPURINOL¹

High-risk patients who maintained normal uric acid levels (≤7.5 mg/dL) between 3 and 7 days after initiation of antihyperuricemic treatment¹,³



Percentage of patients with uric acid ≤7.5 mg/dL

Primary endpoint:

- Results were consistent with the overall study population of intermediate and high-risk adult patients: 87% (n=92) of all patients receiving ELITEK prophylactically maintained uric acid levels ≤7.5 mg/dL vs 66% (n=91) of patients receiving allopurinol (P=0.001)¹
 - ELITEK + allopurinol maintained normal uric acid in 78% (n=92) of patients (P=NS vs allopurinol)

Per-patient incidence of selected adverse reactions by study arm in Study 4:

All Grades ARs in Study 4 (ELITEK alone; ELITEK plus oral allopurinol; oral allopurinol alone) were nausea (57.6%, 60.9%, 54.9%), peripheral edema (50%, 43.5%, 42.9%), vomiting (38%, 37%, 30.8%), anxiety (23.9%, 17.4%, 17.6%), abdominal pain (21.7%, 33.7%, 25.3%), hypophosphatemia (17.4%, 22.8%, 16.5%), hyperbilirubinemia (16.3%, 14.1%, 7.7%), pharyngolaryngeal pain (14.1%, 20.7%, 9.9%), sepsis (12%, 7.6%, 4.4%), fluid overload (12%, 6.5%, 3.3%), increased ALT (10.9%, 27.2%, 17.6%), and hyperphosphatemia (9.8%, 15.2%, 8.8%).²

ALT=alanine aminotransferase; AR=adverse reaction.

Important Safety Information (cont'd)

CONTRAINDICATIONS

ELITEK is contraindicated in patients with a history of anaphylaxis or severe hypersensitivity to rasburicase or in patients with development of hemolytic reactions or methemoglobinemia with rasburicase. ELITEK is contraindicated in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥20%), when used concomitantly with anticancer therapy, are vomiting, nausea, fever, peripheral edema, anxiety, headache, abdominal pain, constipation, diarrhea, hypophosphatemia, pharyngolaryngeal pain, and increased alanine aminotransferase.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Consider the benefits and risks of ELITEK and possible risks to the fetus when prescribing ELITEK to a pregnant woman
- Lactation: Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with ELITEK and for 2 weeks after the last dose

Please see Brief Summary of full Prescribing Information, including Boxed WARNING, on the following pages.

References: 1. Cortes J, Moore JO, Maziarz RT, et al. Control of plasma uric acid in adults at risk for tumor lysis syndrome: efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone—results of a multicenter phase III study. *J Clin Oncol.* 2010;28(27):4207-4213. 2. ELITEK [prescribing information]. Bridgewater, NJ: sanofi-aventis U.S. LLC. 3. Data on file. Bridgewater, NJ: sanofi-aventis U.S. LLC.





(rasburicase) for injection, for intravenous use

Brief Summary of Prescribing Information

WARNING: HYPERSENSITIVITY REACTIONS, HEMOLYSIS METHEMOGLOBINEMIA, AND INTERFERENCE WITH URIC ACID MEASUREMENTS

Hypersensitivity Reactions

Elitek can cause serious and fatal hypersensitivity reactions including anaphylaxis. Immediately and permanently discontinue Elitek in patients who experience a serious hypersensitivity reaction [see Contraindications (4), Warnings and Precautions (5.1), Adverse Reactions (6.2)].

Hemolysis

Do not administer Elitek to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue Elitek in patients developing hemolysis. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek [see Contraindications (4), Warnings and Precautions (5.2)].

Elitek can result in methemoglobinemia in some patients. Immediately and permanently discontinue Elitek in patients developing methemoglobinemia [see Contraindications (4), Warnings and Precautions (5.3)].

Interference with Uric Acid Measurements

Elitek enzymatically degrades uric acid in blood samples left at room temperature. Collect blood samples in prechilled tubes containing heparin and immediately immerse and maintain sample in an ice water bath. Assay plasma samples within 4 hours of collection [see Warnings and Precautions (5.4)].

INDICATIONS AND USAGE

Elitek is indicated for the initial management of plasma uric acid levels in pediatric and adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid. Limitations of Use

Elitek is indicated only for a single course of treatment [see Warnings and Precautions (5.1)].

CONTRAINDICATIONS

Elitek is contraindicated in patients with a history of anaphylaxis or severe hypersensitivity to Linea is contraminucated in patients with a history of anaphylaxis or severe hypersensitivity to rasburicase or in patients with development of hemolytic reactions or methemoglobinemia with rasburicase [see Boxed Warning, Warnings and Precautions (5.1, 5.2, 5.3)]. Elitek is contraindicated in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD) [see Boxed Warning, Warnings and Precautions (5.2)].

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions

Elitek can cause serious and fatal hypersensitivity reactions including anaphylaxis. In clinical studies, anaphylaxis was reported in <1% patients receiving Elitek. This can occur at any time during treatment including the first dose. Signs and symptoms of these reactions include bronchospasm, chest pain and tightness, dyspnea, hypoxia, hypotension, shock, and urticaria. Immediately and permanently discontinue Elitek administration in any patient developing clinical evidence of a serious hypersensitivity reaction [see Boxed Warning, Contraindications (4), Adverse Reactions (6.2)1

The safety and efficacy of Elitek have been established only for a single course of treatment once daily for 5 days.

5.2 Hemolysis

Elitek is contraindicated in patients with G6PD deficiency because hydrogen peroxide is one of the major by-products of the conversion of uric acid to allantoin. In clinical studies, hemolysis occurs in <1% patients receiving Elitek; severe hemolytic reactions occurred within 2-4 days of the start of Elitek. Immediately and permanently discontinue Elitek administration in any patient developing hemolysis. Institute appropriate patient monitoring and support measures (e.g., transfusion support). Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek [see Boxed Warning, Contraindications

Methemoglobinemia

In clinical studies, methemoglobinemia occurred in <1% patients receiving Elitek. These included cases of serious hypoxemia requiring intervention with medical support measures. It is not known whether patients with deficiency of cytochrome bs reductase (formerly known as methemoglobin reductase) or of other enzymes with antioxidant activity are at increased risk for methemoglobinemia or hemolytic anemia. Immediately and permanently discontinue Elitek administration in any patient identified as having developed methemoglobinemia. Institute appropriate monitoring and support measures (e.g., transfusion support, methylene-blue administration) [see Boxed Warning, Contraindications (4)].

5.4 Laboratory Test Interference

At room temperature, Elitek causes enzymatic degradation of the uric acid in blood/plasma/ serum samples potentially resulting in spuriously low plasma uric acid assay readings. Special sample handling procedure must be followed to avoid ex vivo uric acid degradation [see Boxed Warning, Drug Interactions (7)].

ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Anaphylaxis [see Boxed Warning, Contraindications (4), Warnings and Precautions (5.1)]
 Hemolysis [see Boxed Warning, Contraindications (4), Warnings and Precautions (5.2)]
- Methemoglobinemia [see Boxed Warning, Contraindications (4), Warnings and Precautions (5.3)]

6.1 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 data below reflect exposure to Elitek in 265 pediatric and 82 adult patients enrolled in one active-controlled trial (Study 1), two uncontrolled trials (Studies 2 and 3), and an uncontrolled safety trial (n=82). Additional data were obtained from an expanded access program of 356 patients, for whom data collection was limited to serious adverse reactions. Among these 703 patients 63% were male, the median age was 10 years (range 10 days to 88 years), 73% were Caucasian, 9% African, 4% Asian, and 14% other/unknown.

Among the 347 patients for whom all adverse reactions regardless of severity were assessed. the most frequently observed adverse reactions (incidence ≥10%) were vomiting (50%), fever (46%), nausea (27%), headache (26%), abdominal pain (20%), constipation (20%), diarrhea (20%), mucositis (15%), and rash (13%). In Study 1, an active control study, the following adverse reactions occurred more frequently in Elitek-treated subjects than allopurinol-treated subjects: vomiting, fever, nausea, diarrhea, and headache. Although the incidence of rash was similar in the two arms, severe rash was reported only in one Elitek-treated patient.

Further studies, including one-active controlled study (Study 4) and four supportive studies, have been conducted in adult patients. In these studies, Elitek was administered to a total of 434 adult patients (58% male, 42% female; median age 56 years [range 18 years to 89 years]; 52% Caucasian, 7% African, 14% Asian, 28% other/unknown).

Of these 434 patients, 275 adult patients with leukemia, lymphoma, or solid tumor malignancies at risk for hyperuricemia and tumor lysis syndrome (TLS) were randomized in an open label trial receiving either Elitek alone, Elitek in combination with allopurinol, or allopurinol alone (Study

A drug-related adverse reaction in Study 4 of any grade was experienced in 4.3% of Elitek-treated patients, 5.4% of Elitek/allopurinol-treated patients, and 1.1% of allopurinol-treated

Table 1 presents the per-patient incidence of adverse reactions by study arm in Study 4.

Table 1: Per-Patient Incidence of Selected Adverse Reactions by Study Arm in Study 4

Adverse Reaction	Elitek (n=92)				Allopurinol (n=91)	
	All Grades %	Grades 3,4 %	All Grades %	Grades 3,4 %	All Grades %	Grades 3,4 %
Nausea	57.6	1.1	60.9	1.1	54.9	2.2
Peripheral edema	50	2.2	43.5	3.3	42.9	6.6
Vomiting	38	1.1	37	0	30.8	1.1
Anxiety	23.9	3.3	17.4	0	17.6	0
Abdominal pain	21.7	3.3	33.7	4.3	25.3	2.2
Hypophosphatemia	17.4	4.3	22.8	6.5	16.5	6.6
Hyperbilirubinemia	16.3	3.3	14.1	2.2	7.7	4.4
Pharyngolaryngeal pain	14.1	1.1	20.7	0	9.9	0
Sepsis	12	5.4	7.6	6.5	4.4	4.4
Fluid overload	12	0	6.5	0	3.3	1.1
Increased alanine aminotransferase	10.9	3.3	27.2	4.3	17.6	2.2
Hyperphosphatemia	9.8	0	15.2	0	8.8	1.1

Overall incidence ≥10% in any Elitek arm and the difference between any Elitek arm versus the allopurinol arm ≥5%.

*Events were reported and graded according to NCI-CTC version 3.0 and presented as preferred terms MedDRA version 10.1.

Hypersensitivity reactions occurred in 4.3% of Elitek-treated patients and 1.1% of Elitek/ allopurinol-treated patients in Study 4. Clinical manifestations of hypersensitivity included arthralgia, injection site irritation, peripheral edema, and rash.

The following serious adverse reactions occurred at a difference in incidence of ≥2% in patients receiving Elitek compared to patients receiving allopurinol in randomized studies (Study 1 and Study 4): pulmonary hemorrhage, respiratory failure, supraventricular arrhythmias, ischemic coronary artery disorders, and abdominal and gastrointestinal infections.

The incidence of anaphylaxis, hemolysis, and methemoglobinemia was less than 1% of the 887 Elitek-treated patients entered on these clinical trials.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Elitek can elicit antiproduct antibodies that bind to rasburicase and in some instances inhibit the activity of rasburicase in vitro [see Boxed Warning, Warnings and Precautions (5.1)].

In clinical trials of pediatric patients with hematologic malignancies, 24/218 patients tested (11%) developed antibodies by day 28 following Elitek administration as assessed by qualitative

Using quasi-quantitative immunoassays in rasburicase-naive adult patients with hematological malignancies, 47/260 (18%) patients were positive for anti-rasburicase immunoglobulin G (IgG), 21/260 (8%) patients were positive for anti-rasburicase neutralizing IgG, and 16/260 (6%) patients were positive for anti-rasburicase immunoglobulin E (IgE) from day 14 to 24 months after 5 daily doses of Elitek.

The incidence of antibody responses detected is highly dependent on the sensitivity and specificity of the assay, which have not been fully evaluated. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including serum sampling, timing and methodology, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Elitek with the incidence of antibodies to other products may be misleading.

(rasburicase) for injection, for intravenous use

6.3 Postmarketing Experience

The following adverse reactions have been identified from clinical trials and/or postmarketing surveillance. Because they are reported from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Central nervous system disorders: convulsion, muscle contractions involuntary

Immune system disorders: cases of anaphylaxis with fatal outcome have been reported.

7 DRUG INTERACTIONS

Laboratory Test Interference

At room temperature, Elitek causes enzymatic degradation of the uric acid in blood/plasma/ serum samples potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation.

Uric acid must be analyzed in plasma. Blood must be collected into prechilled tubes containing heparin anticoagulant. Immediately immerse plasma samples for uric acid measurement in an ice water bath. Plasma samples must be prepared by centrifugation in a precooled centrifuge (4°C). Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within four hours of collection [see Boxed Warning].

Rasburicase does not metabolize allopurinol, cytarabine, methylprednisolone, methotrexate, 6-mercaptopurine, thioguanine, etoposide, daunorubicin, cyclophosphamide or vincristine in vitro. No metabolic-based drug interactions are therefore anticipated with these agents in patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, Elitek may cause fetal harm when administered to pregnant women. In animal reproduction studies, intravenous administration of rasburicase to pregnant rabbits during organogenesis at 5-times the human exposure (based on AUC) at the recomended human dose of 0.2 mg/kg resulted in adverse developmental outcomes, including structural abnormalities, embryo-fetal mortality, and alterations to growth (see Data). The limited available data with Elitek use in pregnant women are insufficient to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal fetal outcomes. Consider the benefits and risks of Elitek and possible risks to the fetus when prescribing Elitek to a pregnant woman.

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

Intravenous administration of rasburicase at doses of 10, 20, or 50 mg/kg/day (approximately 14, 34, and 100 times the exposure at the recommended human dose of 0.2 mg/kg) to pregnant rats from gestation days (GD) 6 to 17 produced multiple heart and great vessel malformations at 50 mg/kg/day (approximately 100 times the exposure at the recommended human dose). Intravenous administration of rasburicase from GD 6 to 19 at doses of 2, 10, or 20 mg/kg/day (approximately 5, 26, and 54 times the exposure at the recommended human dose) to pregnant rabbits produced increased pre and postimplantation loss, abortion, decreased uterine weight, decreased fetal body weights, and heart and great vessel malformations at all dose levels.

8.2 Lactation

Risk Summary

There are no available data on the presence of rasburicase in human breast milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with Elitek, and for 2 weeks after the last dose.

8.4 Pediatric Use

The safety and effectiveness of Elitek have been established in pediatric patients ages 1 month to 17 years for initial management of plasma uric acid levels in patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid. Elitek was studied in 246 pediatric patients. There were insufficient numbers of patients between 0 and 6 months (n=7) to determine whether they respond differently than older children. Mean uric acid AUC $_{\rm 0-96\ hr}$ was higher in children <2 years of age (n=24; 150 \pm s.e. 16 mg hr/dL) than those age 2 to 17 years (n=222; 108 \pm s.e. 4 mg hr/dL). Children <2 years of age had a lower rate of achieving normal uric acid concentration by 48 hours (83% [95% CI: 62, 95]) than those 2 to 17 years (93% [95% CI: 89, 95]).

8.5 Geriatric Use

Of the total number of adults treated with Elitek (n=434) in clinical studies, 30% were aged 65 and over while 8% were aged 75 and over. No overall differences in pharmacokinetics, safety, and effectiveness were observed between the elderly and younger patients.

10 OVERDOSAGE

Of the six reported cases of overdosage, five cases had no adverse events reported; nonserious adverse events in the sixth case (a single dose of 1.3 mg/kg) included decreased levels of blood potassium and blood albumin, and increased levels of carbon dioxide, blood lactate dehydrogenase, blood urea, blood phosphorus, blood sodium, and blood alkaline phosphatase. Monitor patients who receive an overdose and initiate supportive measures if required.

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EXECUTIVE COUNCIL PROFILE

Jan Montgomery, PharmD, has been a member of the NCODA Executive Council since 2016. Montgomery was Director of Pharmacy at South Carolina Oncology Associates (SCOA). SCOA has been serving patients in Columbia, South Carolina, for more than 40 years and is considered one of the Southeastern leaders in cancer care.

How did you become involved with NCODA and what prompted you to join its Executive Council?

Michael Reff reached out to me by phone six or seven years ago. Mike shared the great work that he and others were doing in the oral dispensing space and invited me to attend an NCODA Summit. The meeting was informative, collaborative and extremely well-done.

I was encouraged to know there were others having the same struggles in the oral arena and that NCODA was leading the charge against the Pharmacy Benefits Managers (PBMs) in favor of the medically integrated pharmacy model. Some months later, Mike asked me to be part of the NCODA grassroots effort and serve on the Executive Council. It has been a great honor to be part do this tremendous organization.

Tell us a little about your expertise and what you bring to the table in helping shape NCODA's strategies.

I joined South Carolina Oncology Associates as the Director of Pharmacy (DOP) in 1991. Having worked in the retail, hospital and homecare settings, I was well-positioned to play a role in transitioning SCOA from a hospital-based practice to a stand-alone clinic.

The next major step for SCOA brought our three clinics and business office together under one roof. We built a very large building in a key location and consolidated medical, gynecology and radiation oncology, as well as pharmacy, laboratory, research, reimbursement and administration.

As DOP for 30 years, my responsibilities included the infusion side of the business and the oral dispensing pharmacy. Meeting with pharmaceutical representatives, handling clinical responsibilities and negotiating/managing contracts were all part of my day. The infusion pharmacy was located center stage in the infusion center, providing services from a state-of-the-art USP 797/800 cleanroom environment called the Misterium (by

JAN MONTGOMERY



SOUTH CAROLINA ONCOLOGY ASSOCIATES

Grifols). Our URAC-accredited oral pharmacy, SC Oncology Retail Pharmacy, is located in close proximity to the infusion center for easy access by patients and family members.

The current payer environment presents challenges both from the perspective of patient care and the business health of the pharmacy practice. What changes would you like to see to help improve the quality of patient care?

The payer environment has grown into a massive and complex maze. Medically Integrated Pharmacies (MIPs) must be savvy in every aspect of business and oncology to navigate the twists and turns every minute of the day.

Our responsibility as part of the oncology healthcare team is to voice our concerns about the inadequacies of the PBM system. Ten days is an unacceptable timeframe for a patient to receive medications from a PBM. We must be allowed to keep the prescriptions in the practice where we provide more timely access. Insurance companies and PBMs cannot keep changing the rules and raising the bar to allow access to their networks.

Additionally, strong-arm tactics such as agreements with pharmacy service administrative organizations (PSAOs) — i.e.,

brand and generic effective rates — are very deceptive business practices. The NCODA membership must speak out for a fair playing field and transparency. Direct and Indirect Remuneration (DIR) fees must be eliminated.

NCODA faces many daunting challenges in trying to bring forth its message of the efficacy of Medically Integrated Pharmacy. How do we keep that message on target?

The phenomenal growth of NCODA as an organization is a testament to its Mission and tagline — Passion for Patients. NCODA's message resonates with every aspect of oncology. The organization has brought together not just pharmacists and technicians, but also administrators, physicians, nurses, the pharmaceutical industry and many other stakeholders who are willing to break down the barriers that prevent our success.

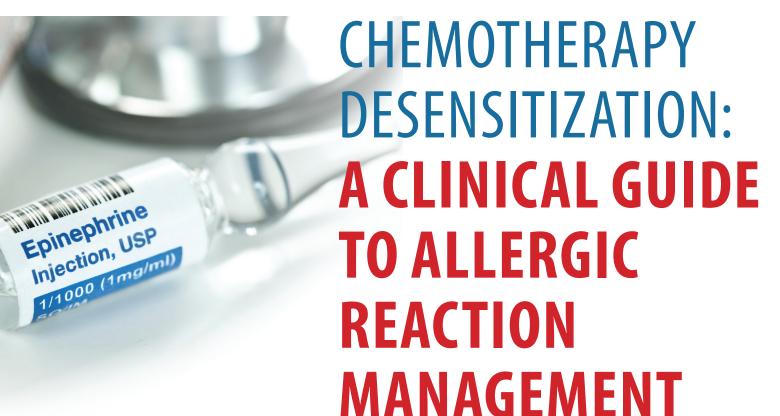
The alliances formed by insurance companies merging with PBMs, limited access to networks, hidden fees, demands for accreditation(s) and — my favorite — network contracts that are strategically designed to discourage even the most sophisticated practice from joining are just a few challenges we all face.

How do we measure success?

Patient satisfaction surveys, call stats, timely adherence calls, care plan resolution and other quality measures are all effective ways to gauge the success of the day-to-day operation. Digital fluency is also a way to evaluate success.

Digital fluency has enabled NCODA and oncology practices across the nation the ability to give MIPs the knowledge and tools to provide medications to the patients with a well-informed and trained staff of professionals. Technology improvements in electronic medical records (EMR), pharmacy software, compliance programs and security all point to digitally mature organizations. It is equally important to have a strong framework which is the digital confidence of the workforce, leadership and culture.

The pandemic highlighted the digital fluency of practices that quickly implemented telemedicine and also moved key departments (i.e., reimbursement) from in-office to working from home status. The COVID pandemic underscored the digital fluency of NCODA, a prime example being the ease with which the NCODA team converted the 2020 Spring Forum from an in-person event to an all-digital platform in a few days. That's a success story!



By Wendy M. Wong, PharmD, BCOP, Dallas Lawry, DNP, FNP-C, OCN, Lorraine Anderson, MD, & Andrew Pham, MD

ith the availability of life-saving medications such as chemotherapy paired with the overall increase of allergies and atopy in the human population, patients with allergies to oncology pharmaceuticals may be robbed of their opportunity for cure, palliation, or increased length of life.

Fortunately, a process that briefly suppresses a patient's immune system, desensitization, allows patients with allergies to receive the full therapeutic dose of a medication.

Presently, desensitization is being used with great success in oncology and allows cancer patients to receive chemotherapy/immunotherapy despite a previous allergic reaction.

CANCER TREATMENT IS REGIMEN-SPECIFIC

Like antibiotics that are somewhat infection-specific, chemotherapies are often

cancer-specific. Whether chemotherapy or immunotherapy, these anticancer treatment regimens undergo rigorous, costly and lengthy clinical trials to gain approval for cancer-specific indications.

If an oncology patient is allergic to a certain anticancer therapy or drug, especially a first-line curative treatment, this can be detrimental to patient outcomes as it limits a patient's options for treatment. This specificity allows for little flexibility with alternative treatments that have been previously studied, especially for rare cancers.

A successful chemotherapy desensitization has the potential to save the lives of cancer patients. However, desensitization is not without risks.¹

Some patients still have hypersensitivity reactions despite being carefully monitored and premedicated. Some desensitization reactions are very manageable, while others are severe enough to permanently discontinue a drug.

The purpose of this article is to discuss common reactions seen during chemotherapy desensitization, and the first-line agents that can be quickly administered to prevent worsening reactions or anaphylaxis.

ALLERGENS AND ALLERGIES

Before discussing desensitization, it is important to understand the mechanism by which someone develops an allergy. To become allergic to an allergen, first an immune system is sensitized to a specific allergen. This initial sensitization process is what triggers an immune reaction for subsequent future allergic reactions.

Sensitization and becoming allergic: A type I hypersensitivity response to an antigen occurs in two phases. The first phase is sensitization during which the patient experiences asymptomatic contact with the antigen.

However, on a molecular level, this antigen is presented to naive T cells by antigen-presenting cells. The naive T cells are activated and becoming type 2 T helper cells (TH2 cells), which stimulate naïve B cells to become memory B cells and plasma cells that produce allergen-specific immunoglobulin E (IgE).

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ALLERGIC REACTION

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These IgE antibodies bind to high-affinity FcɛRI receptors on mast cells and basophils. The end result of this sensitization process is a pool of drug-specific memory type 2 T helper cells (TH2 cells) and IgE+ B cells.² Essentially, this asymptomatic sensitization phase primes a patient for allergy on next encounter.

The second phase is the effects phase and occurs upon subsequent exposure to the antigen.

As the free antigen binds to the antigen-specific IgE on mast cells and basophils, it causes a cross-linking of bound IgE antibodies and activation of mast cells and basophils. This mast cell and basophil activation results in degranulation and release of histamine, prostaglandins, leukotrienes, platelet-activating factors, tryptase, cytokines, and other vasoactive mediators. The vasoactive mediators are potent triggers of vascular leak, intestinal hypermobility, bronchoconstriction, inflammation and vasodilation.

Thus, with subsequent re-exposure to the antigen, the patient experiences various effects of the immunological response, resulting in the classic immediate IgE mediated symptom constellation of nasal congestion, urticaria (hives), pruritus, flushing, angioedema, laryngeal edema, wheezing, shortness of breath, nausea, abdominal cramping, diarrhea, hypotension, syncope and cardiorespiratory collapse.

Due to the mechanism of type I hypersensitivity reactions, upon subsequent exposure to the antigen, this immediate hypersensitivity reaction can occur within minutes or up to six hours after re-exposure; most reactions occur within one hour.

Of note, most chemotherapies routinely require premedications (antihistamines and corticosteroids) which can mask or delay the early signs of immediate hypersensitivity. In type I hypersensitivity, the observed phenotypic clinical features of the hypersensitivity reaction are a direct result of the reaction endotype or specific effector cells and

mediator mechanisms of the underlying hypersensitivity reaction.

Because the clinical signs of reaction can progress to life-threatening anaphylaxis, it is critical that clinicians involved in the desensitization process are adept in managing these side effects, including clinical assessment and use of emergency medications for the proper allergic indication.

DRUG DESENSITIZATION

Drug desensitization is a process that temporarily modifies this immune response, allowing short-term tolerance while a drug is being administered. The allergy will return within 48 to 72 hours after discontinuation of the medication, as is the case between cycles of chemotherapy. For this reason, patients require desensitization for all subsequent and future doses (chemotherapy cycles).

In general, a chemotherapy desensitization is performed within the hospital setting and is closely followed by an allergist, an oncologist, and a team of nurses trained in both chemotherapy and desensitization.

An example of the chemotherapy desensitization process is briefly described here:³

- ▲ The patient is premedicated the night before desensitization and immediately before the procedure, usually 12 hours apart. As an example, a patient would be premedicated at 8 p.m. the night before and at 8 a.m. the morning of desensitization. These premedications are not standard, and they are specific to the patient's prior allergic reaction.³ Medications might include diphenhydramine, famotidine, and montelukast.
- ▲ Chemotherapy is diluted into three or four concentrations ranging from 1/1000 to 1/1 dilution of the drug. Each bag is administered in four steps for a total of 12 to 16 steps, and the patient is monitored at every up-titration with vital signs and symptom management. Bag A might be a 1:100 concentration of the chemotherapy, bag B would be 1:10, and the final bag would be 1:1, or full concentration of the drug.^{3,4}
- Emergency medications should be

readily available at the bedside in order to immediately manage reactions and prevent these reactions from becoming more severe.³

Today, chemotherapy desensitization has become well-established in the world of oncology and immunology and allows oncology patients to be rechallenged with a chemotherapeutic agent that they were previously allergic to.³ Therefore, chemotherapy desensitization has the potential to increase length of life (curative) and quality of life (palliative).

RISKS OF CHEMOTHERAPY DESENSITIZATION

However, rechallenging a patient to a chemotherapy agent that they are allergic to is not without risk. Any sign of reaction, however subtle, is taken very seriously because the patient's immune system has already been suppressed with allergy medications.

There are numerous reactions that can occur during this desensitization process, ranging from mild to severe. The most serious and life-threatening adverse outcome of desensitization is anaphylaxis.³

There are different types of allergic, or hypersensitivity reactions, and the World Allergy Organization has divided them into two categories: immediate and delayed reactions.⁴

Immediate reactions occur within minutes to hours of administration. Some of these reactions include: flushing, pruritis, urticaria (hives), angioedema, nasal congestion, hoarse voice, wheezing and/or bronchospasm, shortness of breath, nausea, vomiting, diarrhea, hypotension and severe anxiety, often described by the literature as an "impending sense of doom." 1,5

Presented on the following two pages is a chart detailing some of the most common immediate-type allergic reactions that occur during a chemotherapy desensitization, and the typical emergency medications that are used to treat them.

Please consider detaching this chart for future clinical guidance.

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IMMEDIATE-TYPE ALLERGIC REACTIONS IN CHEMOTHERAPY DESENSITIZATION & THEIR TREATMENT

DRUG	DRUG CLASS	MECHANISM OF ACTION	INDICATION(S) & DOSING (ADULT)
Diphenhydramine (Benadryl®)	Histamine H1 antagonist, first- generation	Competes with histamine for H1- receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract. Does not relieve upper or lower airway obstruction, hypotension or shock	Anaphylaxis (adjunct to epinephrine): IV: 25-50 mg once, then every four to six hours as needed; administer after epinephrine Mild-moderate cutaneous reactions: P0: 25 mg every four to six hours or 50 mg every six to eight hours as needed IM, IV: 10-50 mg every six hours as needed Angioedema, allergic (acute): off-label use, alternative agent; if anaphylaxis, give epinephrine first P0: 25 mg every four to six hours or 50 mg every six to eight hours as needed IM, IV: 10-50 mg every six hours as needed Infusion or transfusion-related reactions: off-label use, adjunct to other measures (slowing/stopping infusion) P0, IV: 25-50 mg; after 15-30 minutes, if symptoms persist, may repeat dose as needed. Do not exceed 100 mg within a one-hour period. Oral administration has delayed onset of action Urticaria: alternative agent; second-generation histamines preferable; may consider use in younger, healthy patients P0: 25 mg every four to six hours or 50 mg every six to eight hours as
*Diphenhydramine references ⁶⁻¹⁴			needed. Alternatively, may administer 25-50 mg po every bedtime with daytime use of a second-generation antihistamine IM, IV: 10-50 mg every four to six hours as needed
Epinephrine	Adrenergic receptor	Stimulates alpha-, beta1-, beta2-	Anaphylaxis and other severe immediate hypersensitivity
	stimulant	adrenergic receptors resulting in relaxation of smooth muscle of the bronchial tree, cardiac stimulation (increasing myocardial oxygen consumption) and dilation of skeletal muscle vasculature; small doses can cause vasodilation via beta2-vascular receptors; large doses may produce constriction of skeletal and vascular smooth muscle	reactions: IM: 0.3 or 0.5 mg using 1 mg/mL solution; may repeat every five to 15 minutes (or sooner) if no adequate patient response. Consider additional measures (IV fluids, continuous epinephrine infusion) IV, IO: Reserve IV for unresponsive patient from IM administration. Reserve IO for no IV access. Dosing same as IM CIV infusion: off-label. Initial 0.06-0.2 mcg/kg/minute administered with fluid resuscitation
*Epinephrine references ^{7,10,15-18}			
Epinephrine nebulizer, inhaler	Adrenergic receptor stimulant	Stimulates alpha-, beta-1, beta-2 adrenergic receptors resulting in relaxation of smooth muscle of the bronchial tree, cardiac stimulation (increasing myocardial oxygen consumption) and dilation of skeletal muscle vasculature; small doses can cause vasodilation via beta-2 vascular receptors; large doses may produce constriction of skeletal and vascular smooth muscle	Intermittent asthma, temporary relief of mild symptoms: 0.125 mg by oral inhalation; if symptoms not relieved after one minute, may take a second inhalation. Wait at least four hours in between doses. Max eight inhalations/24 hours

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IMMEDIATE-TYPE ALLERGIC REACTIONS IN CHEMOTHERAPY DESENSITIZATION & THEIR TREATMENT

DRUG CLASS	MECHANISM OF ACTION	INDICATION(S) & DOSING (ADULT)
Histamine H2 antagonist	Competitive inhibition of histamine at H2 receptors of the gastric parietal cells, which inhibits gastric acid secretion	Infusion reaction, premedication (adjunct) (off-label): PO, IV: 20 mg 30 to 60 minutes prior to infusion of certain chemotherapy agents or biologics; usually given in conjunction with H1 antihistamine and glucocorticoid. Dose adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database.
·		
Corticosteroid, systemic	Short-acting corticosteroid with minimal sodium-retaining potential; decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability	Anti-inflammatory or immunosuppressive: IM, IV: initial: 100-500 mg every two to six hours P0: initial: 20-240 mg/day Adjust dose depending on condition being treated and patient response. Use lowest possible dose. When dose reduction possible, taper gradually.
•		
Corticosteroid, systemic	Intermediate-acting corticosteroid with minimal sodium-retaining potential. Anti-inflammatory activity five times that of hydrocortisone	Anaphylaxis (adjunct to epinephrine for prevention of late-phase/biphasic reaction): Not for initial or sole treatment of anaphylaxis because corticosteroids do not result in prompt relief of airway obstruction of shock. Consider limiting use to patients with severe or persistent steroid-responsive symptoms (e.g. bronchospasm in patients with asthma). IV (succinate): 1-2 mg/kg or 40-125 mg single dose Angioedema (acute allergic) and/or urticaria (acute): For moderate-severe symptoms without signs of anaphylaxis. If anaphylaxis, use epinephrine. If acute urticaria, consider reserving for
		patients with significant angioedema or unresponsive to antihistamines. Optimal dosing not defined IV (succinate): initial: 60-80 mg; switch to PO corticosteroid as soon as possible, tapering for total treatment duration <=10 days
6,22-27		,
Electrolyte	Isotonic IV fluid	Hypotension:
	Corticosteroid, systemic Corticosteroid, systemic	Histamine H2 antagonist Competitive inhibition of histamine at H2 receptors of the gastric parietal cells, which inhibits gastric acid secretion Corticosteroid, systemic Short-acting corticosteroid with minimal sodium-retaining potential; decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability Corticosteroid, systemic Intermediate-acting corticosteroid with minimal sodium-retaining potential. Anti-inflammatory activity five times that of hydrocortisone



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ONCOLYTIC ALLERGY TREATMENT

ALLERGIC REACTION

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CONCLUSION

Applying the process of drug desensitization to chemotherapy offers cancer patients with chemotherapy allergies a chance for increased length of life or cure.¹

With more and more novel agents on the horizon, and an increasing rate of allergies among humans, onco-therapeutic desensitization will continue to be a beacon of hope for cancer patients with allergies to first-line or life-lengthening treatments.

▲ All four authors practice at UCLA Health. Wendy M. Wong, PharmD, BCOP, is a Board-Certified Oncology Pharmacist.

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CARD Trial: JEVTANA combined with prednisone demonstrated improved efficacy outcomes when compared with a second androgen-signaling-targeted inhibitor (ASTI) (abiraterone or enzalutamide), in patients with mCRPC who had previously received a docetaxel-containing regimen.²

Trial design: CARD was a randomized, open-label, multicenter trial in patients (N=255) with mCRPC who previously received docetaxel and had progressed within 12 months on an androgen-signaling-targeted inhibitor—either abiraterone or enzalutamide. These patients were randomized 1:1 to JEVTANA (n=129) or abiraterone or enzalutamide (n=126); patients received abiraterone if they were previously treated with enzalutamide, or enzalutamide if they were previously treated with abiraterone.^{2,3}

Primary endpoint: radiographic progression-free survival

mCRPC=metastatic castration-resistant prostate cancer; rPFS=radiographic progression-free survival.

JEVTANA is a microtubule inhibitor indicated in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen.

IMPORTANT SAFETY INFORMATION

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

Neutropenia: Neutropenic deaths have been reported.

Monitor for neutropenia with frequent blood cell counts.

JEVTANA is contraindicated in patients with neutrophil counts of ≤1,500 cells/mm³. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m².

Severe hypersensitivity: Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and administration of appropriate therapy. Patients should receive premedication. JEVTANA is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80.

CONTRAINDICATIONS

JEVTANA is contraindicated in patients with neutrophil counts of ≤1,500/mm³, patients with a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80, and patients with severe hepatic impairment (total bilirubin >3x upper limit of normal (ULN)).

WARNINGS AND PRECAUTIONS

Bone Marrow Suppression (BMS): BMS manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported. Monitor blood counts frequently to determine if initiation of G-CSF and/or dosage modification is needed. Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed. Caution is recommended in patients with hemoglobin <10 g/dl.

Increased Toxicities in Elderly Patients: Patients 265 years of age were more likely to experience fatal outcomes not related to disease progression and certain adverse reactions, including neutropenia and febrile neutropenia. Monitor closely.

Hypersensitivity Reactions: Severe hypersensitivity reactions can occur. Premedicate all patients with antihistamines, corticosteroids and $\rm H_2$ antagonists prior to JEVTANA. Observe patients closely, especially during the first and second infusions. Discontinue JEVTANA immediately if severe hypersensitivity occurs and treat as indicated.

Gastrointestinal (GI) Adverse Reactions: Nausea, vomiting, and severe diarrhea may occur. Death related to diarrhea and electrolyte imbalance occurred in the randomized clinical trials and mortality related to diarrhea has been reported. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Rehydrate and treat with antiemetics and antidiarrheals as needed. If experiencing grade ≥3 diarrhea, dosage should be modified.

GI hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, antiplatelet therapy or anticoagulants, and prior history of pelvic radiotherapy, adhesions, ulceration and GI bleeding. Abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious GI toxicity and should be evaluated and treated promptly. JEVTANA treatment delay or discontinuation may be necessary.

Renal Failure: Cases, including those with fatal outcomes, have been reported. Identify cause and manage aggressively.

Head-to-head CARD data may change how you see JEVTANA® (cabazitaxel)

NCCN DESIGNATED CATEGORY 1

Cabazitaxel is a National Comprehensive Cancer Network® (NCCN®) designated Category I option in mCRPC after docetaxel and a novel hormone therapy^{1*}

*Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.



PFS

(median 8.0 months [95% CI: 5.7-9.2] with JEVTANA [n=129] vs 3.7 months [95% CI: 2.8-5.1] with abiraterone or enzalutamide [n=126]; HR=0.54; 95% CI: 0.40-0.73; P<0.0001).²



relative reduction in risk of death (median OS, 13.6 months [95% CI: 11.5-17.5] with JEVTANA [n=129] vs 11.0 months [95% CI: 9.2-12.9] with abiraterone or enzalutamide [n=126]; HR=0.64; 95% CI: 0.46-0.89; P=0.008).^{2,3}

To learn more, visit **JEVTANApro.com**



At the cutoff date, 153 deaths were noted, with 70 (54.3%) in the JEVTANA group and 83 (65.9%) in the abiraterone or enzalutamide group.³

Urinary Disorders including Cystitis: Cystitis, radiation cystitis, and hematuria, including that requiring hospitalization, has been reported with JEVTANA in patients who previously received pelvic radiation. Cystitis from radiation recall may occur late in treatment with JEVTANA. Monitor patients who previously received pelvic radiation for signs and symptoms of cystitis while on JEVTANA. Interrupt or discontinue JEVTANA in patients experiencing severe hemorrhagic cystitis. Medical and/or surgical supportive treatment may be required to treat severe hemorrhagic cystitis.

Respiratory Disorders: Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome. Patients with underlying lung disease may be at higher risk for these events. Acute respiratory distress syndrome may occur in the setting of infection. Interrupt JEVTANA if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat patients receiving JEVTANA. Consider discontinuation. The benefit of resuming JEVTANA treatment must be carefully evaluated.

Use in Patients with Hepatic Impairment: JEVTANA dose should be reduced for patients with mild (total bilirubin >1 to $≤1.5 \times ULN$ or AST $>1.5 \times ULN$) and moderate (total bilirubin >1.5 to $≤3.0 \times ULN$ and any AST) hepatic impairment, based on tolerability data in these patients. Administer JEVTANA 20 mg/m² for mild hepatic impairment. Administer JEVTANA 15 mg/m² for moderate hepatic impairment. Monitor closely.

Embryo-Fetal Toxicity: JEVTANA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEVTANA.

ADVERSE REACTIONS (ARs)

The most common all grades adverse reactions and laboratory abnormalities (\geq 10%) with JEVTANA 20 mg/m² or 25 mg/m² are neutropenia, anemia, diarrhea, nausea, fatigue, asthenia, vomiting, hematuria, constipation, decreased appetite, back pain, and abdominal pain.

DRUG INTERACTIONS

Avoid coadministration of JEVTANA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction.

USE IN SPECIFIC POPULATIONS

- Pregnancy: The safety and efficacy of JEVTANA have not been established in females. There are no human data on the use of JEVTANA in pregnant women to inform the drug-associated risk.
- Lactation: The safety and efficacy of JEVTANA have not been established in females. There is no information available on the presence of JEVTANA in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production.
- Females and Males of Reproductive Potential: Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEVTANA.

Please see Brief Summary of the full Prescribing Information, including Boxed WARNING, on the following pages.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer v2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** JEVTANA Prescribing Information. Bridgewater, NJ: sanofi-aventis U.S. LLC. **3.** de Wit R, de Bono J, Sternberg CN, et al; for the CARD Investigators. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med.* 2019;381(26):2506-2518.

(cabazitaxel) injection, for intravenous use

Brief Summary of Prescribing Information

WARNING: NEUTROPENIA AND HYPERSENSITIVITY

Neutropenia: Neutropenic deaths have been reported. Monitor for neutropenia with frequent blood cell counts. JEVTANA is contraindicated in patients with neutrophil counts of ≤1,500 cells/mm³. Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features.

Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m² [see Contraindications (4) and Warnings and Precautions

Severe hypersensitivity: Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and bronchospasm. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and administration of appropriate therapy. Patients should receive premedication. JEVTANA is contraindicated in patients who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 [see Dosage and Administration (2.1), Contraindications (4), and Warnings and Precautions (5.3)].

INDICATIONS AND USAGE

JEVTANA® is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen.

2 DOSAGE AND ADMINISTRATION

Dosing Information

The recommended dose of JEVTANA is based on calculation of the Body Surface Area (BSA), and is 20 mg/m² administered as a one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout JEVTANA treatment.

A dose of 25 mg/m² can be used in select patients at the discretion of the treating healthcare provider [see Warnings and Precautions (5.1, 5.2), Adverse Reactions (6.1), and Clinical studies (14) in the full prescribing information].

Primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features. Consider primary prophylaxis with G-CSF in all patients receiving a dose of 25 mg/m² [see Contraindications (4) and Warnings and Precautions (5.1, 5.2)]. Premedicate at least 30 minutes prior to each dose of JEVTANA with the following intravenous medications to reduce the risk and/or severity of hypersensitivity [see Warnings and Precautions (5.3)]:

- antihistamine (dexchlorpheniramine 5 mg, or diphenhydramine 25 mg or equivalent antihistamine),
- corticosteroid (dexamethasone 8 mg or equivalent steroid),
- H₂ antagonist.

Antiemetic prophylaxis is recommended and can be given orally or intravenously as needed [see Warnings and Precautions (5.3)].

JEVTANA injection single-dose vial requires two dilutions prior to administration [see Dosage and Administration (2.5)].

2.2 Dose Modifications for Adverse Reactions

Reduce or discontinue JEVTANA dosing for adverse reactions as described in Table

Table 1: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with JEVTANA

Toxicity	Dosage Modification
Prolonged grade ≥3 neutropenia (greater than 1 week) despite appropriate medication including granulocyte-colony stimulating factor (G-CSF)	Delay treatment until neutrophil count is >1,500 cells/mm³, then reduce dosage of JEVTANA by one dose level. Use G-CSF for secondary prophylaxis.
Febrile neutropenia or neutropenic infection	Delay treatment until improvement or resolution, and until neutrophil count is >1,500 cells/mm³, then reduce dosage of JEVTANA by one dose level. Use G-CSF for secondary prophylaxis.
Grade ≥3 diarrhea or persisting diarrhea despite appropriate medication, fluid and electrolytes replacement	Delay treatment until improvement or resolution, then reduce dosage of JEVTANA by one dose level.
Grade 2 peripheral neuropathy	Delay treatment until improvement or resolution, then reduce dosage of JEVTANA by one dose level.
Grade ≥3 peripheral neuropathy	Discontinue JEVTANA.

Patients at a 20 mg/m² dose who require dose reduction should decrease dosage of JEVTANA to 15 mg/m2 [see Adverse Reactions (6.1)].

Patients at a 25 mg/m² dose who require dose reduction should decrease dosage of JEVTANA to 20 mg/m². One additional dose reduction to 15 mg/m² may be considered [see Adverse Reactions (6.1)].

2.3 Dose Modifications for Hepatic Impairment

- Mild hepatic impairment (total bilirubin >1 to ≤1.5 x Upper Limit of Normal (ULN) or AST >1.5 × ULN): Administer JEVTANA at a dose of 20 mg/m².
- Moderate hepatic impairment (total bilirubin >1.5 to $\le 3 \times ULN$ and AST = any): Administer JEVTANA at a dose of 15 mg/m² based on tolerability data in these patients; however, the efficacy of this dose is unknown.
- Severe hepatic impairment (total bilirubin >3 x ULN): JEVTANA is contraindicated in patients with severe hepatic impairment (see Warning and Precautions (5.8) and Clinical Pharmacology (12.3) in the full prescribing information].
 Dose Modifications for Use with Strong CYP3A Inhibitors

Concomitant drugs that are strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of JEVTANA with these drugs. If patients require coadministration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction [see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in the full prescribing information].

2.5 Preparation and Administration

JEVTANA is a cytotoxic anticancer drug. Follow applicable special handling and disposal procedures [see References (15) in the full prescribing information]. If JEVTANA first diluted solution, or second (final) dilution for intravenous infusion should come into contact with the skin or mucous, immediately and thoroughly wash with soap and water.

Do not use PVC infusion containers or polyurethane infusions sets for preparation and administration of JEVTANA infusion solution.

JEVTANA should not be mixed with any other drugs.

Preparation

Read this **entire** section carefully before mixing and diluting. JEVTANA requires **two** dilutions prior to administration. Follow the preparation instructions provided below, as improper preparation may lead to overdose [see Overdosage (10)].

Note: Both the JEVTANA injection and the diluent vials contain an overfill to

compensate for liquid loss during preparation. This overfill ensures that after dilution with the entire contents of the accompanying diluent, there is an initial diluted solution containing 10 mg/mL JEVTANA.

Inspect the JEVTANA injection and supplied diluent vials. The JEVTANA injection is a clear yellow to brownish-yellow viscous solution.

Step 1 - first dilution

Each vial of JEVTANA (cabazitaxel) 60 mg/1.5 mL must first be mixed with the entire contents of supplied diluent. Once reconstituted, the resultant solution contains 10 mg/mL of JEVTANA.

When transferring the diluent, direct the needle onto the inside wall of JEVTANA vial and inject slowly to limit foaming. Remove the syringe and needle and gently mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixing of the drug and diluent. Do not shake.

Let the solution stand for a few minutes to allow any foam to dissipate, and check that the solution is homogeneous and contains no visible particulate matter. It is not required that all foam dissipate prior to continuing the preparation process.

The resulting initial diluted JEVTANA solution (cabazitaxel 10 mg/mL) requires further dilution before administration. The second dilution should be done immediately (within 30 minutes) to obtain the final infusion as detailed in Step 2. Step 2 - second (final) dilution

Withdraw the recommended dose from the JEVTANA solution containing 10 mg/mL as prepared in Step 1 using a calibrated syringe and further dilute into a sterile 250 mL PVC-free container of either 0.9% sodium chloride solution or 5% dextrose solution for infusion. If a dose greater than 65 mg of JEVTANA is required, use a larger volume of the infusion vehicle so that a concentration of 0.26 mg/mL JEVTANA is not exceeded. The concentration of the JEVTANA final infusion solution

should be between 0.10 mg/mL and 0.26 mg/mL.

Remove the syringe and thoroughly mix the final infusion solution by gently inverting the bag or bottle.

As the final infusion solution is supersaturated, it may crystallize over time. Do not use if this occurs and discard.

Fully prepared JEVTANA infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 8 hours at ambient temperature (including the one-hour infusion), or for a total of 24 hours (including the one-hour infusion) under the refrigerated conditions.

Discard any unused portion.

Administration

Inspect visually for particulate matter, any crystals and discoloration prior to administration. If the JEVTANA first diluted solution or second (final) infusion solution is not clear or appears to have precipitation, it should be discarded.

Use an in-line filter of 0.22 micrometer nominal pore size (also referred to as 0.2 micrometer) during administration.

The final JEVTANA infusion solution should be administered intravenously as a one-hour infusion at room temperature.

CONTRAINDICATIONS

JEVTANA is contraindicated in patients with:

- neutrophil counts of ≤1,500/mm³ [see Warnings and Precautions (5.1)]
- history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 [see Warnings and Precautions (5.3)]
- severe hepatic impairment (total bilirubin >3 x ULN) [see Warnings and Precautions (5.8)]

WARNINGS AND PRECAUTIONS

Bone Marrow Suppression

JEVTANA is contraindicated in patients with neutrophils ≤1,500/mm³ [see Contraindications (4)]. Closely monitor patients with hemoglobin <10 g/dL.

Bone marrow suppression manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported.

(cabazitaxel) injection, for intravenous use

 $\frac{\text{TROPIC Trial (JEVTANA 25 mg/m}^2)}{\text{In the TROPIC trial with G-CSF administered only at the investigator's discretion,}}$ 5 patients (1.3%) died from neutropenic infection (sepsis or septic shock); 4 of these patients died in the first 30 days of treatment. One additional patient's death was attributed to neutropenia without a documented infection. Twenty-two (6%) patients discontinued JEVTANA treatment due to neutropenia, febrile neutropenia, infection, or sepsis. Grade 3-4 neutropenia occurred in 82% of patients treated with JEVTANA in the randomized trial [see Adverse Reactions (6.1)].

PROSELICA Trial (comparison of JEVTANA 20 mg/m² versus 25 mg/m²)
In the PROSELICA trial comparing two doses of JEVTANA, primary prophylaxis with G-CSF was not allowed, but could be administered after development of neutropenia at investigators discretion. Eight patients (1%) on the 20 mg/m² arm and 15 patients (3%) on the 25 mg/m² arm died from infection; of these, 4 deaths on the 20 mg/m² arm and 8 deaths on the 20 mg/m² arm occurred within the first 30 days of treatment. Clinically important neutropenia-related events occurred and included febrile neutropenia (2.1% on 20 mg/m² arm and 9.2% on 25 mg/m² arm), neutropenic infection/sepsis (2.1% on 20 mg/m² arm and 6.4% on 25 mg/m² arm), and neutropenic deaths (0.3% on 20 mg/m² arm and 0.7% on 25 mg/m² arm). Fewer patients receiving JEVTANA 20 mg/m² were reported to have infectious adverse reactions. Grade 1-4 infections were experienced by 160 patients (28%) on the 20 mg/m² arm and 227 patients (38%) on the 25 mg/m² arm. Grade 3-4 on the 20 mg/m² arm and 227 patients (38%) on the 20 mg/m² arm and 120 infections were experienced by 57 patients (10%) on the 20 mg/m² arm and 120 patients (20%) on the 25 mg/m² arm. Noninferiority for overall survival was demonstrated between these two arms [see Adverse Reactions (6.1)].

CARD Trial (JEVTANA 25 mg/m² + primary prophylaxis G-CSF)

In the CARD trial where JEVTANA 25 mg/m² was administered with primary prophylaxis of G-CSF, 1 patient (0.8%) died from sepsis within the first 30 days of the control of the contro

treatment. Grade 1–4 neutropenia-related adverse reactions were experienced in 33 patients (26%). Grade 3-4 neutropenias were experienced by 26 patients (21%). Clinically important neutropenia-related events occurred and included febrile neutropenia (3.2%), neutropenic infection/sepsis (0.8%) and neutropenic deaths (0.8%) [see Adverse Reactions (6.1)].

Based on guidelines for the use of G-CSF and the adverse reactions profile of JEVTANA, primary prophylaxis with G-CSF is recommended in patients with high-risk clinical features (older patients, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. Consider primary prophylaxis with G-CSF in all patients receiving JEVTANA 25 mg/m²

Monitoring of complete blood counts is essential on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed [see Dosage and Administration (2.2)]

5.2 Increased Toxicities in Elderly Patients

In a randomized trial (TROPIC), 2% of patients (3/131) <65 years of age and 6% (15/240) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose. Patients ≥65 years of age are more likely to experience certain adverse reactions, including neutropenia and febrile neutropenia. The incidence of the following grade 3-4 adverse reactions was higher in patients ≥65 years of age compared to younger patients; neutropenia (87% vs 74%), and febrile neutropenia (8% vs 6%)

In a randomized clinical trial (PROSELICA) comparing two doses of JEVTANA, deaths due to infection within 30 days of starting JEVTANA occurred in 0.7% (4/580) patients on the 20 mg/m² arm and 1.3% (8/595) patients on the 25 mg/m² arm; all of these patients were >60 years of age. In PROSELICA, on the 20 mg/m² arm, 3% (5/178) of patients <65 years of age and

2% (9/402) \ge 65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose. On the 25 mg/m² arm, 2% (3/175) patients <65 years of age and 5% (20/420) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose [see Adverse Reactions (6) and Use in Specific Populations (8.5)].

In CARD, a death due to infection within 30 days of starting JEVTANA occurred in 0.8% (1/126) patient who was >75 years of age. There were 2.4% (3/126) of patients who died of causes other than disease progression within 30 days of the last JEVTANA dose; all of these patients were >75 years of age.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of JEVTANA, thus facilities and equipment for the treatment of hypotension and bronchospasm should be available. Severe hypersensitivity reactions can occur and may include generalized rash/erythema, hypotension and

Premedicate all patients prior to the initiation of the infusion of JEVTANA [see Dosage and Administration (2.1)]. Observe patients closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions require immediate discontinuation of the JEVTANA infusion and appropriate therapy. JEVTANA is contraindicated in patients with a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80 [see Contraindications (4)].

5.4 Gastrointestinal Adverse Reactions

Nausea, vomiting and severe diarrhea, at times, may occur. Deaths related to diarrhea and electrolyte imbalance occurred in the randomized clinical trials. Intensive measures may be required for severe diarrhea and electrolyte imbalance. Antiemetic prophylaxis is recommended. Treat patients with rehydration, antidiarrheal or antiemetic medications as needed. Treatment delay or dosage reduction may be necessary if patients experience Grade ≥3 diarrhea [see Dosage and Administration (2.2)].

Gastrointestinal (GI) hemorrhage and perforation, ileus, enterocolitis, neutropenic enterocolitis, including fatal outcome, have been reported in patients treated with JEVTANA [see Adverse Reactions (6.2)]. Risk may be increased with neutropenia, age, steroid use, concomitant use of NSAIDs, antiplatelet therapy or anticoagulants,

and patients with a prior history of pelvic radiotherapy, adhesions, ulceration and GI

Abdominal pain and tenderness, fever, persistent constipation, diarrhea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly. JEVTANA treatment delay or discontinuation may be necessary.

The incidence of gastrointestinal adverse reactions is greater in the patients who have received prior radiation. In PROSELICA, diarrhea was reported in 41% (297/732) of patients who had received prior radiation and in 27% (118/443) of patients without prior radiation. Of the patients who had previously received radiation, more patients on the 25 mg/m² arm reported diarrhea, compared to patients on the 20 mg/m² arm.

5.5 Renal Failure

In the randomized clinical trial (TROPIC), renal failure of any grade occurred in 4% of the patients being treated with JEVTANA, including four cases with fatal outcome. Most cases occurred in association with sepsis, dehydration, or obstructive uropathy [see Adverse Reactions (6.1)]. Some deaths due to renal failure did not have a clear etiology. Appropriate measures should be taken to identify causes of renal failure and treat aggressively.

5.6 Urinary Disorders Including Cystitis

Cystitis, radiation cystitis, and hematuria, including that requiring hospitalization, has Cystitis, radiation cystitis, and hematuria, including that requiring nospitalization, has been reported with JEVTANA in patients who previously received pelvic radiation [see Adverse Reactions (6.2)]. In PROSELICA, cystitis and radiation cystitis were reported in 1.2% and 1.5% of patients who received prior radiation, respectively. Hematuria was reported in 19.4% of patients who received prior radiation and in 14.4% of patients who did not receive prior radiation. Cystitis from radiation recall may occur late in treatment with JEVTANA. Monitor patients who previously received pelvis radiation for cities and comprehense of partition while on IEVTANA. received pelvic radiation for signs and symptoms of cystitis while on JEVTANA. Interrupt or discontinue JEVTANA in patients experiencing severe hemorrhagic cystitis. Medical and/or surgical supportive treatment may be required to treat severe hemorrhagic cystitis

5.7 Respiratory Disorders

Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome have been reported and may be associated with fatal outcome [see Adverse Reactions (6.2)]. Patients with underlying lung disease may be at higher risk for these events. Acute respiratory distress syndrome may occur in the setting of infection.

Interrupt JEVTANA if new or worsening pulmonary symptoms develop. Closely monitor, promptly investigate, and appropriately treat patients receiving JEVTANA. Consider discontinuation. The benefit of resuming JEVTANA treatment must be carefully evaluated.

5.8 Use in Patients with Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver.

JEVTANA is contraindicated in patients with severe hepatic impairment (total bilirubin >3 × ULN) [see Contraindications (4)]. Dose should be reduced for patients with mild (total bilirubin >1 to ≤1.5 × ULN or AST >1.5 × ULN) and moderate (total bilirubin >1.5 to ≤3.0 × ULN and any AST) hepatic impairment, based on tolerabilities. data in these patients [see Dosage and Administration (2.3) and Use in Specific Populations (8.7)]. Administration of JEVTANA to patients with mild and moderate hepatic impairment should be undertaken with caution and close monitoring of safety.

5.9 Embryo-Fetal Toxicity

Based on findings in animal reproduction studies and its mechanism of action, JEVTANA can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, intravenous administration of cabazitaxel in pregnant rats during organogenesis caused embryonic and fetal death at doses lower than the maximum recommended human dose (approximately 0.06 times the C_{max} in patients at the recommended human dose). Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEVTANA [see Use in Specific Populations (8.1, 8.3)].

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Bone Marrow Suppression [see Warnings and Precautions (5.1)]
- Increased Toxicities in Elderly Patients [see Warnings and Precautions (5.2)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.3)]
- Gastrointestinal Adverse Reactions [see Warnings and Precautions (5.4)]
- Renal Failure [see Warnings and Precautions (5.5)]
- Urinary Disorders Including Cystitis [see Warnings and Precautions (5.6)]
- Respiratory Disorders [see Warnings and Precautions (5.7)]
- Use in Patients with Hepatic Impairment [see Warnings and Precautions (5.8)]

6.1 Clinical Trials Experience

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

TROPIC Trial (JEVTANA 25 mg/m² compared to mitoxantrone)

The safety of JEVTANA in combination with prednisone was evaluated in 371 patients with metastatic castration-resistant prostate cancer treated in the randomized TROPIC trial, compared to mitoxantrone plus prednisone.

Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) JEVTANA-treated patients and 3 (<1%) mitoxantrone-treated patients. The most common fatal adverse reactions in JEVTANA-treated patients were infections (n=5) and renal failure (n=4). The majority (4 of 5 patients) of fatal infection-related adverse reactions occurred after a single

(cabazitaxel) injection, for intravenous use

dose of JEVTANA. Other fatal adverse reactions in JEVTANA-treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.

The most common (≥10%) grade 1–4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia.

The most common (≥5%) grade 3–4 adverse reactions in patients who received JEVTANA were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatique, and asthenia.

Treatment discontinuations due to adverse reactions occurred in 18% of patients who received JEVTANA and 8% of patients who received mitoxantrone. The most common adverse reactions leading to treatment discontinuation in the JEVTANA group were neutropenia and renal failure. Dose reductions were reported in 12% of JEVTANA-treated patients and 4% of mitoxantrone-treated patients. Dose delays were reported in 28% of JEVTANA-treated patients and 15% of mitoxantrone-treated patients.

Table 2: Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients in TROPIC

IEVTANA 25 mg/m² Mitovontrono 12 mg/m²

Adverse Reactions	every 3 v prednisone	25 mg/m ² veeks with 10 mg daily 371	every 3 v prednisone	ne 12 mg/m ² veeks with 10 mg daily 371
	Grade 1–4 %	Grade 3-4 %	Grade 1-4 %	Grade 3–4 %
Blood and Lymphati	c System Dis	orders		
Anemia [†]	98	11	82	5
Leukopenia [†]	96	69	93	42
Neutropenia [†]	94	82	87	58
Thrombocytopenia [†]	48	4	43	2
Febrile Neutropenia	7	7	1	1
Gastrointestinal Disc	orders			
Diarrhea	47	6	11	<1
Nausea	34	2	23	<1
Vomiting	22	2	10	0
Constipation	20	1	15	<1
Abdominal Pain [‡]	17	2	6	0
Dyspepsia [§]	10	0	2	0
General Disorders a	nd Administra	ation Site Con	ditions	ı
Fatigue	37	5	27	3
Asthenia	20	5	12	2
Pyrexia	12	1	6	<1
Peripheral Edema	9	<1	9	<1
Mucosal Inflammation	6	<1	3	<1
Pain	5	1	5	2
Renal and Urinary T	ract Disorder	S		
Hematuria	17	2	4	<1
Dysuria	7	0	1	0
Musculoskeletal and	Connective	Tissue Disord	ers	
Back Pain	16	4	12	3
Arthralgia	11	1	8	1
Muscle Spasms	7	0	3	0
Metabolism and Nut	rition Disorde	ers		
Anorexia	16	<1	11	<1
Dehydration	5	2	3	<1
Nervous System Dis	orders			•
Peripheral Neuropathy [¶]	13	<1	3	<1
Dysgeusia	11	0	4	0
Dizziness	8	0	6	<1
Headache	8	0	5	0

Table 2: Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients in TROPIC (continued)

		`	,		
Adverse Reactions	JEVTANA 25 mg/m ² every 3 weeks with prednisone 10 mg daily n=371		Mitoxantrone 12 mg/m ² every 3 weeks with prednisone 10 mg daily n=371		
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %	
Respiratory, Thoraci	c and Medias	tinal Disorder	S		
Dyspnea	12	1	4	<1	
Cough	11	0	6	0	
Skin and Subcutane	Skin and Subcutaneous Tissue Disorders				
Alopecia	10	0	5	0	
Investigations					
Weight Decreased	9	0	8	<1	
Infections and Infest	Infections and Infestations				
Urinary Tract Infection#	8	2	3	1	
Cardiac Disorders		•			
Arrhythmia ^Þ	5	1	2	<1	
Vascular Disorders					
Hypotension	5	<1	2	<1	

^{*}Graded using NCI CTCAE version 3.

§Includes gastroesophageal reflux disease and reflux gastritis.

¶Includes peripheral motor neuropathy and peripheral sensory neuropathy.

#Includes urinary tract infection enterococcal and urinary tract infection fungal.

PIncludes atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block complete, bradycardia, palpitations, supraventricular tachycardia, tachyarrhythmia, and tachycardia.

PROSELICA Trial (comparison of two doses of JEVTANA)

In a noninferiority, multicenter, randomized, open-label study (PROSELICA), 1175 patients with metastatic castration-resistant prostate cancer, previously treated with a docetaxel-containing regimen, were treated with either JEVTANA 25 $\rm mg/m^2$ (n=595) or the 20 $\rm mg/m^2$ (n=580) dose.

Deaths within 30 days of last study drug dose were reported in 22 (3.8%) patients in the 20 mg/m² and 32 (5.4%) patients in the 25 mg/m² arm. The most common fatal adverse reactions in JEVTANA-treated patients were related to infections, and these occurred more commonly on the 25 mg/m² arm (n=15) than on the 20 mg/m² arm (n=8). Other fatal adverse reactions in JEVTANA-treated patients include cerebral hemorrhage, respiratory failure, paralytic ileus, diarrhea, acute pulmonary edema, disseminated intravascular coagulation, renal failure, sudden death, cardiac arrest, ischemic stroke, diverticular perforation, and cardiorenal syndrome.

Grade 1–4 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m² versus 20 mg/m² arms were leukopenia, neutropenia, thrombocytopenia, febrile neutropenia, decreased appetite, nausea, diarrhea, asthenia, and hematuria. Grade 3–4 adverse reactions occurring ≥5% more commonly in patients on the 25 mg/m² versus 20 mg/m² arms were leukopenia, neutropenia, and febrile neutropenia.

Treatment discontinuations due to adverse reactions occurred in 17% of patients in the 20 mg/m² group and 20% of patients in the 25 mg/m² group. The most common adverse reactions leading to treatment discontinuation were fatigue and hematuria. The patients in the 20 mg/m² group received a median of 6 cycles (median duration of 18 weeks), while patients in the 25 mg/m² group received a median of 7 cycles (median duration of 21 weeks). In the 25 mg/m² group, 128 patients (22%) had a dose reduced from 25 to 20 mg/m², 19 patients (3%) had a dose reduced from 20 to 15 mg/m² and 1 patient (0.2%) had a dose reduced from 15 to 12 mg/m². In the 20 mg/m² group, 58 patients (10%) had a dose reduced from 20 to 15 mg/m², and 9 patients (2%) had a dose reduced from 15 to 12 mg/m².

[†]Based on laboratory values, JEVTANA: n=369, mitoxantrone: n=370.

[‡]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.

Table 3: Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients in PROSELICA

Adverse Reactions	every 3 v prednisone	20 mg/m ² veeks with 10 mg daily 580	every 3 w prednisone	25 mg/m ² /eeks with 10 mg daily 595
	Grade 1–4 %	Grade 3-4 %	Grade 1–4 %	Grade 3–4 %
Blood and Lymphati	c System Dis	orders		
Anemia [†]	99.8	10	99.7	14
Leukopenia [†]	80	29	95	60
Neutropenia [†]	67	42	89	73
Thrombocytopenia [†]	35	3	43	4
Febrile Neutropenia	2	2	9	9
Gastrointestinal Disc	orders			
Diarrhea	31	1	40	4
Nausea	25	0.7	32	1
Constipation	18	0.3	18	0.7
Vomiting	15	1.2	18	1
Abdominal pain	6	0.5	9	1
Stomatitis	5	0	5	0.3
General Disorders a	nd Administra	ation Site Con	ditions	
Fatigue	25	3	27	4
Asthenia	15	2	20	2
Edema peripheral	7	0.2	9	0.2
Pyrexia	5	0.2	6	0.2
Renal and Urinary D)isorders			
Hematuria	14	2	21	4
Dysuria	5	0.3	4	0
Metabolism and Nut	rition Disorde	ers		
Decreased appetite	13	0.7	19	1
Musculoskeletal and	Connective	Tissue Disord	ers	
Back pain	11	0.9	14	1
Bone pain	8	2	8	2
Arthralgia	8	0.5	7	0.8
Pain in extremity	5	0.2	7	0.5
Nervous System Dis				
Dysgeusia	7	0	11	0
Peripheral sensory neuropathy	7	0	11	0.7
Dizziness	4	0	5	0
Headache	5	0.2	4	0.2
Infections and Infes	tations			
Urinary tract infection [‡]	7	2	11	2
Neutropenic infection§	3	2	7	6
Respiratory, Thoraci	c and Medias	tinal Disorder	s	
Dyspnea	5	0.9	8	0.7
Cough	6	0	6	0
Investigations	1			
Weight decreased	4	0.2	7	0
Skin and Subcutane	ous Tissue D	isorders	ı	1
		0	6.1	

(cabazitaxel) injection, for intravenous use

Table 3: Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients in PROSELICA (continued)

			, , ,	
Adverse Reactions	JEVTANA 20 mg/m ² every 3 weeks with prednisone 10 mg daily n=580		JEVTANA 25 mg/m ² every 3 weeks with prednisone 10 mg daily n=595	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Injury, Poisoning and Procedural Complications				
Wrong technique in drug usage process	0.3	0	5	0

^{*}Grade from NCI CTCAE version 4.03.

§Includes neutropenic sepsis.

CARD Trial (JEVTANA 25 mg/m2 + primary prophylaxis with G-CSF)

The safety of JEVTANA 25 mg/m² in combination with prednisone/prednisolone and primary prophylaxis G-CSF was evaluated in a randomized, open-label study (CARD) in patients with metastatic castration-resistant prostate cancer who progressed after receiving prior docetaxel-containing regimens and abiraterone acetate or enzalutamide [see Clinical Studies 14.3 in the full prescribing information]. This study compared JEVTANA 25 mg/m² in combination with prednisone/prednisolone and primary prophylaxis with G-CSF to either abiraterone acetate 1000 mg once daily plus prednisone/prednisolone 5 mg twice daily or enzalutamide 160 mg once daily. Among patients receiving JEVTANA, 35% remained on treatment at 6 months and 4.7% remained on treatment at 12 months.

Serious adverse reactions occurred in 39% of patients receiving JEVTANA. Serious adverse reactions in $\geq 3\%$ of patients included neutropenia (6%), infections (4.8%), and diarrhea, fatigue, pneumonia, and spinal cord compression (3.2% each). Deaths due to causes other than disease progression were reported in 2.4% of JEVTANA treated patients. Fatal adverse reactions in JEVTANA-treated patients were septic shock, urinary tract infection (UTI), and aspiration (0.8% each).

Treatment discontinuations due to adverse drug reactions occurred in 20% of patients who received JEVTANA and 8% of patients who received abiraterone acetate plus prednisone/prednisolone or enzalutamide. The adverse reactions leading to treatment discontinuation in >1% of patients in JEVTANA arm were nervous system disorders, infections/infestations, and gastrointestinal disorders.

Dose interruptions (alone or in combination with dose reduction) due to an adverse reaction occurred in 31% of patients receiving JEVTANA. Dose reductions were reported in 18% of JEVTANA-treated patients. The most frequent adverse reactions leading to dose interruption of JEVTANA were fatigue (7%) and hypersensitivity reaction (3.2%); the most frequent adverse reaction leading to reduction of JEVTANA were neutropenia and peripheral neuropathy (3.9% each).

Table 4 summarizes the adverse reactions and laboratory hematologic abnormalities in patients in CARD.

The most common (≥10%) adverse reactions were fatigue, diarrhea, musculoskeletal pain, nausea, infections, peripheral neuropathy, hematuria, constipation, abdominal pain, decreased appetite, vomiting, dysgeusia, edema peripheral and lower urinary tract symptoms.

The most common (≥10%) hematologic abnormalities were anemia, lymphopenia, neutropenia and thrombocytopenia.

Table 4: Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients in CARD Trial

Adverse Reactions	JEVTANA 2 predn prednisoloi	25 mg/m² + isone/ ne + G-CSF	prednise	erone + isone/ olone or tamide	
71avoros risasiisiis	(N=	126)	(N=	124)	
	Grade 1-4 %	Grade 3-4 %	Grade 1–4 %	Grade 3–4 %	
Blood and Lymphatic	Blood and Lymphatic System Disorders				
Anemia [†]	99	8	95	4.8	
Lymphopenia [†]	72	27	55	17	
Neutropenia [†]	66	45	7	3.2	
Thrombocytopenia [†]	41	3.2	16	1.6	

[†]Based on laboratory values, JEVTANA 20 mg/m²: n=577, JEVTANA 25 mg/m²:

[‡]Includes urinary tract infection staphylococcal, urinary tract infection bacterial, urinary tract infection fungal, and urosepsis.

Table 4: Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients in CARD Trial (continued)

Adverse Reactions	JEVTANA 25 mg/m ² + prednisone/ prednisolone + G-CSF (N=126)		Abiraterone + prednisone/ prednisolone or Enzalutamide (N=124)	
	Grade 1–4	Grade 3–4	Grade 1–4	Grade 3–4
General Disorders an	d Administrat	ion Site Cond	ditions	ı
Fatigue [‡]	53	4	36	2.4
Edema peripheral§	11	0.8	10	1.6
Pyrexia	6	0	7	0
Pain	6	0	6	0.8
Gastrointestinal Diso	rders			
Diarrhea [¶]	40	4.8	6	0
Nausea	23	0	23	0.8
Constipation	15	0	11	0
Abdominal pain#	14	1.6	6	0.8
Vomiting	13	0	12	1.6
Stomatitis	8	0	1.6	0
Dyspepsia	4.8	0	2.4	0
Musculoskeletal and	Connective Ti	ssue Disorde	rs	
Musculoskeletal pain ^P	27	1.6	40	6
Pain in extremity	4.8	0	11	2.4
Bone fracture ^B	3.2	1.6	8	2.4
Infections and Infesta	ations			
Infectionsà	19	4	14	6
Nervous System Disc	orders		1	
Peripheral neuropathy ^è	18	1.6	4.8	0
Dysgeusia	11	0	4	0
Polyneuropathy	6	1.6	0	0
Dizziness	0.8	0	4.8	0
Renal and Urinary Di	sorders			
Hematuria ^ð	16	0.8	6	1.6
Lower urinary tract symptoms [®]	10	0	9	0
Acute kidney injuryý	5	2.4	10	4
Metabolism and Nutr	ition Disorder	s		
Decreased appetite	14	0.8	15	2.4
Hypokalemia	3.2	0	6	0
Neoplasms Benign, M	Malignant and	Unspecified (incl cysts an	d polyps)
Cancer pain	8	1.6	9	2.4
Cardiac disorders [£]	6	0.8	6	3.2
Respiratory, Thoracio	and Mediasti	nal Disorders	1	
Pneumonia [¥]	6	1.6	3.2	0.8
Dyspnea	6	0	2.4	0
Skin and Subcutaned	ous Tissue Dis	orders	•	•
Alopecia	6	0	0	0
Injury, Poisoning and	Procedural C	complications	•	
Fall	4.8	0	0	0
Vascular Disorders				
Hypertension ^Œ	4	2.4	8	2.4

(cabazitaxel) injection, for intravenous use

Table 4: Adverse Reactions and Hematologic Abnormalities in ≥5% of Patients in CARD Trial (continued)

Adverse Reactions	JEVTANA 25 mg/m² + prednisone/ prednisolone + G-CSF (N=126)		predn prednise Enzalu	erone + isone/ olone or tamide
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Investigations				
Weight decreased	4	0	6	0
Psychiatric Disorders				
Insomnia	3.2	0	4.8	0

^{*}Grade from NCI CTC version 4.0.

§includes lymphoedema, edema peripheral, peripheral swelling.

¶includes colitis, diarrhea, diarrhea hemorrhagic, gastroenteritis.

#includes abdominal pain, abdominal pain lower, abdominal pain upper, flank pain, gastrointestinal pain.

Pincludes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, noncardiac chest pain.

Bincudes femoral neck fracture, pathological fracture, rib fracture, spinal compression fracture, sternal fracture, thoracic vertebral fracture.

àincludes bacteremia, bacteriuria, cellulitis, device related sepsis, Enterobacter sepsis, erysipelas, furuncle, influenza, influenza like illness, localized infection, oral fungal infection, perineal cellulitis, pulmonary sepsis, pyelocaliectasis, pyelone-phritis, pyelonephritis acute, respiratory tract infection, respiratory tract infection viral, sepsis, septic shock, subcutaneous abscess, upper respiratory tract infection, ureteritis, urinary tract infection, urinary tract infection bacterial, urosepsis, viral infection.

èincludes neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy.

ðincludes hematuria, cystitis hemorrhagic.

øinclude lower urinary tract symptoms, micturition urgency, nocturia, pollakiuria, urinary incontinence, urinary retention, dysuria.

ýincludes acute kidney injury, blood creatinine increased, renal failure, renal impairment.

£includes aortic valve incompetence, aortic valve stenosis, atrial fibrillation, atrial flutter, atrioventricular block complete, atrioventricular block second degree, bradycardia, sinus bradycardia, tachycardia, cardiac failure, acute coronary syndrome, angina pectoris.

¥includes lower respiratory tract infection, lung infection, lung infiltration, pneumonia. Œincludes hypertension, hypertensive crisis.

Clinically relevant ≥ Grade 3 adverse reactions in <5% of patients who received JEVTANA in combination with prednisone and primary prophylaxis G-CSF: febrile neutropenia (3.2%), pulmonary embolism (1.6%), and neutropenic infection (0.8%). Hematuria

In study TROPIC, adverse reactions of hematuria, including those requiring medical intervention, were more common in JEVTANA-treated patients. The incidence of grade ≥2 hematuria was 6% in JEVTANA-treated patients and 2% in mitoxantrone-treated patients. Other factors associated with hematuria were well-balanced between arms and do not account for the increased rate of hematuria on the JEVTANA arm.

In study PROSELICA, hematuria of all grades was observed in 18% of patients overall.

In CARD, hematuria of all grades was observed in 16% of patients receiving JEVTANA.

Hepatic Laboratory Abnormalities

The incidences of grade 3–4 increased AST, increased ALT, and increased bilirubin were each ≤1%.

6.2 Postmarketing Experience

The following adverse reactions have been identified from clinical trials and/or postmarketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

Gastrointestinal: Gastritis, intestinal obstruction.

Respiratory: Interstitial pneumonia/pneumonitis, interstitial lung disease and acute respiratory distress syndrome.

Renal and urinary disorders: Radiation recall hemorrhagic cystitis.

7 DRUG INTÉRACTIONS

7.1 CYP3A Inhibitors

Cabazitaxel is primarily metabolized through CYP3A [see Clinical Pharmacology (12.3) in the full prescribing information]. Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of JEVTANA with strong CYP3A inhibitors. If patients require coadministration of a strong CYP3A inhibitor, consider

[†]Based on laboratory values - % calculated using the number of patients with at least one event(n) over the number of patients assessed for each parameter during the on-treatment period.

[‡]includes asthenia, fatigue, lethargy, malaise.

a 25% JEVTANA dose reduction [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in the full prescribing information].

8 USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The safety and efficacy of JEVTANA have not been established in females. There are no human data on the use of JEVTANA in pregnant women to inform the drug-associated risk. In animal reproduction studies, intravenous administration of cabazitaxel in pregnant rats during organogenesis caused embryonic and fetal death at doses lower than the maximum recommended human dose [see Data]. Data

Animal data

In an early embryonic developmental toxicity study in rats, cabazitaxel was administered intravenously for 15 days prior to mating through day 6 of pregnancy, which resulted in an increase in pre-implantation loss at 0.2 mg/kg/day and an increase in early resorptions at ≥0.1 mg/kg/day (approximately 0.06 and 0.02 times the C_{max} in patients at the recommended human dose, respectively).

the C_{max} in patients at the recommended human dose, respectively). In an embryo-fetal developmental toxicity study in rats, cabazitaxel caused maternal and embryo-fetal toxicity consisting of increased postimplantation loss, embryole-thality, and fetal deaths when administered intravenously at a dose of 0.16 mg/kg/day (approximately 0.06 times the C_{max} in patients at the recommended human dose). Decreased mean fetal birthweight associated with delays in skeletal ossification was observed at doses ≥0.08 mg/kg. Cabazitaxel crossed the placenta barrier within 24 hours of a single intravenous administration of 0.08 mg/kg to pregnant rats at gestational day 17. A dose of 0.08 mg/kg in rats resulted in a C_{max} approximately 0.02 times that observed in patients at the recommended human dose. Administration of cabazitaxel did not result in fetal abnormalities in rats or rabbits at exposure levels significantly lower than the expected human exposures. rabbits at exposure levels significantly lower than the expected human exposures.

8.2 Lactation Risk Summary

The safety and efficacy of JEVTANA have not been established in females. There is no information available on the presence of cabazitaxel in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Cabazitaxel or cabazitaxel metabolites are excreted in maternal milk of lactating rats [see Data]. Data

Animal data

In a milk excretion study, radioactivity related to cabazitaxel was detected in the stomachs of nursing pups within 2 hours of a single intravenous administration of cabazitaxel to lactating rats at a dose of 0.08 mg/kg (approximately 0.02 times the C_{max} in patients at the recommended human dose). This was detectable 24 hours post dose. Approximately 1.5% of the dose delivered to the mother was calculated to be delivered in the maternal milk.

8.3 Females and Males of Reproductive Potential

Contraception

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of JEVTANA [see Use in Specific Populations (8.1)]. Infertility

Based on animal toxicology studies, JEVTANA may impair human fertility in males of reproductive potential [see Nonclinical Toxicology (13.1) in the full prescribing information).

8.4 Pediatric Use

The safety and effectiveness of JEVTANA in pediatric patients have not been established.

JEVTANA was evaluated in 39 pediatric patients (ages 3 to 18 years) receiving prophylactic G-CSF. The maximum tolerated dose (MTD) was 30 ${\rm mg/m^2}$ intravenously over 1 hour on Day 1 of a 21 day cycle in pediatric patients with solid tumors based on the dose-limiting toxicity (DLT) of febrile neutropenia. No objective responses were observed in 11 patients with refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG). One patient had a partial response among the 9 patients with ependymoma.

Infusion related/hypersensitivity reactions were seen in 10 patients (26%). Three patients experienced serious adverse events of anaphylactic reaction. The incidence of infusion related/hypersensitivity reactions decreased with steroid premedication. The most frequent treatment-emergent adverse events were similar to those reported in adults.

Based on the population pharmacokinetics analysis conducted with data from 31 pediatric patients with cancer (ages 3 to 18 years), the clearances by body surface area were comparable to those in adults.

8.5 Geriatric Use

In the TROPIC study, of the 371 patients with prostate cancer treated with JEVTANA every three weeks plus prednisone, 240 patients (64.7%) were 65 years of age and over, while 70 patients (18.9%) were 75 years of age and over. No overall differences in effectiveness were observed between patients ≥65 years of age and younger patients. Elderly patients (≥65 years of age) may be more likely to experience certain adverse reactions. The incidence of death due to causes other than disease progression within 30 days of the last cabazitaxel dose were higher in patients who were 65 years of age or greater compared to younger patients *[see Warnings and Precautions (5.2)]*. The incidence of grade 3–4 neutropenia and febrile neutropenia were higher in patients who were 65 years of age or greater reorine neutropenia were nigner in patients who were so years of age or greater compared to younger patients. The following grade 1–4 adverse reactions were reported at rates ≥5% higher in patients 65 years of age or older compared to younger patients: fatigue (40% vs 30%), neutropenia (97% vs 89%), asthenia (24% vs 15%), pyrexia (15% vs 8%), dizziness (10% vs 5%), urinary tract infection (10% vs 3%), and dehydration (7% vs 2%), respectively.

In the PROSELICA study, the grade 1–4 adverse reactions reported at rates of at

least 5% higher in patients 65 years of age or older compared to younger patients

(cabazitaxel) injection, for intravenous use

were diarrhea (43% vs 33%), fatigue (30% vs 19%), asthenia (22% vs 13%), constipation (20% vs 13%), clinical neutropenia (13% vs 6%), febrile neutropenia (11% vs 5%), and dyspnea (10% vs 3%).

In the CARD study, the grade 1-4 adverse reactions reported at rates of at least 5% higher in patients 65 years of age or older compared to younger patients were decreased appetite (16% vs 7%), hypertension (5% vs 0), constipation (18% vs 7%), paresthesia (6% vs 0), stomatitis (10% vs 3%), musculoskeletal pain (5% vs 0), fatigue (31% vs 23%), asthenia (30% vs 19%), and edema peripheral (11% vs 0). Based on a population pharmacokinetic analysis, no significant difference was observed in the pharmacokinetics of cabazitaxel between patients <65 years (n=100) and older (n=70).

8.6 Renal Impairment

No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting with end-stage renal disease (creatinine clearance CL_{CR} <15 mL/min/1.73 m²), should be monitored carefully during treatment [see Clinical Pharmacology (12.3) in the full prescribing information].

8.7 Hepatic Impairment

Cabazitaxel is extensively metabolized in the liver. Patients with mild hepatic impairment (total bilirubin >1 to \le 1.5 \times ULN or AST >1.5 \times ULN) should have JEVTANA dose of 20 mg/m². Administration of cabazitaxel to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety [see Clinical Pharmacology (12.3) in the full prescribing information]. The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin >1.5 to \leq 3.0 × ULN and AST = any) was 15 mg/m², however, the efficacy at this dose level was unknown. JEVTANA is contraindicated in patients with severe hepatic impairment (total bilirubin >3 × ULN) [see Contraindications (4)]

10 OVERDOSAGE

There is no known antidote for JEVTANA overdose. Overdose has resulted from improper preparation [see Dosage and Administration (2.5)]. Read the entire section Dosage and Administration (2) carefully before mixing or diluting. Complications of overdose include exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders. Overdose has led to fatal outcome. In case of overdose, the patient should be kept in a specialized unit where vital signs, chemistry and particular functions can be closely monitored. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other

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appropriate symptomatic measures should be taken, as needed.

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MANAGEMENT OF CRITICAL IMMUNE-RELATED ADVERSE EVENTS ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITORS IN CANCER THERAPIES

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mmune checkpoint inhibitors (ICIs) utilize the human body's native defense system to fight against cancerous diseases.¹

The immune system can search for active T cells and attack cancer cells.¹ Cancer cells have the innate ability to inactivate and evade T cells, rendering them undetectable and preventing them from mounting an immune response against malignant cells.¹ ICIs help T cells to detect cancer cells, initiate an attack against malignant cells and ultimately cause apoptosis.¹

Ipilimumab is an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) used to treat melanoma and malignant pleural mesothelioma (MPM).^{1,2} PD-1 (programmed cell death protein-1) checkpoint inhibitors such as nivolumab and pembrolizumab and PD-L1 (programmed cell death 1 ligand) checkpoint inhibitors such as atezolizumab, avelumab and durvalumab are used to treat a variety of hematological and oncological malignancies.^{1,2}

The combination of nivolumab and ipilimumab is indicated in the treatment of a variety of solid malignancies, such as hepatocellular and metastatic colorectal cancer.^{1,2}

The mechanism of action of the ICIs may result in inflammation to healthy cells in any tissue site of the body.¹











Janine Smith

Eduardo Guizan Corrales Elizabeth Osmon Khurrum Qu

NCCN GRADE OR ASSESSMENT	NCCN MANAGEMENT RECOMMENDATIONS
Mild (Grade 1)	Maintain ICI therapy
Macules/papules covering < 10% of	Initiate moderate-potency topical corticosteroid
body surface area (BSA) with or without symptoms; symptoms do not affect quality of life	Oral antihistamine to relieve itching
Moderate (Grade 2)	Maintain ICI therapy
Macules/papules covering 10% – 30% of BSA with or without symptoms; limits	• Initiate moderate- to high-potency topical corticosteroid
	Oral antihistamine to relieve itching
instrumental activities of daily living (ADLs)	• Contemplate prednisone at a dose of 0.5 mg/kg/day if there is an inadequate response to topical corticosteroids
	• Contemplate restarting if resolution is ≤ Grade 1
Severe (Grade 3 – 4)	Hold ICI therapy
Macules/papules covering > 30% of	Initiate high-potency topical corticosteroid
BSA with or without symptoms; limits self-care ADLs	• Initiate prednisone 0.5 mg/kg/day (maximum dose is 2 mg/kg/day if there is no resolution)
	• Immediate dermatology consult
	Datient may require clip bioncy
	Patient may require skin biopsy
	Hospitalization may be required

This type of T cell attack on healthy body organs and tissues can lead to immune-related adverse events (irAEs) which can potentially cause inflammation in all body organ sites.¹

This article will review the manage-

ment of critical dermatologic, infusion-related reactions, gastrointestinal, hepatic, endocrine, pulmonary and cardiac irAEs.

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DERMATOLOGIC irAEs (TABLE 1)

ICIs may cause immune-mediated dermatologic reactions such as maculo-papular rash, itching, rash, skin peeling or blistering, toxic epidermal necrolysis (TEN), drug rash with eosinophilia (DRESS) or Stevens-Johnson syndrome (SJS). Usually, this specific irAE occurs within the initial two cycles of ICI therapy. Patients may also experience oral stomatitis as well as ulcers or sores in the genital areas, nose, mouth or throat.

INFUSION-RELATED REACTIONS (TABLE 2)

Infusion-related reactions (IRRs) correlated with ICIs are frequently mild and correlated with chills, low-grade fever, headache, or nausea. Severe infusion-related reactions only occur in < 1% of patients receiving ICIs. The prevalence of infusion-related irAEs for other ICIs is 1.3% with atezolizumab, 2.2% with durvalumab, PD-1 inhibitors < 10%, and ipilimumab < 1%.

GASTROINTESTINAL irAEs (TABLE 3)

Gastrointestinal irAEs can happen early in the onset of ICI therapy with symptoms typically appearing within six to eight weeks. ^{1,3} The most common clinical presentation includes diarrhea and colitis. ^{1,3,4}

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The mechanism of action of the ICIs may result in inflammation to healthy cells in any tissue site of the body. This type of T cell attack on healthy body organs and tissues can lead to immune-related adverse events (irAEs) which can potentially cause inflammation in all body organ sites.

TABLE 2: MANAGEMENT OF INFUSION-RELATED REACTIONS¹

NCCN GRADE OR ASSESSMENT	NCCN MANAGEMENT RECOMMENDATIONS	
Mild (Grade 1)	Pause therapy, then resume infusion upon symptom resolution	
Temporary reaction	No treatment required	
	• Add premedication including acetaminophen, H1-antagonist and H2-antagonist prior to future infusions	
Moderate (Grade 2)	Refer to institutional protocol	
Infusion interruption indicated but	Hold infusion or decrease the infusion rate by 50%	
responds intervention	No need to discontinue ICI	
	• Add premedication including acetaminophen, H1-antagonist and H2-antagonist prior to future infusions	
	Consider corticosteroids as last-line option	
Severe (Grade 3 – 4)	Refer to institutional protocol	
Life-threatening; does not rapidly respond to intervention; hospitalization required	Stop ICI permanently	

TABLE 3: MANAGEMENT OF DIARRHEA AND COLITIS¹

NCCN GRADE OR ASSESSMENT	NCCN MANAGEMENT RECOMMENDATIONS		
Mild (Grade 1)	Contemplate holding ICI		
< Four bowel movements above baseline, no colitis symptoms	Antidiarrheal agents such as loperamide or diphenoxylate/ atropine for two to three days		
	Ensure patient receives adequate hydration		
	Rigorous patient monitoring		
	• For continued or increasing symptoms:, monitor lactoferrin. If lactoferrin is positive, medically manage as grade 2 If negative for lactoferrin & infection, maintain Grade 1 symptom management with mesalamine and cholestyramine		
Moderate (Grade 2)	Hold ICI therapy		
Four to six bowel movements above	Prednisone/methylprednisolone 1-2 mg/kg/day		
baseline, colitis symptoms no interference with ADLs	Continue until improvement to \leq Grade 1 then taper over four to six weeks		
	If no response in two to three days, increase corticosteroid dose to 2 mg/kg/day and consider the addition of infliximab or vedolizumab within a period of two weeks		
Severe (Grade 3 – 4)	Grade 3: Stop anti-CTLA-4 but PD-1 or PD-L1 inhibitors		
>Six bowel movements above baseline,	may be resumed after toxicity has abated		
colitis symptoms, interferes with ADLs,	Grade 4: ICI must be permanently stopped. Contemplate patient beginstellington.		
hemodynamic instability, hospitalization	patient hospitalization. • Methylprednisolone 1–2 mg/kg/day: Maintain until improvement to Grade ≤ 1 then taper over four to six weeks. If no response in two days, then maintain corticosteroids & contemplate addition of infliximab or vedolizumab		

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HEPATIC irAEs (TABLE 4)

In patients presenting with elevated transaminases (alanine transaminase (ALT) and aspartate transaminase (AST)) with or without elevated bilirubin while on immunotherapy, a viral etiology must be ruled out. These cases may require the initiation of corticosteroids in cases of life-threatening transaminases.

ENDOCRINE irAEs: HYPERGLYCEMIA (TABLE 5)

Further management is required for patients presenting with a fasting

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TABLE 5: MANAGEMENT OF HYPERGLYCEMIA¹

NCCN GRADE OR ASSESMENT	NCCN MANAGEMENT RECOMMENDATIONS		
Glucose < 200 mg/ dL and/or past medi- cal history (PMH) of T2DM or cortico- steroid induced hyperglycemia	Allow maintenance of ICI therapy Offer counseling of diet and lifestyle changes Initiate medical therapy as per institutional guidelines Monitor blood glucose with each dose		
Fasting glucose > 200 mg/dL, random glucose > 250 mg/dL, and/or PMH of T2DM in addition to random fasting glucose > 250 mg/dL	Contemplate diagnosis for T1DM Workup for diabetic ketoacidosis (DKA) If negative, manage as above If positive, hold ICI therapy until resolution DKA diagnosis Consultation from endocrinology needed Hospitalization required Medical management of DKA as documented in institutional protocol Resume ICI therapy after resolution of DKA and once glucose level is stabilized		

TABLE 4: MANAGEMENT OF HEPATOTOXICITY¹

NCCN GRADE OR ASSESSMENT	NCCN MANAGEMENT RECOMMENDATIONS				
Mild (Grade 1)	Proceed with ICI therapy, contemplate withholding for abnormal				
AST and ALT $<$ 3 x ULN without bilirubin elevation	trended lab results				
	Evaluate liver function tests (LFTs) and bilirubin on a more frequent basis				
Moderate (Grade 2)	Pause ICI therapy				
AST and ALT 3-5 x ULN without bilirubin elevation	• Increase LFT monitoring to an interval of approximately each three to five days				
	• May initiate prednisone 0.5-1 mg/kg/day, with a taper for a minimum of one month if toxicity improves to ≤ Grade 1 and titrate the dose if necessary				
Severe (Grade 3)	Pause ICI therapy				
AST/ALT > 5-20 x ULN without bilirubin elevation	Start prednisone or methylprednisone at a dose of 1–2 mg/kg/day				
	Consider hospitalization				
	Hepatic lab panel every 72 hours Consult with hepatology specialist				
	Contemplate the use of mycophenolate after three days in steroid refractory patients				
	• Do not use infliximab				
Life-threatening (Grade 4)	•Stop ICI therapy permanently				
AST and $ALT > 20 x$ ULN without bilirubin	• Start prednisone/methylprednisolone at a dose of 1–2 mg/kg/day				
elevation	Contemplate the use of mycophenolate after three days in steroid refractory patients				
	Hospitalization required				
	Hepatic lab panel daily				
	Hepatology specialist consult				
	If not contraindicated may consider a liver biopsy				
	Avoid infliximab				
Grade > 1 transaminases with elevated bilirubin	Bilirubin 1-2 x ULN				
(unless Gilbert's syndrome)	• Pause ICI therapy				
(unless dilberts syndrome)	Start prednisone or methylprednisolone at a dose of 1–2 mg/kg/ day				
	Hospitalization should be considered				
	Hepatic lab panel every three days				
	Hepatology specialist consult Contamplete the use of mycophonelate after those days in steerid				
	Contemplate the use of mycophenolate after three days in steroid refractory patients				
	Avoid infliximab				
	Bilirubin 3-4 x ULN				
	Discontinue ICI therapy permanently				
	Start prednisone/methylprednisolone 1-2 mg/kg/day				
	Hospitalization required				
	Hepatic panel daily				
	Consult with hepatology specialist				
	Contemplate the use of mycophenolate after three days in steroid refractory patients				
	• Do not use infliximab				

I M M U N E C H E C K P O I N T I N H I B I T O R S

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blood glucose (FBG) greater than 200 mg/dL, random blood glucose greater than 250 mg/dL, or a history of type 2 diabetes mellitus (T2DM) with a fasting or random glucose greater than 250 mg/dL.¹ Patients will require hospitalization and discontinuation of immunotherapy.¹

NCCH MANACEMENT

TABLE 6: MANAGEMENT OF THYROID TOXICITY¹

NCCH CDADE

NCCN GRADE OR ASSESMENT	NCCN MANAGEMENT RECOMMENDATIONS
No symptoms/ subclinical hypothyroidism	•TSH 4 to < 10, normal FT4: maintain ICI and monitor thyroid levels
,, ,	•TSH > 10, normal FT4: maintain ICI and contemplate levothyroxine
	Normal or low TSH, FT4: Evaluate for central hypothyroidism
Primary hypothyroidism	Evaluate TSH levels once approx. every four to six weeks
	Maintain ICI therapy
Elevated TSH, low FT4, clinical	• Endocrine consultation may be contemplated
symptoms	Start thyroid hormone supple- mentation with levothyroxine
	•TSH should be done again in 4–6 weeks for dose adjustments
	• Rule out diagnosis of possible adrenal insufficiency by evalu- ating the am cortisol lab value
Thyrotoxicosis	ICI may continue if no symptoms are present
Decreased/elevated TSH with elevated FT4/total T3	Contemplate propranolol 10-20 mg q four to six hours p.m. for symptomatic management (alternatives are atenolol or metoprolol)
	Reiterate thyroid function tests in four to six weeks
	• Temporary discontinuation of ICI should be considered with the goal to resume once symptoms resolve and levels are normal

Corticosteroids do not have a place in the management of irAE hyperglycemia¹

ENDOCRINE irAEs: THYROID DYSFUNCTION (TABLE 6)

Primary hypothyroidism is defined by an elevated thyroid-stimulating hormone (TSH) level (> 10~mIU/L) and low free T4 (FT4) with clinical symptoms. The corresponding incidence rates of anti-CT-

LA-4, anti-PD-1, and anti-PD-L1 hypothyroidism were 3.8%, 7.0%, and 3.9%, respectively in a meta-analysis. 1,5,6,7

The etiology of ICI thyroid dysfunction is not well established; however, it is theorized that thyroid dysfunction was associated with cytotoxic T lymphocyte-mediated destruction of thyroid tissue.^{1,5,6,7}

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TABLE 7: MANAGEMENT OF PNEUMONITIS¹

NCCN GRADE OR ASSESSMENT	NCCN MANAGEMENT RECOMMENDATIONS			
Mild (Grade 1) Asymptomatic: involving one lobe of the lung or < 25% of lung parenchyma (clinical or diagnostic observations only)	Contemplate withholding ICI Assessment in one to two weeks with pulse oximetry and physical examination CT with contrast to exclude other etiologies; may repeat in at least one month or sooner if the patient is symptomatic Contemplate restarting ICI if improvement seen on imaging			
Moderate (Grade 2) Presence of new or worsening symptoms: shortness of breath, cough, chest pain, fever, and increased oxygen requirement	 Pause ICI therapy May initiate prednisone/methylprednisolone at a dose of 1-2 mg/kg/day Contemplate bronchoalveloar lavage (BAL)m, bronchoscopy and transbrohchial lung biopsy if clinically indicated. Contemplate initiation of broad spectrum antibiotics if infection is in differential diagnosis Monitor weekly with pulse oximetry, history and physical 72 hours after corticosteroid therapy, use grade 3 management parameters 			
Severe (Grade 3 to Grade 4)	• Stop ICI permanently			
Grade 3: all lung lobes included or >50% of the lung parenchyma, self-care activities of daily living limited, oxygen therapy recommended Grade 4: life-threatening respiratory	Hospitalization recommended Less invasive approach: Infectious evaluation Viral pathogen nasal swab, including COVID-19 testing Blood culture, sputum culture, urine antigen (pneumococcus, legionella) Offer cardiovascular assessment to rule out cardiac causes More invasive approach: may perform a bronchoscopy with BAL and			
compromise	 consider biopsy May use antibiotics empirically, including atypical microorganisms coverage Consult infectious disease and pulmonology Initiate methylprednisolone 1-2 mg/kg/day, re-evaluate within 48 hours and taper over at least six weeks For patients with lack of improvement within at least two days on corticosteroids consider adding either: Infliximab single dose of 5 mg/kg IV and offer repeat dose two weeks later if indicated Intravenous immunoglobulin (IVIG) 2 g/kg over at least two days in divided doses Mycophenolate mofetil 1-1.5 g every 12 hours and taper as indicated by pulmonology recommendation 			

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PULMONARY irAEs: PNEUMONITIS (TABLE 7)

Pneumonitis is the inflammation of the lining of the lung with symptoms such as a dry cough, fever, shortness of breath and pain in the chest.

High-grade pneumonitis has an incidence rate of 1% of PD-1/PD-L1 ICIs and approximately 5% for all grades. 1,9,10,11

Patients may need increased oxygen requirements. ^{1,9,10,11} Pneumonitis is usually diagnosed via imaging by a computerized tomography (CT) scan. ^{1,9,10,11}

CARDIAC irAEs: MYOCARDITIS (TABLE 8)

Myocarditis is a rare irAE which is correlated with an incidence rate of 0.04% to 1.14% and a mortality rate of 25% to 50%.^{1,12}

Myocarditis has a non-specific symptoms and may be associated with myositis and myasthenia gravis. 1,12

The occurrence of myocarditis is increased with the use of combination immunotherapy.^{1,12}

CONCLUSION

Immune checkpoint inhibitors are a major medical breakthrough for cancer patients, but unfortunately are associated with adverse effects.^{3,12}

Grade 2 irAEs usually require holding ICI therapy initially and then resuming after successfully being managed. 12

Depending on the affected organ system, grade 3 irAEs may require holding ICI therapy and administering high-dose corticosteroids.¹²

Grade 4 ir AEs generally require discontinuation of ICI therapy. 12

Pharmacists must be aware of these side effects and should offer counseling to patients, caregivers and healthcare professionals on how to manage irAEs in cancer patients being administered immunotherapy.

TABLE 8: MANAGEMENT OF MYOCARDITIS^{1,12}

NCCN GRADE OR ASSESSMENT | NCCN MANAGEMENT RECOMMENDATIONS

Suspected myocarditis

Signs and symptoms may include: Arrhythmias, tachycardia, heart failure, cardiogenic shock, myositis, and pericardial effusion

- Stop ICI permanently
- Administer high dose corticosteroids with pulse dosing of methylprednisolone 1 q daily IV for three to five days
- Change to oral prednisone then gradually taper over four to six weeks with an assessment of clinical response and enhanced biomarkers
- If there is no recovery in 24 hours while on corticosteroids, consider the following:
 - Mycophenolate
- Abatacept
- ° IVIG
- Alemtuzumab
- Infliximab (must use great safety measures in patients with decreased ejection fraction)
- Anti-thymocyte globulin (ATG)
- o Intensive care unit (ICU) monitoring

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FDA DRUG APPROVALS FOR Q2 & Q3 2021

By Carter Friedt, Kirollos Hanna, PharmD, BCPS, BCOP & Derek Gyori, PharmD, BCOP

uring Q2 and Q3 2021, the U.S. Food & Drug Administration (FDA) approved nine oral oncology agents through Aug. 31, 2021.

In the chart below, the symbol + stands for **New Formulations**; the symbol * stands for **New Indications**. Further information can be found on the FDA website, in the medication-specific prescribing information or clinical trials.

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DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
LORBRENA® (lorlatinib) ¹⁻³	3/3/2021*	Metastatic ALK- positive Non-Small Cell Lung Cancer (First Line): 100 mg once daily until disease progression or unacceptable toxicity	CROWN Trial (N=296) Randomized 1:1 Lorlatinib or Crizotinib Progression-Free Survival (PFS) at 12 months: lorlatinib 80% (95% CI, 73-86) and crizotinib 35% (95% CI 27 - 43) [hazard ratio (HR) 0.21; 95% CI, 0.14 to 0.31] Central Nervous System (CNS) Objective Response Rate (ORR): Lorlatinib 82% (95% CI 57-96) versus Crizotinib 23% (95% CI 5-54) Overall Survival (OS) was immature at PFS analysis	≥20%: edema, peripheral neuropathy, weight gain, cognitive effects, fatigue, dyspnea, arthralgia, diarrhea, mood effects, hypercholesterolemia, hypertriglyceridemia, cough	Administer with or without food Available as a 25 mg and 100 mg tablet Third-generation ALK inhibitor that is able to penetrate into the CNS ALK-positive tumors detected by the VENTANA ALK (D5F3) CDx assay
FOTIVDA® (tivozanib) ⁴⁻⁶	3/10/2021+	Relapsed or refractory advanced renal cell Carcinoma: 1.34 mg once daily on days 1- 21 of a 28-day cycle	TIVO-3 Trial (N=350) Randomized 1:1 Tivozanib or Sorafenib Median PFS at 5.6 months for tivozanib (95% CI 5.29-7.33) and 3.9 months for sorafenib (95% CI 3.71-5.55) [HR 0.73; 95% CI 0.56-0.94] ORR: Tivozanib 18% (95% CI 12%-24%) versus Sorafenib 8% (95% CI 4%-13%)	≥ 20%: fatigue, hypertension, diarrhea, decreased appetite, nausea, dysphonia, hypothyroidism, cough and stomatitis Lab abnormalities ≥5%: decreased sodium, increased lipase and decreased phosphate	Administer with or without food Available as 0.89 mg and 1.34 mg capsule

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DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
LUMAKRAS™ (sotorasib) ⁷⁻⁹	5/28/2021+	KRAS G12C-mutated Non-Small Cell Lung Cancer (NSCLC): 960 mg once daily until disease progression or unacceptable toxicity	CodeBreaK 100 Trial (N=126) Median PFS at 6.8 months (95% CI, 5.1-8.2) ORR: Sotorasib 37.1% (95% CI: 28.6%-46.2%) Median duration of response (DoR): 11.1 months	≥ 20%: diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity and cough Lab abnormalities ≥ 25%: lymphocytes, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, decreased calcium, increased alkaline phosphatase, increased urine protein and decreased sodium	Administer at the same time each day with or without food Available as 120 mg tablets
TRUSELTIQ™ (infigratinib) 10-12	5/28/2021+	Unresectable locally advanced or metastatic Cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) fusion: 125 mg once daily for 21 consecutive days followed by 7 days off, in 28-day cycles until disease progression or unacceptable toxicity	CBGJ398X2204 Trial (N= 61) ORR: 14% (95% CI, 7-26.2%) Median PFS at 5.8 months (95% CI, 4.3-7.6)	≥20%: hyperphosphatemia (72.1%), increased creatinine, nail toxicity, stomatitis, dry eye, fatigue, alopecia, palmarplantar erythrodysesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhea, dry skin, decreased appetite, vision blurred and vomiting	Administer on an empty stomach Available as 25 mg and 100 mg capsules Prophylactic sevelamer was given to manage hyperphosphatemia
AYVAKIT™ (avapritinib) 13-14	6/16/2021*	Advanced Systemic Mastocytosis: 200 mg orally once daily until disease progression or unacceptable toxicity	EXPLORER/ PATHFINDER (N=53) ORR: 57% (95% C, 42-70), with 28% complete remissions and 28% partial remissions Median DoR: 8.3 months (95% CI: 19-not estimable)	≥20%: edema, diarrhea, nausea, and fatigue/ asthenia	Administer on an empty stomach, one hour before or two hours after a meal Antiemetics are recommended to prevent nausea and vomiting Available in 25 mg, 50 mg, 100 mg, 200 mg, 300 mg tablets Not recommended for the treatment of patients with Advanced Systemic Mastocytosis with platelet counts of less than 50x109/L

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
REZUROCK™ (belumosudil) ¹⁵⁻¹⁷	07/16/2021+	Chronic graft-versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy for pediatric and adult patients over the age of 12: 200 mg orally daily or twice daily	ROCKstar Trial (n=66 daily, n=66 twice daily) Randomized 1:1 Belumosudil daily versus belumosudil twice daily after two or more prior lines of therapy ORR: belumosudil daily 73% (95%CI, 60%-83%) versus belumosudil twice daily 74% (95% CI, 62%-84%) High ORRs were seen in all patient subgroups, regardless of length of time from diagnosis to treatment	≥20%: infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache and hypertension. Lab abnormalities ≥20%: Decreased phosphate, increased gamma glutamyl transferase, decreased lymphocytes	Administer with a meal at approximately the same time each day Available in 200 mg tablets
LENVIMA® (lenvatinib) 18-20	7/21/2021*	Advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) in combination with Keytruda: 20mg orally daily with pembrolizumab 200 mg every three weeks or 400 mg every six weeks Advanced Renal Cell Carcinoma: lenvatinib 20 mg orally once daily with pembrolizumab pembrolizumab pembrolizumab pembrolizumab pewery three weeks or 400 mg every six weeks	Study 309/KEYNOTE-775 (N= 827) Randomized 1:1 Pembrolizumab 200 mg IV every three weeks with lenvatinib 20mg orally daily versus investigators choice of doxorubicin or paclitaxel Median PFS: 6.6 months (95% Cl: 5.6-7.4) in the lenvatinib group versus 3.8 months (95% Cl: 3.6-5.0) for investigators choice Median OS: 17.4 months (95% Cl: 14.2-19.9) in the lenvatinib group versus 12 months (95% Cl: 10.8-13.3) for investigators choice CLEAR: Study 307/KEYNOTE-581 (N=355) PFS: 23.9 months (95% Cl, 20.8 - 27.7) compared with 9.2 months (95% Cl, 6.0 - 11.0) for those receiving sunitinib (HR 0.39; 95% Cl, 0.32 - 0.49; p<0.0001) Median OS was not reached in either arm (HR 0.66; 95% Cl, 0.49 - 0.88; p=0.0049)	≥20%: Hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal disorders, nausea, decreased appetite, vomiting, stomatitis, weight loss, abdominal pain, urinary tract infection, proteinuria, constipation, headache, hemorrhagic events, palmar- plantar erythrodysesthesia, dysphonia and rash	Administer at the same time each day. May be administered with or without food Antiemetics are recommended to prevent nausea and vomiting Available in 4 mg and 10 mg capsules Treatment can be given up to two years, until disease progression or until unacceptable toxicity

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ORAL ONCOLOGY APPROVALS

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
WELIREG™ (belzutifan) ²¹⁻²²	08/13/2021+	Adult patients with von Hippel-Lindau (VHL) disease who require therapy for Associated Renal Cell Carcinoma (RCC), Central Nervous System (CNS) Hemangioblastomas, or Pancreatic Neuroendocrine Tumors (pNET), not requiring immediate surgery: 120 mg orally daily until disease progression or unacceptable toxicity	Study 004 (NCT03401788) (N=61) ORR: 49% (95% CI: 26-62) Median DoR was not reached; 56% of responders had DoR ≥ 12 months and a median TTR of eight months	≥20%: decreased hemoglobin, anemia, fatigue, increased creatinine, headache, dizziness, increased glucose and nausea	Administer with or without food Available in 40 mg tablets
TIBSOVO® (Ivosidenib) ²³⁻²⁵	08/25/2021+	Locally advanced or Metastatic Cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation: 500 mg orally daily	Study AG120-C-005 (N=185) Randomized 2:1 Ivosidenib versus placebo PFS: 2.7 months (95% Cl: 1.6-4.2) for ivosidenib versus 1.4 months (95% Cl: 1.4-1.6) for placebo	≥15%: fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia and rash	Administer at the same time each day, either with or without food Available in 250 mg tablets Oncomine Dx Target Test approved as a companion diagnostic device to aid in selection of patients

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NEW PUBLICATIONS PROVIDE CONVENIENT REVIEW OF NCODA INTERNATIONAL FORUMS AND SUMMITS

CODA has launched two new tools to assist members interested in reviewing key sessions from its annual Spring Forum and Fall Summit — FORUMRewind and SUMMITRewind.

Each publication offers a simple, easy-to-read breakdown of the primary presentations from the 2 1/2-day educational events, including information on:

- ▲ Presenters and their expertise;
- ▲ A synopsis and descriptive outline of the presentation;
- ▲ Discussion elements, including key questions and answers;
- ▲ Bulleted takeaway points; and
- ▲ A convenient QR code to the slides used in the presentation.

"In addition to offering another valuable educational tool to our members, FORUMRewind and SUMMITRewind also provide NCODA members unable to attend the events an opportunity to watch select session recordings and claim continuing education credit," said Michael Reff, RPh, MBA, Founder & Executive Director of NCODA.

FORUMRewind and SUMMITRewind are



published shortly after each international event, with copies then distributed to NCODA members worldwide.

FORUMRewind launched in May 2021, following the 2021 NCODA Spring Forum. SUMMITRewind will be published this Fall, following the 2021 NCODA Fall Summit on Oct. 20-22.

Articles within each publication are written by members of NCODA's Professional Student Organization (PSO),

overseen by an Editorial Board comprised of NCODA Manager of Patient-Centered Communications Ginger Blackmon, PharmD, and NCODA Managers of Clinical Initiatives Julianne Darling, PharmD, BCOP, and Natasha Olson, PharmD.

"FORUMRewind and SUMMITRewind also provide NCODA's PSO students with the experience of producing published articles, as well as a meaningful way to connect with clinical and industry professionals," Reff said.

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NEW FDA APPROVALS FOR NON-SMALL CELL LUNG CANCER TREATMENT

By Allison Burdick

ung cancer continues to be the leading cause of cancer-related deaths in the United States in both men and women.¹ According to the American Cancer Society, it is estimated that approximately 235,760 new cases of lung cancer will be diagnosed and 131,800 deaths from lung cancer will occur in 2021.¹

The decline of smoking rates in the United States has likely had an impact on decreased rates of diagnoses. While ultimately the number of diagnoses con-



Allison Burdick

tinues to decrease, five-year survival for patients already diagnosed continues to be relatively low. For patients with distant disease, five-year survival is only 7%.²

Non-small cell lung cancer (NS-

CLC) is the most common type of lung cancer, making up 84% of all diagnoses.² Advancements in early detection and mutation testing are driving innovation of targeted therapies in this large population with diverse subsets of mutations.

Here are the notable examples of targeted therapies approved in 2021:

LUMAKRAS™ (SOTORASIB)

Approved: 5/28/2021

LUMAKRAS™ (sotorasib) is the first treatment for patients whose tumors have the Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C mutation that have received at least one prior

Non-small cell lung cancer
(NSCLC) is the most common
type of lung cancer, making
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systemic therapy. This mutation accounts for approximately 13% of mutations in non-small cell lung cancers and leads to uncontrolled cell growth due to hyperactivation of downstream oncogenic pathways.³ KRAS mutations have been considered resistant to drug therapy, creating a demand for agents that targets these tumors

Sotorasib works by covalently binding to a pocket of the switch-II region present in the inactive guanosine diphosphate (GDP)- bound conformation that can trap KRAS G12C in the inactive state and inhibit its downstream oncogenic effects.³

Approval is based on the Phase II CodeBreaK 100 trial that showed a median overall survival of 12.5 months, an objective response rate of 37.1%, a duration of response of 11.1 months, and a disease control rate of 80.6%. The dose used in the trial was 960 milligrams, but the FDA is requiring a post-market trial to evaluate if a lower dose would be able to achieve similar results. 5

The study showed side effects of sotorasib were mostly grade 1 or grade 2 that primarily consisted of hepatic and gastrointestinal effects. The most common adverse events were diarrhea, nausea, fatigue, arthralgia and increased liver enzymes.³

Currently, the standard of care for patients with disease progression after platinum-based chemotherapy is treatment with docetaxel with or without an antiangiogenic therapy or single-agent pemetrexed. Sotorasib now provides another option for patients who have progressed after first-line therapy. Phase III trials are currently being conducted to study sotorasib in combination with docetaxel and to identify patients who may benefit from sotorasib as first-line treatment.

RYBREVANT™ (AMIVANTAMAB-VMJW)

Approved: 5/21/2021

RYBREVANT™ (Amivantamab-vmjw) is the first treatment for patients whose tumors have the epidermal growth factor receptor (EGFR) exon 20 insertion mutations. These mutations make up a small subset of non-small cell lung cancer patients with about 2% to 3% harboring an alteration. Of the known EGFR mutations, the exon 20 insertion mutations are the third most prevalent.⁷ The currently available EGFR tyrosine kinase inhibitors (TKI) are generally less effective in treating patients with these mutations and do not have FDA approval in this patient population.8 Prognosis of patients with NSCLC that is driven by EGFR exon 20 insertion mutations are worse and show shorter survival rates than patients with other EGFR mutations.9

Approval is based on the ongoing Phase I CHRYSALIS trial, which studied amivantamab-vmjw in patients with EGFR exon 20 insertion mutations who progressed on or after platinum-based chemotherapy. This study showed an overall response rate of 40%, a median progression-free survival of 8.3 months, a median duration of response of 11.1 months and a median overall survival of 22.8 months.

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L U N G C A N C E R

NSCLC

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The doses being evaluated were determined by weight, with patients weighing less than 80 kg receiving 1,050 mg and patients at least 80 kg receiving 1,400 mg weekly for four weeks. The first infusion is split over two days and following the first four-week cycle, infusions are administered every two weeks until disease progression or toxicity. ¹⁰ The most common adverse events in the study include rash, infusion-related reactions, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation and vomiting. ¹⁰

Approved with amivantamab-vmjw, Guardant360 CDx liquid biopsy blood test is an alternative to polymerase chain reaction (PCR)-based tests where exon 20 insertion mutations go undetected about 50% of the time. This novel test allows for better detection rates of these mutations to better identify patients who may benefit from this therapy.

Amivantamab-vmjw is a breakthrough development as this patient population has had no prior approved treatment options that target their disease. Two phase III trials are being conducted to assess efficacy of amivantamab-vmjw in combination with other treatment modalities. The MARIPOSA trial is studying amivantamab-vmjw in combination with lazertinib and the PAPILLON trial, in combination with carboplatin-pemetrexed. 12,13

TEPMETKO® (TEPOTINIB)

Approved: 2/3/2021

TEPMETKO® (tepotinib) is a treatment that targets mesenchymal-epithelial transition (MET) exon 14 skipping mutation. This mutation accounts for 3% to 4% of patients with non-small cell lung cancer.¹⁴ The MET exon 14 skipping mutation encodes a TKI and binds to its ligand hepatocyte growth factor (HGF) which induces downstream signaling in the RAS-RAF and phosphoinositide 3-kinase (PI3K) pathways. This increased signaling leads to aberrant cell proliferation and enhanced survival.¹¹5

Approval is based on the phase II VISION trial that evaluated a dose of 450 mg orally once daily until disease progression or toxicity in advanced or metastatic patients. The overall response rate was 43% in both the treatment-naïve and previously treated groups with a median duration of response of 10.8 months in the treatment-naïve group and 11.1 months in the previously treated group. ¹⁶ The results are favorable when compared to results of other MET inhibitor studies. The PROFILE 1001 trial of crizotinib reported a response rate of 32% with

a median duration of progression-free survival of 7.3 months.¹⁷ Additionally, the GEOMETRY mono-1 trial of capmatinib showed a response rate of 41% in patients previously treated and 68% in treatment-naïve patients with a median duration of progression-free survival of 5.4 months and 9.7 months respectively.¹⁸

The most common adverse events observed include edema, fatigue, nausea, diarrhea, musculoskeletal pain and dyspnea. Edema was the most common adverse event leading to dose reduction, interruption or discontinuation of treatment. ¹⁶ This adverse event profile is similar to what has been observed in other agents targeting the MET or HGF pathway.

Approval of tepotinib adds yet another oral treatment option for patients with advanced or metastatic disease harboring a MET exon 14 skipping mutation.

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LIBTAYO works with the immune system to help treat the following types of cancer¹:

- The first-line treatment of patients with non—small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations, and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation OR metastatic
- The treatment of patients with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog
 pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate
- The treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation



Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1/PD-L1—blocking antibodies. The definition of immune-mediated adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

No dose reduction for LIBTAYO is recommended. In general, withhold LIBTAYO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue LIBTAYO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated adverse reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids.

Withhold or permanently discontinue LIBTAYO depending on severity. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Immune-mediated pneumonitis: LIBTAYO can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1—blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%). Pneumonitis led to permanent discontinuation in 1.4% of patients and withholding of LIBTAYO in 2.1% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld, 9 reinitiated after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated colitis: LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1—blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%). Colitis led to permanent discontinuation in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated hepatitis: LIBTAYO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%). Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis. Additional immunosuppression with mycophenolate was required in 19% (3/16) of these patients. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld, 3 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence.

<u>For hepatitis with no tumor involvement of the liver</u>: Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or if total bilirubin increases to more than 1.5 and up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 8 times the ULN or total bilirubin increases to more than 3 times the ULN.

For hepatitis with tumor involvement of the liver: Withhold LIBTAYO if baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN. Also, withhold LIBTAYO if baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times ULN or if total bilirubin increases to more than 3 times ULN. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated endocrinopathies: For Grade 3 or 4 endocrinopathies, withhold until clinically stable or permanently discontinue depending on severity.

• Adrenal insufficiency: LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%). Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff

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

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

Immune-mediated endocrinopathies: (cont'd)

- **Hypophysitis:** LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue depending on severity. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff
- Thyroid disorders: LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy.

 Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated.

 Withhold or permanently discontinue LIBTAYO depending on severity
- Thyroiditis: Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported
- **Hyperthyroidism:** Hyperthyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%). No patient discontinued treatment and LIBTAYO was withheld in 0.5% of patients due to hyperthyroidism. Systemic corticosteroids were required in 3.8% (1/26) of patients. Hyperthyroidism resolved in 50% of 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism
- **Hypothyroidism:** Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%). Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy
- Type 1 diabetes mellitus, which can present with diabetic ketoacidosis: Monitor for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity. Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%). No patient discontinued treatment due to type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients

Immune-mediated nephritis with renal dysfunction: LIBTAYO can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%), and Grade 2 (0.4%). Nephritis led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. Withhold LIBTAYO for Grade 2 or 3 increased blood creatinine, and permanently discontinue for Grade 4 increased blood creatinine. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated dermatologic adverse reactions: LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1—blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reactions, 7 reinitiated LIBTAYO after symptom improvement; of these, 43% (3/7) had recurrence of the dermatologic adverse reaction. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold LIBTAYO for suspected SJS, TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS, TEN, or DRESS. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 810 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1—blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

- Cardiac/vascular: Myocarditis, pericarditis, and vasculitis. Permanently discontinue for Grades 2, 3, or 4 myocarditis
- Nervous system: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation),
 Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy. Withhold for Grade 2 neurological toxicities and permanently discontinue for
 Grades 3 or 4 neurological toxicities. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently
 discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day
 (or equivalent) within 12 weeks of initiating steroids

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

Other immune-mediated adverse reactions: (cont'd)

- Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada—like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
- Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis
- Musculoskeletal and connective tissue: Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
- Endocrine: Hypoparathyroidism
- Other (hematologic/immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Infusion-related reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash and dyspnea. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

Complications of allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1—blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1—blocking antibody prior to or after an allogeneic HSCT.

Embryo-fetal toxicity

LIBTAYO can cause fetal harm when administered to a pregnant woman due to an increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

Adverse Reactions

- In the pooled safety analysis of 810 patients, the most common adverse reactions (≥15%) with LIBTAYO were musculoskeletal pain, fatigue, rash, and diarrhea
- In the pooled safety analysis of 810 patients, the most common Grade 3-4 laboratory abnormalities (≥2%) with LIBTAYO were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia

Use in Specific Populations

- Lactation: Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO
- Females and males of reproductive potential: Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO

Please see Brief Summary of Prescribing Information on the following pages.

ALK, anaplastic lymphoma kinase, EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; PD-L1, programmed death ligand-1; ROS1, c-ros oncogene 1 receptor tyrosine kinase.

Reference: 1. LIBTAYO (cemiplimab-rwlc) injection full U.S. prescribing information. Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC.









LIBTAYO® (cemiplimab-rwlc) injection, for intravenous use

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Cutaneous Squamous Cell Carcinoma

LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.

1.2 Basal Cell Carcinoma

LIBTAYO is indicated for the treatment of patients:

 with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.

Non-Small Cell Lung Cancer

LIBTAYO is indicated for the first-line treatment of patients with non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test [see Dosage and Administration (2.1) in the full prescribing information]), with no EGFR, ALK or ROS1 aberrations, and is:

- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
- metastatic.

CONTRAINDICATIONS

4

None.

WARNINGS AND PRECAUTIONS

Severe and Fatal Immune-Mediated Adverse Reactions

LIBTAYO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes. creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

LIBTAYO can cause immune-mediated pneumonitis. The definition of immune-mediated pneumonitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%) adverse reactions. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.4% of patients and withholding of LIBTAYO in 2.1% of the patients.

Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld for pneumonitis, 9 reinitiated LIBTAYO after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis.

Immune-Mediated Colitis

LIBTAYO can cause immune-mediated colitis. The definition of immunemediated colitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. The primary component of the immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%) adverse reactions. Colitis led to permanent discontinuation of LIBTAYO in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients.

Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld for colitis, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence of colitis.

Immune-Mediated Hepatitis

LIBTAYO can cause immune-mediated hepatitis. The definition of immunemediated hepatitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%) adverse reactions. Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in all patients with hepatitis. Nineteen percent (19%) of these patients (3/16) required additional immunosuppression with mycophenolate. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld for hepatitis, 3 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

Hypophysitis

LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]

Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

Thyroid Disorders

LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Thyroiditis: Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff.

Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported.

Hyperthyroidism: Hyperthyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%) adverse reactions. No patient discontinued treatment due to hyperthyroidism. Hyperthyroidism led to withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in 3.8% (1/26) of patients with hyperthyroidism. Hyperthyroidism resolved in 50% of the 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

Hypothyroidism: Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%) adverse reactions. Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients.

Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis.

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%) adverse reactions. No patient discontinued treatment due to Type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

Immune-Mediated Nephritis with Renal Dysfunction

LIBTAYO can cause immune-mediated nephritis. The definition of immune-mediated nephritis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

Immune-mediated nephritis occurred in 0.6% (5/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients.

Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld for nephritis, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients.

Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reaction, 7 reinitiated LIBTAYO after symptom improvement; of these 43% (3/7) had recurrence of the dermatologic adverse reaction.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in 810 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica

Endocrine: Hypoparathyroidism

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

5.2 Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash and dyspnea.

Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction [see Dosage and Administration (2.3) in the full prescribing information].

5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]
- Infusion-Related Reactions [see Warnings and Precautions (5.2)]
- Complications of Allogeneic HSCT [see Warnings and Precautions (5.3)]

6.1 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 data described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label randomized multi-center study (Study 1624). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 132 patients with advanced BCC (Study 1620), 355 patients with NSCLC

(Study 1624), and 104 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=235), 350 mg every 3 weeks (n=543), or other doses (n=32; 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks). Among the 810 patients, 57% were exposed for \geq 6 months and 25% were exposed for \geq 12 months. In this pooled safety population, the most common adverse reactions (\geq 15%) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities (\geq 2%) were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

Cutaneous Squamous Cell Carcinoma (CSCC)

The safety of LIBTAYO was evaluated in 219 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 [see Clinical Studies (14.1) in the full prescribing information]. Of these 219 patients, 131 had mCSCC (nodal or distant) and 88 had laCSCC. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=162) or 350 mg every 3 weeks (n=56) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 38 weeks (2 weeks to 110 weeks).

The safety population characteristics were: median age of 72 years (38 to 96 years), 83% male, 96% White, and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (44%) and 1 (56%).

Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in at least 2% of patients were pneumonitis, cellulitis, sepsis, and pneumonia.

Permanent discontinuation due to an adverse reaction occurred in 8% of patients. Adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonia, encephalitis, aseptic meningitis, hepatitis, arthralgia, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, psoriasis, rash maculopapular, proctitis, and confusional state.

The most common (\geq 20%) adverse reactions were fatigue, rash, diarrhea, musculoskeletal pain, and nausea. The most common Grade 3 or 4 adverse reactions (\geq 2%) were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepsis, skin infection, and hypercalcemia. The most common (\geq 4%) Grade 3 or 4 laboratory abnormalities worsening from baseline were lymphopenia, anemia, hyponatremia, and hypophosphatemia.

Table 2 summarizes the adverse reactions that occurred in $\geq 10\%$ of patients and Table 3 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in $\geq 1\%$ of patients receiving LIBTAYO.

Table 2: Adverse Reactions in ≥ 10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

Adverse Reactions	LIBTAYO N=219		
	All Grades %	Grades 3-4 %	
General and Administration	Site		
Fatigue ^a	34	3	
Skin and Subcutaneous Tiss	ue		
Rashb	31	1	
Pruritus ^c	18	0	
Gastrointestinal			
Diarrhea ^d	25	0.5	
Nausea	21	0	
Constipation	13	0.5	
Vomiting	10	0.5	
Musculoskeletal and Connec	ctive Tissue		
Musculoskeletal paine	24	3	
Arthralgia	11	1	
Respiratory		1	
Cough ^f	14	0	

(continued)

Table 2: Adverse Reactions in ≥ 10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

Adverse Reactions	LIBTAYO N=219		
	All Grades %	Grades 3-4 %	
Hematology			
Anemia	11	4	
Endocrine			
Hypothyroidism	10	0	
Metabolism and Nutrition			
Decreased appetite	10	0	

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03

- a. Composite term includes fatigue and asthenia
- b. Composite term includes rash, rash maculopapular, erythema, dermatitis, dermatitis bullous, rash generalized, pemphigoid, rash erythematous, rash macular, rash pruritic, drug eruption, psoriasis, and skin reaction
- c. Composite term includes pruritus and pruritus allergic
- d. Composite term includes diarrhea and colitis
- e. Composite term includes back pain, pain in extremity, myalgia, musculoskeletal pain, and neck pain
- f. Composite term includes cough and upper airway cough syndrome

Table 3: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

Laboratory Abnormality	Grade 3-4 (%) ^a	
Chemistry		
Increased aspartate aminotransferase	2	
Increased INR	2	
Hematology		
Lymphopenia	9	
Anemia	5	
Electrolytes		
Hyponatremia	5	
Hypophosphatemia	4	
Hypercalcemia	2	

Toxicity graded per NCI CTCAE v. 4.03

Basal Cell Carcinoma (BCC)

The safety of LIBTAYO was evaluated in 132 patients with advanced BCC (mBCC N=48, laBCC N=84) in an open-label, single-arm trial (Study 1620) [see Clinical Studies (14.2) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks as an intravenous infusion for up to 93 weeks or until disease progression or unacceptable toxicity. The median duration of exposure was 42 weeks (range: 2.1 weeks to 94 weeks).

The safety population characteristics were: median age of 68 years (38 to 90 years), 67% male, 74% White, and ECOG performance score (PS) of 0 (62%) and 1 (38%).

Serious adverse reactions occurred in 32% of patients. Serious adverse reactions that occurred in > 1.5% (at least 2 patients) were urinary tract infection, colitis, acute kidney injury, adrenal insufficiency, anemia, infected neoplasm, and somnolence. Fatal adverse reactions occurred in 1.5% of patients who received LIBTAYO, including acute kidney injury and cachexia.

Permanent discontinuation of LIBTAYO due to an adverse reaction occurred in 13% of patients. Adverse reactions resulting in permanent discontinuation of LIBTAYO in > 1.5% (at least 2 patients) were colitis and general physical health deterioration.

Dosage delays of LIBTAYO due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage delay in > 2% of patients (at least 3 patients) included blood creatinine increased, diarrhea, colitis, fatigue, headache, pneumonitis, and urinary tract infection.

The most common adverse reactions reported in at least 15% of patients were fatigue, musculoskeletal pain, diarrhea, rash, pruritus, and upper respiratory tract infection.

The most common Grade 3 or 4 adverse reactions (> 2%) were hypertension, colitis, fatigue, urinary tract infection, pneumonia, increased blood pressure,

a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter

hypokalemia and visual impairment. The most common (> 3%) laboratory abnormality worsening from baseline to Grade 3 or 4 was hyponatremia.

Table 4 summarizes the adverse reactions that occurred in $\geq 10\%$ of patients and Table 5 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in \geq 1% of patients receiving LIBTAYO.

Table 4: Adverse Reactions in ≥ 10% of Patients with Advanced BCC Receiving LIBTAYO in Study 1620

All Grades % n site conditions 49 ue disorders 33	Grades 3-4 %
49 ue disorders	
ue disorders	
	1.5
33	1.5
	1.5
	•
25	0
12	0.8
11	0.8
lers	
22	0.8
20	0
15	0
12	2.3
14	1.5
rs	
13	0.8
	•
12	1.5
al disorders	
	0
11	· ·
11	<u> </u>
	12 11 11 1ers 22 20 15 12 14 rs 13

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03

- a. Composite term includes fatigue, asthenia, and malaise
- Composite term includes arthralgia, back pain, myalgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal stiffness, musculoskeletal chest pain, musculoskeletal discomfort, and spinal pain
- Composite term includes rash maculo-papular, rash, dermatitis, dermatitis acneiform, erythema, rash pruritic, dermatitis bullous, dyshidrotic eczema, pemphigoid, rash erythematous, and urticaria
- Composite term includes upper respiratory tract infection, nasopharyngitis, rhinitis, sinusitis, pharyngitis, respiratory tract infection, and viral upper respiratory tract infection
- Composite term includes dyspnea and dyspnea exertional
- Composite term includes hypertension and hypertensive crisis

Table 5: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced BCC Receiving LIBTAYO in Study 1620

Laboratory Abnormality	Grade 3-4 (%) ^a
Laboratory Abnormanty	Grade 5-4 (76)
Electrolytes	
Hyponatremia	3.1
Hypokalemia	1.5
Coagulation	
Activated partial thromboplastin time prolonged	2.3
Hematology	
Lymphocyte count decreased	2.3

Toxicity graded per NCI CTCAE v. 4.03

Non-Small Cell Lung Cancer (NSCLC)

The safety of LIBTAYO was evaluated in 355 patients with locally advanced or metastatic NSCLC in Study 1624 [see Clinical Studies (14.3) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator's choice of chemotherapy (n=342), consisting of paclitaxel plus cisplatin or carboplatin; gemcitabine plus cisplatin or carboplatin; or pemetrexed plus cisplatin or carboplatin followed by optional pemetrexed maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (18 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥ 6 months and 22 % were exposed for \geq 12 months.

The safety population characteristics were: median age of 63 years (31 to 79 years), 44% of patients 65 or older, 88% male, 86% White, 82% had metastatic disease and 18% had locally advanced disease and ECOG performance score (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients; adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonitis, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

Table 6 summarizes the adverse reactions that occurred in \geq 10% of patients and Table 7 summarizes Grade 3 or 4 laboratory abnormalities in patients receiving LIBTAYO.

Table 6: Adverse Reactions in ≥ 10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

Adverse Reactions	LIBTAYO N=355		Chemotherapy N=342	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Musculoskeletal and	connective tiss	ue disorders		
Musculoskeletal pain ^a	26	0.6	27	1.5
Skin and subcutaneous tissue disorders				
Rashb	15	1.4	6	0
Blood and lymphatic system disorders				
Anemia	15	3.4	50	16
General disorders ar	General disorders and administration site conditions			
Fatigue ^c	14	1.1	26	2
Metabolism and nutrition disorders				
Decreased appetite	12	0.6	18	0.3
Infections and infestations				
Pneumonia ^d	11	5	12	5
Respiratory, thoracic and mediastinal disorders				
Coughe	11	0	8	0.3

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03

- a. Musculoskeletal pain is a composite term that includes back pain, arthralgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, neck pain, spinal pain, and musculoskeletal stiffness
- b. Rash is a composite term that includes rash, dermatitis, urticaria, rash maculopapular, erythema, rash erythematous, rash pruritic, psoriasis, autoimmune dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, drug eruption, dyshidrotic eczema, lichen planus, and skin reaction
- c. Fatigue is a composite term that includes fatigue, asthenia, and malaise
- d. Pneumonia is a composite term that includes atypical pneumonia, embolic pneumonia, lower respiratory tract infection, lung abscess, paracancerous pneumonia, pneumonia, pneumonia bacterial, and pneumonia klebsiella
- e. Cough is a composite term that includes cough and productive cough

a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter

Table 7: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

Laboratory Abnormality	LIBTAYO N=355	Chemotherapy N=342
	Grades 3-4ª %	
Chemistry		
Increased aspartate aminotransferase	3.9	1.2
Increased alanine aminotransferase	2.7	0.3
Increased alkaline phosphatase	2.4	0.3
Increased blood bilirubin	2.1	0.3
Hypoalbuminemia	1.8	1.3
Increased creatinine	1.2	1.6
Hematology		
Lymphopenia	7	9
Anemia	2.7	16
Electrolytes		
Hyponatremia	6	7
Hyperkalemia	4.2	1.9
Hypocalcemia	3.9	3.4
Hypophosphatemia	2.4	4.1
Hypermagnesemia	2.1	1.6
Hypokalemia	1.5	2.2
Hypercalcemia	1.2	2.2

Toxicity graded per NCI CTCAE v. 4.03

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab-rwlc in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies (ADA) were tested in 823 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 2.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immunemediated rejection of the developing fetus resulting in fetal death (see Data). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise 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% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO [see Use in Specific Populations (8.1)].

Contraception

LIBTAYO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of LIBTAYO have not been established in pediatric patients.

8.5 Geriatric Use

Of the 810 patients who received LIBTAYO in clinical studies, 32% were 65 years up to 75 years and 22% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 219 patients with mCSCC or IaCSCC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 132 patients with BCC who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

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a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.



ana Wright, CPhT, is NCODA's Regional Leader for Region 11, which includes the state of Florida.

Wright, a graduate of Old Dominion University in Norfolk, Virginia, is an oncology pharmacy technician at Cancer Specialists of North Florida (CSNF) in Jacksonville, Florida, where she has worked for nearly 12 years.

Prior to joining CSNF, she worked as a pharmacy technician in the clinical field for several years before a pharmacist colleague convinced her to interview with a small oncology practice that wanted to hire him.

"We worked great together as a team before and he asked me, 'Do you think you'd be interested in learning about oncology as well?" Wright said. "He would only take the job if he could bring his own technician."

Later, after her colleague retired, Wright joined CSNF, where she "sits on both sides of the fence," providing support for the practice's infusion center as well as its satellite retail pharmacies.

Patient education is a key part of her job. "I usually come out and meet the patients with the nurses," Wright said. "We explain the process when they're taking oral oncolytics."

Patients often don't understand concepts like prior authorization, copay cards, grants or financial assistance, she said — and especially the high cost of oral oncolytics.

"We have a social worker on-site that gets involved with financial assistance," Wright said. "We explain the whole process to them, so they understand and are not thrown off by some stranger calling them at their house."

Wright assists patients at either CSNF's medically integrated pharmacy or — if dictated by insurance — at the mail-order pharmacy where the prescriptions are being transferred. Regardless of where the prescription gets filled, CSNF patients receive comprehensive education about their oral oncolytic.

Wright said she got involved with NCODA after her former manager, Ginger Blackmon, PharmD, convinced her to attend a Fall Summit.

"I didn't even know NCODA existed out there, I mean it was like a whole new world to me," she said.

After Blackmon left CSNF earlier this year to become Manager of Clinical Initiatives at NCODA, she encouraged Wright to take over as Regional Leader for Region 11. "After she stepped down, she gave me a call and said, 'I really think you would be good at this," Wright said. "I looked at everything she had done, and I was hesitant. She said, 'I know you can do this, I know you can.' So I told her I'd give it a try."

Spreading the word about NCODA has become her new mission. "Most people think this is a Google world, but NCODA has so much more to offer. The NCODA website is so easily navigated and much easier for healthcare providers and patients to understand," she said.

Wright lives in Jacksonville with her husband, Jack, and their two sons, Hunter and Chase. "Because I have boys, there's a lot of football and basketball in my life," she said. "We're an outdoors family and spend a lot of time at the beach and sporting events, as well as hiking and kayaking."

Wright said the best part of her job is being able to provide affordable medication for people.

"When they see the high cost of the prescriptions, it's just devastating to them," she said. "They think, 'I can't afford \$10,000 or \$15,000 for this.' But they don't know that there are options out there to help them. So, when I'm able find a patient assistance to get the medicine they need, that's the most rewarding part of my job."

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CANCER DIAGNOSIS: THE START OF A PROFOUND JOURNEY FOR PATIENT, CAREGIVER, ONCOLOGIST

ancer is a deeply personal journey not only for the patient, but for their caregivers and healthcare providers as well.

Nowhere is this odyssey better illustrated than in the experience of Liza Marshall and her husband, John Marshall, MD, as they coped with Liza's diagnosis of triple-negative breast cancer over the past 15 years.

Liza, who left practice as a communications attorney in 2005 to channel her talents and energy into her family, was diagnosed with the deadliest form of breast cancer a year later at age 43.

"I looked in the mirror one morning and saw I had a swollen breast," Liza recalled. "I did not know that breast cancer could present in that way. I had my little breast self-examination pamphlet in my drawer and pulled it out every month and did my routine breast exam looking for lumps. So, I was lulled into a little security because I didn't think that was what it was."

Her doctor ordered a biopsy at Georgetown University Hospital, where John — an internationally recognized expert in gastrointestinal cancers and the development of new treatments for cancer — is a medical oncologist and professor. He found out about her diagnosis before she did, when the pathology

"It was very strange.
We were talking on the phone one morning and John said, 'You have breast cancer.' I thought he was joking."

Liza Marshall



Liza and John Marshall, MD, recently published a book about their 15-year journey battling Liza's triple-negative breast cancer.

report was accidentally carbon-copied to him.

"It was very strange," Liza said. "We were talking on the phone one morning and John said, 'You have breast cancer.' I thought he was joking."

That was the moment when their lives changed. For Liza, it began a long road of difficult healthcare decisions. The revelation came as a shock, she said, and life suddenly became very confusing.

"No matter how much you think you understand it — and I understood a fair bit about healthcare and Georgetown in general and cancer because I had been living with it through John's experience for so long — it was still utterly confusing," Liza said.

"It was very hard to figure out what was going on around me and what decisions I was supposed to be making and then, once I knew what decision I was supposed to be making, how to understand the information that was being given to me to make the decision. For many, perhaps for all cancer patients, you're in such a fog for a few days until you start to do something."

For John, it was the moment he began the transition from healthcare provider to caregiver.

"One of my colleagues — the woman who Liza's pathology report was supposed to go to — came into my office and said, 'Did you see this?'" John recalled.

"She literally took the phone from my hand and started talking to Liza. It was really at that moment that I knew I was going to have to build a new structure around all of this because I needed to be

CONTINUED ON NEXT PAGE

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JOURNEY

CONTINUED FROM PREVIOUS PAGE

her caregiver and that was new to me."

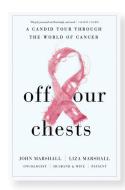
The abruptness of the moment was shattering, he said.

"It was immediate and sudden and that's very much the way these cancer diagnoses go for everybody," John said. "It's out of the blue, immediate, sudden and life-transforming. I began my own personal lessons on how to be a caregiver at that moment."

Following the diagnosis, Liza had a mastectomy and then began a series of clinical trials, infusion therapy, radiation

"It was immediate and sudden and that's very much the way these cancer diagnoses go for everybody. It's out of the blue and life-transforming. I began my own personal lessons on how to be a caregiver at that moment."

John Marshall



Off Our Chests: A Candid Tour Through the World of Cancer, is the Marshalls' memoir about their experiences with Liza's breast cancer and their personal journeys as patient, oncologist and caregiver.

and, finally, prophylactic surgery on her other breast. To add insult to injury, she later received word that her breast implants had been recalled. But now, after years of treatment, Liza is in remission. It's been a long road but, in the end, she has found peace.

"Anxiety was certainly high for me the first three years, but I don't worry so much now," she said. "I've come to the realization that life is unpredictable, and we don't know how long we're going to live. So try to live the moments you have and don't live them worrying."

For John, Liza's experience has come as a revelation, a revelation that he said has made him a better doctor.

"I came to the realization that there was a need to better inform the patient and the caregiver," he said, "But also on us as a cancer center to try and deliver care that was clearer, better-outlined and warmer so that we could bridge that gap for all our patients."

Early on, he asked the hospital to create a job description for a nurse navigator,

someone who could coach new patients through the experience and help educate them for the road ahead. It was clear, he came to realize, that healthcare was best managed comprehensively, utilizing a team of doctors, nurses, pharmacists, techs and other healthcare providers.

"Oncologists like to think of ourselves as the quarterback or the point guards of the team, but we could not win any games without all those with us working togeth-

er," he said.

The couple's experience also has led them in new directions.



Liza helped found Hope Con-

nections for Cancer Support, an organization that offers support groups, mind/body classes, and educational and social programs to anyone who has been affected by a cancer diagnosis including people with cancer, caregivers and the bereaved.

The couple also collaborated on a recently released book, Off Our Chests: A Candid Tour Through the World of Cancer, a memoir about the love, pain, strength and resilience they experienced during their cancer journey. The book, featured in The Washington Post's "10 Books to Read in May 2021," is available through Amazon.

For more information on the Marshalls' book, visit www.offourchestsbook.com/our-book.

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ADAPT, IMPROVISE, OVERCOME: NCODA STRIVES TO EMPOWER MEMBERS IN CHAOTIC COVID WORLD

s we reawaken to a new world in the wake of COVID-19 and its still-emerging variants, one message is clear: we must continue evolving to face the challenges ahead.

In that same vein, NCODA is striving — as television survivalist Bear Grylls is fond of saying — to "adapt, improvise and overcome" in our Mission to empower the medically integrated



Michael Reff

oncology team to deliver positive, patient-centered outcomes by providing leadership, expertise, quality standards and best practices.

Throughout 2020 on into Spring 2021, when

COVID was still running rampant in most of the world, NCODA accomplished this goal by shifting to the safety of digital media.

Our 2020 Spring Forum, 2020 Fall Summit and 2021 Spring Forum were all hosted virtually, enabling both presenters and participants to interact without risk. In the Spring and Summer of 2020, NCODA also hosted the nine-part virtual webinar series, "Supporting Patients and Practices Through the COVID-19 Pandemic" to keep our members informed of the latest developments as the pandemic unfolded.

It's been a long road, to say the least. But thanks to vaccines, education and lifestyle changes — and despite the uncertainty of emerging COVID variants and related ongoing controversies — life is slowly returning to normal.

So much so that NCODA's 2021 Fall Summit, slated for Oct. 20-22 in Scottsdale, Arizona, will be hosted on-site.

NCODA also hosted the first annual meeting of our Professional Student

Organization (PSO) on Sept. 16-17 in Detroit, Michigan, bringing together more than 200 pharmacy students from over 100 different pharmacy schools in the U.S. and Canada.

In addition to the return to on-site conferences, NCODA also has launched several new initiatives this year.

First and foremost is our collaboration with Prime Therapeutics. NCODA will offer accreditation for Prime's new Integrated Rx™ pharmacy program through our new NCODA Center of Excellence (CoE) Medically Integrated Pharmacy (MIP) Accreditation Program.

The accreditation program, based on compliance with the Patient-Centered Standards for Medically Integrated Dispensing: ASCO/NCODA Standards, is unique. Unlike existing pharmacy accreditation programs, which are tailored exclusively for mail-order pharmacies, the MIP Accreditation Program focuses solely on enhanced patient care and quality of services.

Elizabeth Bell, our newly named Director of Medically Integrated Pharmacy Accreditation, will oversee the CoE accreditation program, under the guidance, insight and support of an Executive Accreditation Council and an Accreditation Working Group made up of key oncology thought leaders.

NCODA also is in the process of applying for CE Provider Status through the Accreditation Council for Pharmacy Education (ACPE). This will allow NCODA to provide CE for our pharmacist and pharmacy technician members.

We've also strived to find new ways to reach out to members, including **The PQI Podcast**, FORUMRewind and SUMMITRewind, and OPTAReview.

The PQI Podcast is a new digital medium for NCODA. Podcast episodes cover a variety of topics including clinical, operational and patient interest stories. Presented by NCODA Manager of

Patient-Centered Communications Ginger Blackmon, PharmD, the podcast epsiodes provide a new way to hear firsthand from clinical and administrative experts across the country about new developments, current industry issues, shared stories from cancer survivors and, most importantly, how practices utilize PQIs to positively impact their practice and overall care.

Our new publications, FORUMRewind and SUMMITRewind, offer simple, easy-to-read breakdowns of the primary presentations from our Spring Forums and Fall Summits. Articles contained within each publication are written by PSO members and overseen by NCODA clinical managers.

OPTAReview is the new full-color reboot of the digital monthly newsletter for the Oncology Pharmacy Technician Association (OPTA). The newly designed newsletter provides updates on the latest oncology drugs, profiles of OPTA leaders and members, monthly meeting recaps and summations of hot topic discussions on industry trends and practices.

Finally, in addition to reaching forward to new oral therapies, NCODA — in collaboration with three other national oncology organizations — also is reaching back to existing intravenous therapy regimens. Starting this year, Intravenous Cancer Treatment Education (IVE) sheets will be added to a new NCODA digital library, which can be found at www.ivcanceredsheets.com.

Adapt, improvise, overcome. The world of oncology continues to evolve, and so does NCODA.

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Michael J. Reff, RPh, MBA
Executive Director & Founder | NCODA

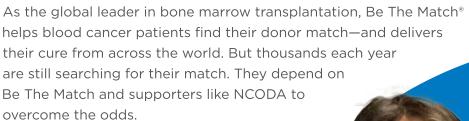
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