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$8,418,923

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

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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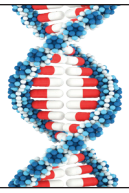

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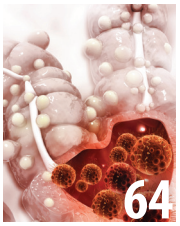

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WINTER'S ONSLAUGHT PROVIDES TIME TO REFLECT ON HOW FAR WE'VE COME

Like most of the country, we just got through one of the harshest winter storms we've ever experienced here in Texas.

The scenes on the national news (and international – my daughter saw the carnage in Australia) tell an accurate story of the water line breaks, power outages and life grinding to a halt.

Our power was out for 10 hours followed by four hours of power.

I had a lot of time to get reacquainted with my wife and younger daughter in front of the fireplace, where my daughter beat us at all board games (I threw the match).

Jim Schwartz

Looking back at that experience a week later, it reminded me of the atmosphere around the use of oral oncolytic drugs that existed for too long.

Being in oncology pharmacy for more than 25 years, I remember the introduction of the first widely used oral cancer drug (Xeloda) many years ago.

And, following that drug, there has been an endless stream of new oral agents that have become integral parts of cancer treatment.

Physicians at first were somewhat hesitant about prescribing oral oncolytics. Common concerns included:

▲ How will I know if the patient has taken their medication?

▲ Is the patient taking their medication correctly?

▲ How do we monitor the side effects, etc.?

The need for programs and tools to make better use of these oral agents to maximize the patients' response to treatment was present, but practices all over the country stumbled along doing their best.

Everyone tried their best, but there were no standards or guidelines on best practices, let alone the fact that there was no attempt by any of the professional organizations to step in and provide adequate leadership in this new phase of cancer treatment.

And then the biggest change in this area — the formation of NCODA — took place in the quaint town of Cazenovia, New York.

Almost overnight a core group of pharmacy oncology healthcare members began to develop and disseminate the leadership and information that was needed to assist oncology providers in maximum utilization of these new oral agents.

Over the last six-plus years, NCODA has built a website loaded with helpful tools and information to assist cancer care providers in their use of oral oncolytics.

The list of these resources is longer than this article should be, but includes:

▲ **Oral Chemotherapy Education** (OCE) sheets;

▲ The **Financial Assistance** tool for patients;

▲ **Positive Quality Intervention** (PQI) documents to educate and assist health care providers in managing the side effects of oral chemotherapy; and

▲ The **Cost Avoidance & Waste Tracker** tool to provide information on the dollars unnecessarily spent on unneeded, expensive prescriptions.

And on top of this treasure trove of valuable patient care information, NCODA has organized and presented semiannual international meetings (the Spring Forum and the Fall Summit) at no cost to participants.

I've been to every NCODA meeting (starting with the first at a relatively small Marriott in Atlanta) and I have always come away amazed at the quality and importance of all the presentations and speakers.

Given all the meetings I've been to put on by other professional organizations, I can honestly say that none of them touches the quality of what NCODA has done each and every time.

So, just like the fact that the winter storm and its damage will pass, the confusion and lack of coordination in the provision of oral chemotherapy care has been corrected through the work of each and every member of NCODA.

We have a great group of healthcare professionals fulfilling our Mission to provide better care for patients.

On a personal note, at the end of June 2021, I will be stepping down from my position as Executive Director of Pharmacy with Texas Oncology. But I will be staying on part-time with that physician group for a while to manage a few big projects that are developing.

And I will continue to be a part of the NCODA Mission, along with each member and the very valuable sponsors who provide the support needed for the betterment of cancer care.

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

A LOOK AT THE IMMUNE RESPONSE TO COVID-19 IN CANCER PATIENTS

INCIDENCE OF SARS-COV-2 IGG ANTIBODIES AMONG CANCER PATIENTS IN A HEMATOLOGY-ONCOLOGY CLINIC

By Mohammed Abdulaaima, MD, Ritu Chakrabarti, MD, Sabrina Gaiazov, MPH, Amit A. Patel, MD, Aaisha Shah, Jennifer Tharakan, & Kevin Tharakan

As the COVID-19 pandemic rages on, the effects of the virus remain poorly studied in cancer patients who are considered a "high risk" group due to the inherent nature of their cancers, their routine need for immuno-modulating treatments, frequent follow-ups and exposure to the healthcare system.

Early studies indicated that cancer patients suffered more severe outcomes — including intubation and mortality — than the general population, and have lower rates of seroconversion and detection of COVID-19 antibodies than health care workers.[1,2,3]

These studies demonstrated that the increased mortality from COVID-19 in cancer patients may have been "principally driven by age, gender and comorbidities,"[3] and not necessarily related to recent cytotoxic chemotherapies, anti-cancer treatments or active cancer.

Antibody formation represents the body's initial immunological response as well as ability to defend against COVID-19 and may provide insight into determining markers of disease severity and response to vaccination.

However, there have been few studies investigating the effect of COVID-19 and antibody production in cancer patients.

Herein, we present a study to compare the incidence of SARS-CoV-2 IgG antibody among cancer vs. non-cancer patients in the outpatient setting.

We identified cancer patients with recent anti-tumor or maintenance therapy (chemotherapy, immunotherapy, biologics, steroids, hormonal therapies and immunosuppressant) and compared them to non-cancer patients receiving treatment for primarily hematologic non-malignant conditions, such as anemia, baseline exposure to health-care-associated environments and infections deduced to be similar among these patients.

Further within our cancer cohort, we investigated if race and ethnicity, BMI, time since last anti-cancer therapy, type of anti-cancer therapy or stage and type of malignancy impacted incidence of SARS-CoV-2 antibodies.

METHODS

This is a single-center retrospective study identifying the incidence of SARS-CoV-2 IgG antibody among cancer and non-cancer patients in an outpatient hematology and oncology clinic between April and July 2020.

Patient data was collected from EMR in Cerner Millennium as well as OncoEMR with removal of all patient health information.

The baseline characteristics including patients' demographics (age, sex, BMI), type and stage of cancer, and recent anti-tumor therapy (treatment received one, three or six months before antibody detection). SAS V.9.4 was used for analyses and statistical significance was defined by a p value of < 0.05. Total sample size was 499 (243 cancer patients and 256 non-cancer patients).

All outliers were identified utilizing boxplot graphs and interquartile method and were removed prior to the detailed analysis. IRB exemption was provided.

RESULTS

Using a Fisher's exact test, we found that cancer patients had significantly less SARS-CoV-2 IgG antibodies (6.187%) compared to non-cancer patients (15.23%) (p=0.001).

Among cancer patients, there was no significant difference in antibody incidence between patients who had hematologic malignancies and patients who had solid tumors. Similarly, there was no significant relationship between type of cancer, stage or treatment type and COVID-19 antibody production.

Among cancer patients, those who had their antibody tested between one to three months after their last treatment were significantly more likely to have COVID-19 antibodies compared to other groups (p=0.002).

Additionally among cancer patients we used logistic regression to analyze sex, age, BMI, race, ethnicity, treatment type and time since treatment as potential predictors of antibody production.

Age proved to be a significant risk factor among cancer patients (p=0.015, OR=0.934, 95% CI (0.884, 0.987)), with older patients more likely to have negative antibody testing.

DISCUSSION

Our data suggest that cancer patients have a lower incidence of SARS-CoV-2 IgG antibody production than non-cancer patients, which corresponds

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COVID-19

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with previous studies, and may suggest decreased potential to produce a robust and long-lasting immunological response to COVID-19 infection.

Among our cancer patients with seroconversion, antibodies were most commonly present within one to three months post-therapy.

While our study was conducted soon after the pandemic arose in the U.S., and is limited by unknown dates of initial COVID-19 exposure, this timeframe for presence of antibodies suggests normal seroconversion and persistence of antibodies despite potential immunomodulation from recent treatment.[5,6,7]

Among all the factors analyzed, only age was significantly associated with decreased antibody production which has also been demonstrated in previous studies among the general population.[8] Interestingly, treatment type did not impact antibody production, which corresponds with data indicating that cytotoxic chemotherapy or immunotherapy were not associated with worse COVID-19 disease severity.[9]

While cancer patients had decreased incidence of SARS-CoV-2 IgG antibodies, this may inherently be related to the advanced age at which cancer often arises or other comorbidities rather than cancer or treatment type.

This insight will be increasingly important as we begin to vaccinate our cancer population against COVID-19.

Understanding this immune response in cancer patients is of extreme value to clinicians as we plan for surveillance, treatment and patient monitoring, as well as consideration of their safety in regular check-ups, clinical trial enrollment and exposure at health care settings during the continued COVID-19 pandemic.

▲ **Mohammed Abdulaaima**, MD, **Ritu Chakrabarti**, MD, **Sabrina Gaiazov**, MPH, **Amit Patel,** MD, **Aaisha Shah**, **Jennifer Tharakan** and **Kevin Tharakan** practice at Jersey City Medical Center RWJBH in Jersey City, New Jersey.

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

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NCODA, THE MEDICALLY INTEGRATED TEAM & PQI: LEADING THE WAY TO BETTER PATIENT CARE

Mitchell Cancer Institute Pharmacy Manger Brittney Carden, PharmD, uses the PQI to provide patient education and counseling on ixazomib.

By Ginger Blackmon, PharmD

In an effort to promote higher quality patient care, NCODA created the Positive Quality Intervention (PQI) as 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.

Ginger Blackmon

The PQI in Action, in turn, explores how two medically integrated teams incorporate the PQI as part of their daily workflow and manage specific drug therapies.

NCODA'S LATEST PQI IN ACTION

In Fall 2020, teams at Cancer Specialists of North Florida (CSNF) in Jacksonville, Florida, and the University of South Alabama Mitchell Cancer Institute (MCI) in Mobile, Alabama, participated in a PQI In Action article on the use of ixazomib in multiple myeloma.

The teams incorporated the **Ixazomib in the Treatment of Multiple Myeloma PQI** into their patient care process. Both teams discussed the value PQI utilization to ensure that all team members are on the same page and uniform in monitoring parameters, managing side effects and educating patients.

SCAN QR CODE TO VIEW THE IXAZOMIB PQI IN ACTION

CSNF and MCI are both proponents of Medically Integrated Dispensing (MID), which NCODA defines

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PQI IN ACTION

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as a dispensing pharmacy within an oncology center of excellence that promotes a patient-centered, multidisciplinary team approach. MID is an outcome-based collaborative and comprehensive model that involves oncology health care professionals and other stakeholders who focus on the continuity of coordinated, quality care and therapies for cancer patients.[1]

MID models help decrease fragmentation of care for the patient. Using resources like the PQI and following the **Patient-Centered Standards for Medically Integrated Dispensing: ASCO/NCODA Standards** helps set the stage for better team alignment and patient management.

SCAN QR CODE TO VIEW ASCO/NCODA MID STANDARDS

Both CSNF and MCI are advocates of the team effort and believe medically integrated pharmacies provide better continuity of care. Both believe it is important to incorporate the PQI because it gives the team a concise resource that highlights background of the therapy, expectations after therapy, possible clinical interventions and resources for assistance.

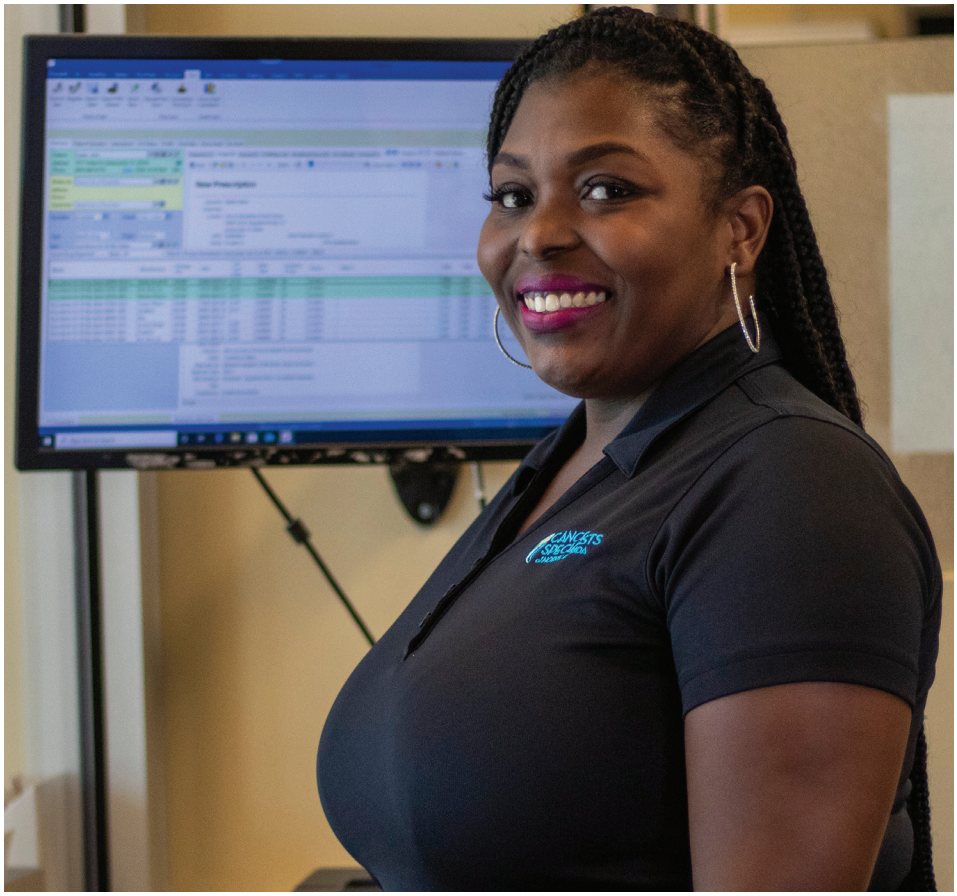
The ixazomib PQI lays out laboratory monitoring parameters, possible dosing adjustments, prophylactic therapies and drug interactions for the team.

CSNF and MCI pharmacists have access to their clinics' EMR system and check lab values with each prescription for ixazomib. The pharmacists also review the patient profile to screen for potential drug interactions and to ensure all necessary prophylactic therapies have been prescribed.

Being a part of the medically integrated team allows the pharmacist to simply email, call or even walk over to a physician if they wish to make a recommendation. CSNF pharmacists attach the PQI as a quick reference for the physician.

IXAZOMIB IN MULTIPLE MYELOMA THERAPY

Ixazomib is part of triplet therapy and the PQI discusses the importance of providing a therapy calendar for multiple myeloma patients to help stay on track with their regimen. Proper patient education is also key in more complicated therapies to help patients understand the dosing schedule and the purpose and importance of each medication.



Jessica Simmons, CPhT, said retail pharmacy technicians at Cancer Specialists of North Florida now use PQIs to determine whether copay cards are available for their patients' medication.

Both teams provide therapy calendars for their patients and utilize Oral Chemotherapy Education (OCE) sheets as a tool to help educate their patients.

CSNF pharmacists provide the OCE sheet to each patient filling ixazomib in their pharmacy. Participants noted OCE sheets are laid out in a way that makes it easy for patients to read, understand and avoid becoming overwhelmed.

MCI also sends OCE sheets home with their patients and directs them to refer to the side-effect management section once they start taking the medication. MCI pharmacists also send OCE sheets to their physicians so they can have a quick educational guide when speaking with patients.

One of the biggest benefits of the MID model is the assistance with finding coverage for patients with high copays on oral medications. Both CSNF and MCI have staff dedicated to completing prior authorizations and obtaining financial assistance for patients. The ixazomib PQI provides a manufacturer link to help the team in this task, a resource that pharmacy technicians at both practices said they appreciated.

A VALUABLE EXPERIENCE FOR PARTICIPANTS

In a follow-up interview several months after participating in the PQI in Action article, CSNF staff discussed their current PQI utilization.

CSNF Pharmacy Manager Ernestine Wigelsworth, PharmD, and Pharmacy Team Lead Jessica Simmons, CPhT, said participating in the PQI In Action process was a valuable experience.

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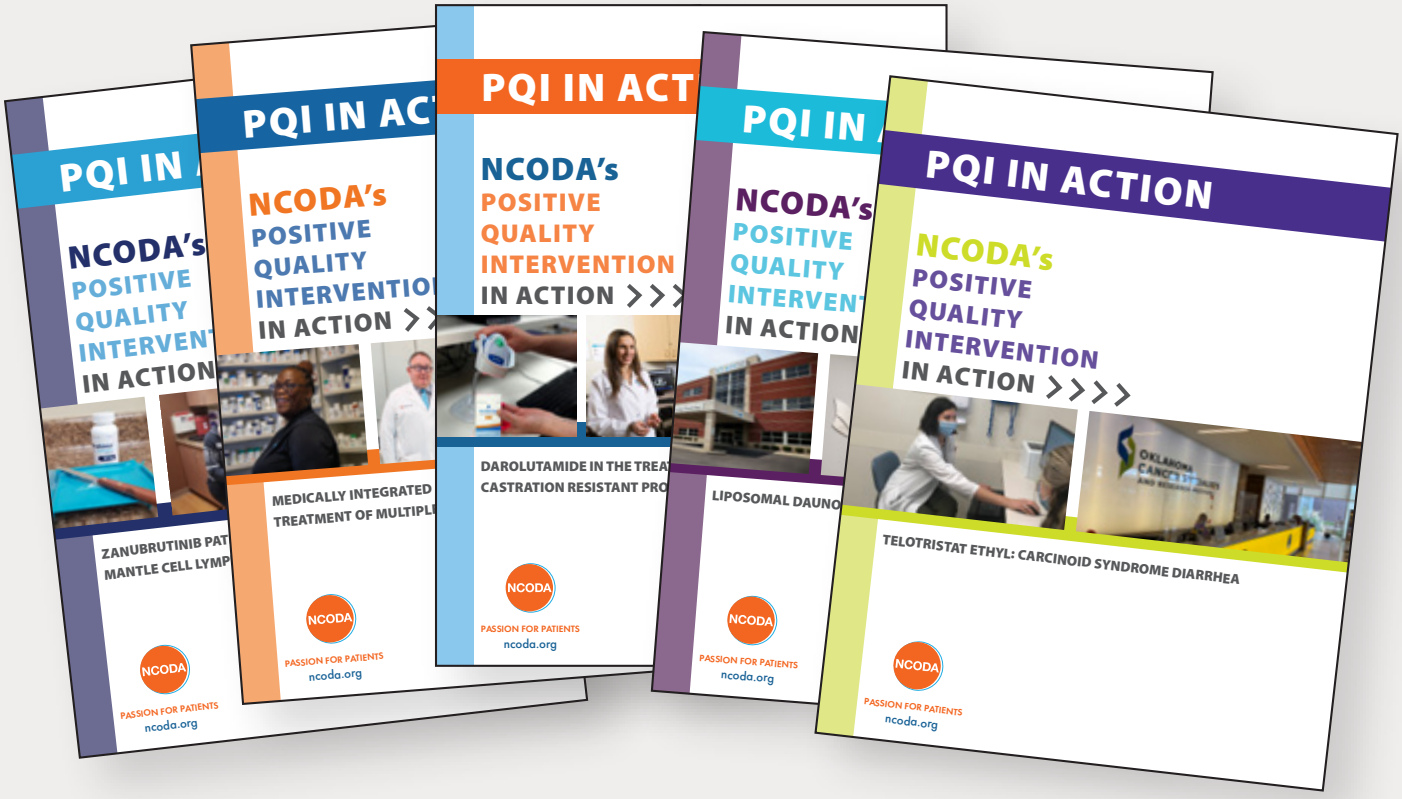

The NCODA website now features 10 PQI In Action articles available for download on such topics as Zanubrutinib Patient Selection And Management In Mantle Cell Lymphoma, Darolutamide In The Treatment Of Non-Metastatic Castration-Resistant Prostate Cancer (nm-CRPC) and Telotristat Ethyl: Carcinoid Syndrome Diarrhea. To view all PQI in Action articles, scan the QR code at right.

PQI IN ACTION

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"I thought it was really easy to participate in and did not require much on our part other than discussing the PQI and how we are using it," Wigelsworth said. "I thought it was beneficial because it made us more knowledgeable about all of the PQIs out there, especially those on the IV side."

Wigelsworth noted that CSNF pharmacists now utilize PQIs when completing pre-verifications of oral chemotherapy. They also use the PQI to check on pertinent ancillary medications and for alerts of any lab values to be checked in EMR when making sure the prescription is appropriate for the patient.

Wigelsworth also uses PQIs as a training tool for new employees and as a refresher for for existing staff.

Simmons said she has technician staff present a PQI once a month during team meetings. CSNF retail pharmacy technicians now use the PQI to check whether a copay card is available for a medication, she said.

Cancer Specialists of North Florida Pharmacy Manager Ernestine Wigelsworth, PharmD, said participating in the Ixazomib PQI In Action was a valuable experience.

Since participating in the article, CSNF has asked all of its IV pharmacy technicians to join NCODA. CSNF also has begun creating its own IV reference guide to utilitze the positive quality interventions.

▲ **Ginger Blackmon**, PharmD, is Manager of Patient-Centered Communications at NCODA.

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DID YOU YOU KNOW?

NCODA has openings for practices to participate in 2021 PQI in Action articles. Openings are available for both oral and IV therapies. For more information, contact Ginger Blackmon at Ginger.Blackmon@NCODA.org.

NCODA PARTNERSHIP LAUNCHES REGIMEN-BASED INTRAVENOUS EDUCATION SHEET INITIATIVE

NCODA is partnering with the Association of Community Cancer Centers (ACCC), the Hematology/Oncology Pharmacy Association (HOPA) and the Oncology Nursing Society (ONS) to create chemotherapy education sheets for patients on regimens containing intravenous therapies.

The project, similar to the group's collaboration on Oral Chemotherapy Education sheets (OCE), has been named IVE for Intravenous Education.

NCODA members draft the sheets, while ONS and HOPA members provide clinical review. Following the two separate clinical reviews, NCODA updates the formatting and layout. The IVE sheets are then made available online.

IVE sheets are regimen-based. The FOLFIRINOX regimen, for example, will provide education on fluorouracil, leucovorin, irinotecan and oxaliplatin.

IVE sheets also will provide a visual schedule for patients, as show in **Table 1.**

TABLE 1 | IVE PATIENT SCHEDULE

SCHEDULE | TREATMENT DAY											
Drug	Cycle 1 Day 1	2	3	4	5	6	7	...	21	Cycle 2 Day 1	2
Docetaxel	X									X	
Cyclophosphamide	X									X	
Growth Factor		X									X

Basic information regarding pre- and post-medication will be included in the sheet, allowing end-users to fill in relevant institution-specific data and patient information.

The authors utilized product-specific prescribing information as well as primary literature to support information listed in the sheet.

Aside from these enhancements, the sheets should appear familiar to those who have utilized OCE sheets at their practice.

NCODA commends everyone who participated in the initiative. While working on the IVE project, many contributors also helped manage COVID-19 patients at their respective institutions, worked at field hospitals and vaccinated the public.

Anyone interested in assisting with the project should contact **Britny Brown**, PharmD, BCOP, at brownbr@uri.edu or **Latha Radhakrishnan**, PharmD, BCPS, BCOP, at lradha15@gmail.com.

NCODA ANNOUNCES SIX NEW EXECUTIVE COUNCIL MEMBERS

NCODA is pleased to announce the addition of six new members to the Executive Council:

▲ **Paul Chadwick**, Florida Cancer Specialists & Research Institute,

▲ **Lucio Gordan**, MD, Florida Cancer Specialists & Research Institute,

▲ **Benjamin Lowentritt**, MD, Chesapeake Urology,

▲ **Stacey McCullough**, PharmD, Tennessee Oncology | Park Pharmacy,

▲ **Rajiv Panikkar**, MD, Geisinger Cancer Institute, and

▲ **Michelle Taymuree**, PharmD, MBA, Sutter Health.

All six joined the Executive Council in February 2021.

"These new Executive Council members are well positioned to help us continue executing our Mission in 2021," NCODA President Jim Schwartz, RPh, said.

NCODA Founder and Executive Director Michael Reff, RPh, MBA noted that The new Executive Council members will be integral to NCODA's continued growth and success in the years to come.

"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!"

LARGEST ONCOLOGY PROVIDER IN MICHIGAN TOUTS VALUE OF TREATMENT SUPPORT KITS

Lucius Daniel knows all about both the challenge and the value of patient care kits.

In 2020, Daniel, Lead Clinical Pharmacy Specialist with Karmanos Specialty Pharmacy (KSP), was tasked with creating kits for the thousands of new cancer patients being treated through Karmanos Cancer Institute.

Given the Institute's patient load, the project was easier said then done. The Detroit-based cancer center is the largest oncology provider in Michigan, with 16 outpatient fusion centers. It serves 12,000 patients and conducts 300 clinical trials annually.

Daniel eventually realized that there was a better option.

"We had worked on the kits for eight or nine months, but we just couldn't put them together as efficiently and as cost-effectively as NCODA could," Daniel said.

Daniel had heard about NCODA through colleagues, and the institute was using its Oral Chemotherapy Education (OCE) sheets.

"So we already had the connection with NCODA, and it was just a natural progression to use the resources that were there," Daniel said.

The decision to partner with NCODA and use its Treatment Support Kits (TSKs) proved to be a logical one, he said, for several reasons:

▲ **COST:** "We looked at the price points and found that there was no comparison. NCODA's kits were much more cost-effective."

▲ **BRANDING:** "It made more sense to partner with NCODA in a co-branding sense; our brand is actually on the TSK." *(NCODA offers this same service on all of its TSKs)*

▲ **TURNAROUND:** "I had no idea how long it would take, but NCODA turned it around very quickly because the kits were already created."

The NCODA TSKs for Karmanos Specialty Pharmacy are co-branded with the KSP logo.

▲ **CONCEPT:** "The kits were already created for the specific oral oncolytics, so we didn't have to recreate the wheel."

"We could not do it in a comprehensive way as well as NCODA did," Daniel said. "It would have taken us a lot more time and cost us a lot more money to put 3,000 kits together. It made sense to partner rather than to produce them ourselves."

Patient support kits have become a priority. As more and more oral oncolytics come to market, the need to manage potential side effects has become paramount, both for the patient and the healthcare team that services them.

"Even though orals are great agents and they are very effective, they also have their own set of dose-limiting and adherence-limiting toxicities," Daniel explained. "Whether its diarrhea, hand-foot syndrome, rash or neutropenia, in order to better serve the patient, you need to have agents readily available to address the typical toxicity issues."

"The kits give us a way to take the burden of our care teams — our mid-level providers, nurses and attendants — and allow them to focus on the patient. So instead of them having to manage hand-foot syndrome, we already have a product that is there. They don't have to scramble and try to figure out 'How are we going to address this?'"

KSP began using the following TSKs last winter: capecitabine, neratinib and selinexor.

Utilizing the TSKs throughout the system proved to be relatively easy.

"I had sought input from all stakeholders when we were trying to develop our own kits," Daniel explained. "So when the TSKs got here, we already had buy-in throughout the organization."

KSP manages the kits through prescriptions. When a prescription comes in, it's identified either as new or a refill. Kits are set up even before the prescription is filled, so once it's verified and released, the kit has been packaged.

Daniel makes sure providers are reminded what resources are available in the kits, such as thermometers for febrile neutropenia and loperamide for diarrhea.

"I tell them to let the pharmacy team know what is going on with the patient and we will help manage the process all the way through," he explained. "Our providers really like that. They say, 'Oh, this is great, now we don't have to figure how we're going to address the issue.'"

For practices interested in establishing their own patient care kits, Daniel encourages them to reach out to NCODA.

"I would tell other practices that the pricing is much better, but sometimes it's not obvious until you learn this on your own," he said. "TSKs are within NCODA's wheelhouse. It's one of the things they do best."

SCAN QR CODE TO LEARN MORE ABOUT NCODA'S TSKs

JAMES GILMORE

GEORGIA CANCER SPECIALISTS

James Gilmore, PharmD, has been a member of the NCODA Executive Council since 2019. Gilmore is Executive Vice President at Georgia Cancer Specialists (GCS). GCS is a national leader in advanced cancer treatment and research. Their 50 physicians provide care in 26 Northside Hospital Cancer Institute locations across Metro Atlanta, and North and Central Georgia.

How did you become involved with NCODA and what prompted you to join its Executive Council?

Several years ago, Michael Reff shared his vision for NCODA with me. I thought it was a good idea, and there was a real unmet need in the oncology space for an organization that was focused on medically integrated dispensing (MID) of oral oncology medications.

I watched NCODA grow, expand its Mission and was able to participate in several meetings. Michael asked me to increase my participation by joining the Executive Council. I was excited to become more involved. It has been a very rewarding experience.

Tell us a little about your expertise and what you bring to the table in helping shape NCODA's strategies.

It's hard to believe, but I've been in working in the oncology space for 29 years now. I spent the first nine years or so in a hospital setting working as a staff pharmacist, clinical pharmacist, clinical research pharmacist and ultimately managing the hospital's oncology program.

For the last 20 years, I have worked in various roles within Georgia Cancer Specialists, ultimately serving as Executive Vice President. We were one of the first practices in the country to integrate oral dispensing. Our practice is also nine years into an affiliation with Northside Hospital Cancer Institute, a large health system in our market.

Through my career, I have gained exposure to all aspects of oncology care from a health system and community practice perspective, including working within both 340B and GPO classes of trade. I try to leverage these experiences to inform and support the decisions and initiatives put forth by NCODA.

The current payer environment presents challenges both from the perspective of patient care and the business health of the dispensing practice. What changes would you like to see to help improve the quality of patient care?

I would like to see parity where all dispensing sites have the ability to fill all of our patients' oncology prescriptions. We are certainly best positioned to provide efficient and effective oversight of our patients' oncology medication needs. We can generally get the drug to the patient quicker and we are able to help them adhere to the therapies better, which leads to reduced waste.

I would also like to see elimination or restriction of DIR fees. The current system puts us at a disadvantage and creates an unfair business environment. When we adjudicate a claim, we should know at that time what our ultimate reimbursement will be. We should not have to wait months to find out the payer has clawed back a portion of our reimbursement.

How can NCODA members (nurses, physicians, pharmacists, technicians, administrators, pharmaceutical partners, etc.) who share your expertise best focus their efforts to improve delivery of oral oncolytics and ultimately improve the level of patient care?

We need to be able to demonstrate our ability to provide better service and associated outcomes to our patients. We need to work together to adhere to the ASCO/NCODA Quality Standards, and develop and report on objective metrics related to time to fill, medication possession ratio and specific outcome measurements.

Practices with MID should invest in patient advocates to help patients tap into all potential benefits available to them, such as patient assistance programs from manufacturers and foundations.

Practices should also consider obtaining NCODA's Treatment Support Kits (TSK) for relevant oncology products. These kits have proven to be very helpful with adherence to oral therapies.

NCODA faces many daunting challenges in trying to bring forth its message of the efficacy of Medically Integrated Dispensing to a diverse audience that includes providers, payers, legislators and manufacturers. How do we keep that message on target, and how do we measure success?

I think we need to share our perspective with all the stakeholders. Everyone should be aligned around a few key principals:

- Quick, easy access to oncology medications;
- Lower cost alternatives (less waste);
- Enhanced continuity of care (integration of provider and pharmacy); and
- Better adherence rates, better outcomes and better patient satisfaction scores. We can track and share adherence metrics, customer satisfaction scores, waste and certain clinical outcomes to measure our success.

ORAL ONCOLOGY NURSING EVOLVING IN RESPONSE TO COVID-19 PANDEMIC

By the NCODA Nursing Committee

The COVID-19 pandemic has had a significant effect on healthcare across the globe, and the field of oncology nursing proved to be no exception.

Members of the NCODA Nursing Committee recently discussed the impact of COVID-19 on their practices, and some common themes emerged:

TRANSITION TO ORAL THERAPIES: Several members noted an increase in oral oncolytic prescriptions including, for some patients, transition from parenteral to oral therapy.

This has led to an increased workload for many nurses, including more teaching sessions and monitoring of new starts.

TELEHEALTH: Although nurse-patient communication is frequently conducted by telephone, the pandemic brought about a significant increase in the number of remote teaching sessions and symptom management follow-up visits conducted by phone, tablet or computer.

Elizabeth Bettencourt, RN, MSN, OCN, an oral chemotherapy nurse navigator at Palo Alto Medical Foundation in Sunnyvale, California, said many of her patient education visits have transitioned from face-to-face to phone calls, requiring additional time to pull together and mail patient education materials.

Shawn Costanzo, BSN, RN, OCN, of Asheville, an oral oncolytic nurse navigator with AdventHealth Hendersonville in North Carolina, also uses telehealth for teaching sessions.

"I send an informational binder packet to the patient via FedEx," Costanzo said. "After the patient has reviewed the materials and made notes for questions, we get together on the phone and have an education session."

Costanzo noted the format allows for more time with the patient, better flexibility in scheduling and a more relaxed environment.

In addition, visual computer platforms such as such as Zoom allow nurses to better assess patient response by observing facial expressions to determine the individual's understanding. Zoom teaching sessions also provide the opportunity for several healthcare professionals to work with one patient at the same time.

WORKING REMOTELY: As the pandemic worsened in the U.S., many nurses who focus on oral therapies transitioned their role at hospitals or clinics to working remotely from home. As a result of the change, many had to develop new communication skills.

"I have honed my phone interviewing techniques and assessment skills to ensure I can extract all the information needed to report to the provider," Bettencourt said.

Also, since many patients have become reluctant to enter the cancer center during the pandemic unless it's absolutely necessary, remote communication is becoming the new normal.

Amanda McCauley, BSN, RN, OCN, an oncology nurse at Norton Cancer Institute in Louisville, Kentucky, has found innovative ways to obtain and monitor screening labs. She sends laboratory orders to outpatient facilities near the patient's home to cut down on their need to travel.

She noted this can be a challenge when the reports do not communicate well with the electronic health record, as many labs will need to send a paper copy.

McCauley said she also has seen increasing popularity with the utilization of the "MyChart" patient access portal at her facility.

ALL HANDS ON DECK: In many centers, nurses are collaborating with fellow team members to address needs outside of the oral oncolytic delivery.

Mary Anderson, BSN, RN, OCN, an oncology nurse navigator at Norton Cancer Insitute, noted that nurses who usually work in other roles are helping in the infusion center to "maximize patient flow and to prevent our oncology population from coming in contact with patients receiving (monoclonal antibody treatments)."

Nurses have also picked up the load for colleagues when their roles have changed during the pandemic, Anderson said.

The role of the oncology nurse is ever-evolving; whether the nurse is changing the process of education to meet the needs of the patient and keep everyone safe, or the needs of the hospital in caring for those affected by the coronavirus.

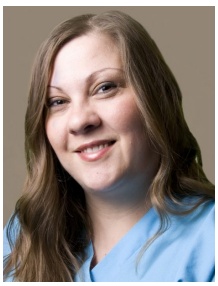
SCAN QR CODE TO VIEW NCODA'S ONCOLOGY NURSE RESOURCES

PHARMACY TECHNICIANS KEY TO BETTER MEDICATION ADHERENCE

By Becki Tinder, CPhT

According to the U.S. Food & Drug Administration, medication is not taken as prescribed 50% of the time.

As a result, it is estimated that non-adherence to medication leads to $100 billion-$290 billion in direct and indirect costs annually. These costs are especially high among patients with chronic conditions, who may experience complications that lead to emergency room visits or hospital stays.



Becki Tinder

However, recent studies have shown that training a pharmacy technician to facilitate and coordinate the drug procurement and dispensing process can make a big difference.

At the 2020 NCODA Fall Summit, co-presenter Rebecca Garland and I shared how we address adherence in our practices.

What we found was that we did many of the same things despite being in two very different practice settings. While her large practice utilizes a more refined approach with scripted phone calls and checklists, my small practice takes a more informal path. But both have an impact on our patients and their medication adherence.

We also found out, through feedback from the Fall Summit audience, that most practices have a policy in place to address adherence. Most participants indicated they either heard something new during our presentation that they wanted to implement, or that it validated what they were already doing.

Regardless of your practice's approach, the goal is to identify adherence issues as soon as possible so there is an opportunity to curb non-adherence and get the patient back on the right track.

For those practices that do not have a program to help patients with their medication adherence, here are some examples of what we shared at the Fall Summit:

- **Build** oral treatment plans into EMR;
- **Schedule** follow-up calls;
- **Manage** refills on a calendar or spreadsheet;
- **Utilize**, if possible, the patient's medical record to evaluate whether their medication is on hold or if the dose has changed;
- **Have** a script so that every technician asks the same questions every time;
- **Work** with your clinical team to condense educational material so it is easy to understand;
- **Encourage** your providers to put indications on prescriptions so you can put them on the pharmacy labels; and
- **Provide** a medication calendar to patients.

When assessing adherence with your patients, be sure to use open-ended questions to get an accurate feel for how they are taking their medication.

Avoid using "Yes" or "No" questions and have a scripted set of questions to guide the conversation to ensure everyone is asking the same questions every time.

Here are some examples of open-ended questions you can ask when you are refilling medication:

- **"How are you taking your medication?"** By asking this question, you are allowing the patient to explain in their own words how they believe they are to take their medication.
- **"How many pills do you have left in your bottle/pack?"** Use this information to compare the patient's answer to your timeline for their upcoming refill. If there is a discrepancy, this could indicate that the patient is skipping doses or not taking the medication as prescribed.
- **"How many doses have you missed since your last fill?"** They may not come out and tell you unless you ask. If you know why they are missing doses, chances are you can help get them back on track.

Expanding the scope of practice for pharmacy technicians further into patient adherence assessments can enable other team members to spend more time on clinical activities.

Adherence is a responsibility of the patient, and it relies upon their understanding of the therapy. But it also may involve other factors, including physical, emotional, financial or educational concerns.

By correctly identifying barriers that interfere with the patient's ability to take their medication correctly, you can provide real-time solutions and help improve their outcomes. While there might be some limitations to what a pharmacy technician can do in some instances, it should not stop us from recognizing potential issues.

Patients require constant support and reinforcement to achieve successful therapeutic outcomes. Having a policy in place at your practice and utilizing your pharmacy technicians could make the difference.

Becki Tinder, CPhT, is a pharmacy technician and Director of Dispensing Services at the Ghosh Center for Oncology & Hematology in Cedar Rapids, Iowa. She serves as Chair of the leadership team for NCODA's Oncology Pharmacy Technician Association (OPTA).

BRING ERYTHROID MATURATION TO LIFE

REBLOZYL is the first and only erythroid maturation agent FDA approved for anemia

IN MDS

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

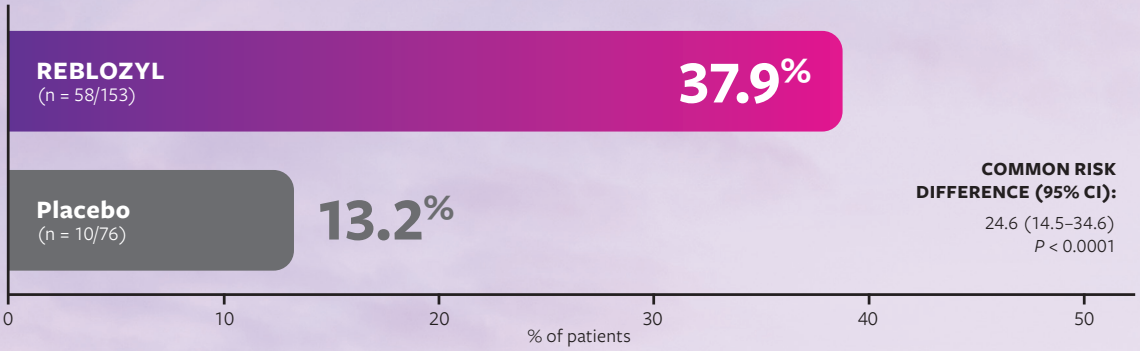
for patients with ring sideroblasts who are failing an ESA and require ≥2 RBC units/8 weeks[1]

REBLOZYL is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

REBLOZYL provided substantial clinical benefit through RBC transfusion independence vs placebo[1]

PRIMARY ENDPOINT: RBC-TI ≥8 WEEKS DURING WEEKS 1 TO 24



CI, confidence interval; ESA, erythropoiesis-stimulating agent; RBC-TI, red blood cell transfusion independence.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thrombosis/Thromboembolism
In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. TEEs included deep vein thrombosis, pulmonary embolus, portal vein thrombosis, and ischemic stroke. Patients with known risk factors for thromboembolism (splenectomy or concomitant use of hormone replacement therapy) may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients at increased risk of TEE. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly.

Hypertension
Hypertension was reported in 10.7% (61/571) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 1.8% to 8.6%. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥130 mm Hg and 23 (16.4%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new or exacerbations of preexisting hypertension using anti-hypertensive agents.

Embryo-Fetal Toxicity
REBLOZYL may cause fetal harm when administered to a pregnant woman. REBLOZYL caused increased post-implantation loss, decreased litter size, and an increased incidence of skeletal variations in pregnant rat and rabbit studies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the final dose.

ADVERSE REACTIONS

Grade ≥3 (≥2%) adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. A fatal adverse reaction occurred in 5 (2.1%) patients.

REBLOZYL provided RBC-TI vs placebo in patients with MDS-RS and MDS/MPN-RS-T[1]

KEY SECONDARY ENDPOINTS: RBC-TI ≥12 WEEKS

Endpoint	REBLOZYL (n = 153)	Placebo (n = 76)	Common risk difference (95% CI)	*P* value
RBC-TI ≥12 weeks during weeks 1–24	**28.1%** (43)	**7.9%** (6)	20.0 (10.9, 29.1)	0.0002
RBC-TI ≥12 weeks during weeks 1–48[a]	**33.3%** (51)	**11.8%** (9)	21.4 (11.2, 31.5)	0.0003

[a]The median (range) duration of treatment was 49 weeks (6–114 weeks) on the REBLOZYL arm and 24 weeks (7–89 weeks) on the placebo arm.

RBC-TI ≥8 WEEKS DURING WEEKS 1 TO 24 BY DIAGNOSIS AND BASELINE TRANSFUSION BURDEN IN MEDALIST

	Responders/N		% Response (95% CI)	
	REBLOZYL	Placebo	REBLOZYL	Placebo
WHO 2016 diagnosis				
MDS-RS	46/135	8/65	**34.1%** (26.1, 42.7)	**12.3%** (5.5, 22.8)
MDS/MPN-RS-T	9/14	2/9	**64.3%** (35.1, 87.2)	**22.2%** (2.8, 60.0)
Other[a]	3/4	0/2	**75.0%** (19.4, 99.4)	**0.0%** (0.0, 84.2)
Baseline RBC transfusion burden				
2–3 units/8 weeks[b]	37/46	8/20	**80.4%** (66.1, 90.6)	**40.0%** (19.1, 63.9)
4–5 units/8 weeks[c]	15/41	1/23	**36.6%** (22.1, 53.1)	**4.3%** (0.1, 21.9)
≥6 units/8 weeks	6/66	1/33	**9.1%** (3.4, 18.7)	**3.0%** (0.1, 15.8)

[a]Includes MDS-EB-1, MDS-EB-2, and MDS-U.
[b]Includes patients who received 3.5 units.
[c]Includes patients who received 5.5 units.

REBLOZYL was studied in the pivotal phase 3 MEDALIST trial of 229 patients with IPSS-R very low-, low-, or intermediate-risk MDS who have ring sideroblasts and require RBC transfusions (≥2 RBC units/8 weeks) who were randomized 2:1 to REBLOZYL (n = 153) or placebo (n = 76). Patients were required to have had an inadequate response to prior treatment with an ESA, be intolerant of ESAs, or be ineligible for ESAs (serum EPO >200 U/L). MEDALIST excluded patients with del 5q MDS, white blood cell count >13 Gi/L, neutrophils <0.5 Gi/L, platelets <50 Gi/L, or with prior use of a disease-modifying agent for treatment of MDS. REBLOZYL was administered 1 mg/kg subcutaneously every 3 weeks. Two dose-level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg) if the patient had an RBC transfusion within the prior 6 weeks. All patients received best supportive care, which included RBC transfusions as needed.

del 5q, deletion 5q; EPO, erythropoietin; IPSS-R, Revised International Prognostic Scoring System; MDS-EB-1, myelodysplastic syndromes with excess blasts (5%–9% in the bone marrow or 2%–4% in the blood); MDS-EB-2, myelodysplastic syndromes with excess blasts (10%–19% in the bone marrow or 5%–19% in the blood); MDS-U, myelodysplastic syndromes, unclassifiable; RBC, red blood cell; WHO, World Health Organization.

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS (CONT'D)

The most common (≥10%) adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection.

LACTATION

It is not known whether REBLOZYL is excreted into human milk or absorbed systemically after ingestion by a nursing infant. REBLOZYL was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because many drugs are excreted in human milk, and because of the unknown effects of REBLOZYL in infants, a decision should be made whether to discontinue nursing or to discontinue treatment. Because of the potential for serious adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for 3 months after the last dose.

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

Reference: 1. REBLOZYL [Prescribing Information]. Summit, NJ: Celgene Corporation; 2020.

Learn more, sign up for updates, and find out how to access REBLOZYL at:
REBLOZYLpro.com/discoverMDS

Bristol Myers Squibb™ | ACCELERON

06/20 US-RBZ-20-0260

REBLOZYL® (luspatercept-aamt) for injection, for subcutaneous use
Initial U.S. Approval: 2019

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

1 INDICATIONS AND USAGE

1.2 Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/ Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia

REBLOZYL is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

1.3 Limitations Of Use

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

2 DOSAGE AND ADMINISTRATION

2.2 Recommended Dosage for Myelodysplastic Syndromes with Ring Sideroblasts (MDS-RS) or Myelodysplastic/ Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis (MDS/MPN-RS-T) Associated Anemia

The recommended starting dose of REBLOZYL is 1 mg/kg once every 3 weeks by subcutaneous injection for patients with anemia of MDS-RS or MDS/MPN-RS-T. Prior to each REBLOZYL dose, review the patient's hemoglobin and transfusion record. Titrate the dose based on responses according to Table 3. Interrupt treatment for adverse reactions as described in Table 4. Discontinue REBLOZYL if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time.

If a planned administration of REBLOZYL is delayed or missed, administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses.

Dose Modifications for Response

Assess and review hemoglobin results prior to each administration of REBLOZYL. If an RBC transfusion occurred prior to dosing, use the pretransfusion hemoglobin for dose evaluation.

If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the REBLOZYL dose to 1.33 mg/kg (Table 3). If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg /kg dose level, increase the REBLOZYL dose to 1.75 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 1.75 mg/kg.

In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or if the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL as described in Table 3. If, upon dose reduction, the patient loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks in the absence of transfusion, increase the dose by one dose level. Wait a minimum of 6 weeks between dose increases.

Dose modifications for response are provided in Table 3.

Table 3: MDS-RS and MDS/MPN-RS-T Associated Anemia - REBLOZYL Dose Titration for Response

	REBLOZYL Dosing Recommendation*
Starting Dose	• 1 mg/kg every 3 weeks
Dose Increases for Insufficient Response at Initiation of Treatment	
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose	• Increase the dose to 1.33 mg/kg every 3 weeks
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at 1.33 mg/kg	• Increase the dose to 1.75 mg/kg every 3 weeks
No reduction in RBC transfusion burden after at least 3 consecutive doses (9 weeks) at 1.75 mg/kg	• Discontinue treatment

(continued)

Table 3: MDS-RS and MDS/MPN-RS-T Associated Anemia - REBLOZYL Dose Titration for Response

	REBLOZYL Dosing Recommendation*
Dose Modifications for Predose Hemoglobin Levels or Rapid Hemoglobin Rise	
Predose hemoglobin is greater than or equal to 11.5 g/dL in the absence of transfusions	• Interrupt treatment • Restart when the hemoglobin is no more than 11 g/dL
Increase in hemoglobin greater than 2 g/dL within 3 weeks in the absence of transfusions and	
• current dose is 1.75 mg/kg	• Reduce dose to 1.33 mg/kg
• current dose is 1.33 mg/kg	• Reduce dose to 1 mg/kg
• current dose is 1 mg/kg	• Reduce dose to 0.8 mg/kg
• current dose is 0.8 mg/kg	• Reduce dose to 0.6 mg/kg
• current dose is 0.6 mg/kg	• Discontinue treatment

* Do not increase the dose if the patient is experiencing an adverse reaction as described in Table 4.

Dose Modifications for Toxicity

For patients experiencing Grade 3 or higher adverse reactions, modify treatment as described in Table 4.

Table 4: MDS-RS and MDS/MPN-RS-T Associated Anemia - REBLOZYL Dosing Modifications for Adverse Reactions

	REBLOZYL Dosing Recommendation*
Grade 3 or 4 hypersensitivity reactions	• Discontinue treatment
Other Grade 3 or 4 adverse reactions	• Interrupt treatment • When the adverse reaction resolves to no more than Grade 1, restart treatment at the next lower dose level** • If the dose delay is > 12 consecutive weeks, discontinue treatment

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

**Per Table 3 dose reductions above.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombosis/Thromboembolism

In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. Reported TEEs included deep vein thromboses, pulmonary embolus, portal vein thrombosis, and ischemic strokes. Patients with known risk factors for thromboembolism, e.g. splenectomy or concomitant use of hormone replacement therapy, may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients with beta thalassemia at increased risk of TEE. Monitor patients receiving REBLOZYL for signs and symptoms of thromboembolic events and institute treatment promptly.

5.2 Hypertension

Hypertension was reported in 10.7% (61/571) of REBLOZYL-treated patients. Across clinical studies, the incidence of grade 3-4 hypertension ranged from 1.8% to 8.6%. In adult patients with beta thalassemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) ≥130 mm Hg and 33 (16.6%) patients developed diastolic blood pressure (DBP) ≥80 mm Hg. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥130 mm Hg and 23 (16.4%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new-onset hypertension or exacerbations of preexisting hypertension using anti-hypertensive agents.

5.3 Embryo-Fetal Toxicity

Based on findings from animal reproductive studies, REBLOZYL may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of luspatercept-aamt to pregnant rats and rabbits during organogenesis resulted in adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) of 1.75 mg/kg.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with REBLOZYL and for at least 3 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Thrombosis/Thromboembolism *[see Warnings and Precautions (5.1)]*
- Hypertension *[see Warnings and Precautions (5.2)]*

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 REBLOZYL as a single agent administered across a range of doses (0.125 mg/kg to 1.75 mg/kg) in 571 patients in 4 trials.

Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic / Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia

The safety of REBLOZYL at the recommended dose and schedule was evaluated in 242 patients with MDS with ring sideroblasts (n=192) or other myeloid neoplasms (n=50). The safety population included 63% males and 37% females of median age 72 years (range, 30 – 95 years); of these patients, 81% were White, 0.4% Black, 0.4% Other, and race was not reported in 18.2% of patients. The median time on treatment with REBLOZYL was 50.4 weeks (range, 3 – 221 weeks); 67% of patients were exposed for 6 months or longer and 49% were exposed for greater than one year.

Among the 242 patients treated with REBLOZYL, 5 (2.1%) had a fatal adverse reaction, 11 (4.5%) discontinued due to an adverse reaction, and 7 (2.9%) had a dose reduction due to an adverse reaction. The most common (≥10%) all-grade adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection. The most common (≥2%) Grade ≥ 3 adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. Selected laboratory abnormalities that changed from Grade 0-1 at baseline to Grade ≥ 2 at any time during the studies in at least 10% of patients included creatinine clearance decreased, total bilirubin increased, and alanine aminotransferase increased.

Table 8 shows the most common adverse reactions for patients treated with REBLOZYL or placebo through the first 8 cycles in the MEDALIST trial

Table 8: Adverse Reactions (≥5%) in Patients Receiving REBLOZYL with a Difference Between Arms of >2% in MEDALIST Trial Through Cycle 8

Body System / Adverse Reaction	REBLOZYL (N=153)		Placebo (N=76)	
	All Grades n (%)	Grade 3 n (%)	All Grades n (%)	Grade 3 n (%)
General disorders and administration site conditions				
Fatigue [a, b]	63 (41)	11 (7)	17 (22)	2 (3)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [b]	30 (20)	3 (2)	11 (14)	0 (0)
Nervous system disorders				
Dizziness/vertigo	28 (18)	1 (<1)	5 (7)	1 (1)
Headache [b]	21 (14)	0 (0)	5 (7)	0 (0)
Syncope / presyncope	8 (5)	5 (3)	0 (0)	0 (0)
Gastrointestinal disorders				
Nausea [b]	25 (16)	1 (<1)	8 (11)	0 (0)
Diarrhea [b]	25 (16)	0 (0)	7 (9)	0 (0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea [b]	20 (13)	2 (1)	4 (5)	1 (1)
Immune system disorders				
Hypersensitivity reactions [b]	15 (10)	1 (<1)	5 (7)	0 (0)

(continued)

Table 8: Adverse Reactions (≥5%) in Patients Receiving REBLOZYL with a Difference Between Arms of >2% in MEDALIST Trial Through Cycle 8

Body System / Adverse Reaction	REBLOZYL (N=153)		Placebo (N=76)	
	All Grades n (%)	Grade 3 n (%)	All Grades n (%)	Grade 3 n (%)
Renal and urinary disorders				
Renal impairment [b]	12 (8)	3 (2)	3 (4)	0 (0)
Cardiac disorders				
Tachycardia [b]	12 (8)	0 (0)	1 (1)	0 (0)
Injury poisoning and procedural complications				
Injection site reactions	10 (7)	0 (0)	3 (4)	0 (0)
Infections and infestations				
Upper respiratory tract infection	10 (7)	1 (<1)	2 (3)	0 (0)
Influenza / influenza like illness	9 (6)	0 (0)	2 (3)	0 (0)

[a] Includes asthenic conditions.
[b] Reaction includes similar/grouped terms.

Other clinically relevant adverse reactions reported in <5% of patients include bronchitis, urinary tract infection, and hypertension *[see Warnings and Precautions (5.2)]*.

Shifts from Grades 0-1 to Grades 2-4 abnormalities for selected laboratory tests during the first 8 cycles in the MEDALIST trial are shown in Table 9.

Table 9: Selected Grades 2-4 Treatment-Emergent Laboratory Abnormalities Through Cycle 8 in the MEDALIST Trial

Parameter	REBLOZYL		Placebo	
	N[a]	n (%)	N[a]	n (%)
ALT elevated	151	13 (9)	74	5 (7)
AST elevated	152	6 (4)	76	0 (0)
Total bilirubin elevated	140	17 (12)	66	3 (5)
Creatinine clearance reduced	113	30 (27)	62	13 (21)

[a] Number of patients at Grades 0-1 at baseline.
ALT = alanine aminotransferase; AST = aspartate aminotransferase.

6.2 Immunogenicity

As with all therapeutic proteins, there is 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 luspatercept in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Of 284 patients with beta thalassemia who were treated with REBLOZYL and evaluable for the presence of anti-luspatercept-aamt antibodies, 4 patients (1.4%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 2 patients (0.7%) who had neutralizing antibodies.

Of 260 patients with MDS who were treated with REBLOZYL and evaluable for the presence of anti-luspatercept-aamt antibodies, 23 patients (8.9%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 9 patients (3.5%) who had neutralizing antibodies.

Luspatercept-aamt serum concentration tended to decrease in the presence of neutralizing antibodies. There were no severe acute systemic hypersensitivity reactions reported for patients with anti-luspatercept-aamt antibodies in REBLOZYL clinical trials, and there was no association between hypersensitivity type reaction or injection site reaction and presence of anti-luspatercept-aamt antibodies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies, REBLOZYL may cause fetal harm when administered to a pregnant woman. There are no available data on REBLOZYL use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal

reproduction studies, administration of luspatercept-aamt to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes including embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) (*see Data*). Advise pregnant women of the potential risk to a 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
In embryo-fetal development studies, luspatercept-aamt was administered subcutaneously at 5, 15, or 30 mg/kg on gestation days 3 and 10 (rats) or 5, 20, or 40 mg/kg on gestation days 4 and 11 (rabbits). Effects in both species included reductions in numbers of live fetuses and fetal body weights, and increases in resorptions, post-implantation losses, and skeletal variations (such as asymmetric sternal centra in rats and angulated hyoid in rabbits). Effects were observed at exposures (based on AUC) approximately 7-times (rats) and 16-times (rabbits) the MRHD of 1.75 mg/kg.

In a pre- and postnatal development study, pregnant rats were administered luspatercept-aamt subcutaneously at 3, 10, or 30 mg/kg once every 2 weeks during organogenesis and through weaning, gestation day 6 through postnatal day 20. At all dose levels lower F1 pup body weights and adverse kidney findings (such as membranoproliferative glomerulonephritis, tubular atrophy/hypoplasia, and vessel ectasia occasionally associated with hemorrhage) were observed. These effects were observed at exposures (based on AUC) approximately 1.6-times the MRHD of 1.75 mg/kg.

8.2 Lactation
Risk Summary

Luspatercept-aamt was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There are no data on the presence of REBLOZYL in human 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 REBLOZYL, and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential
Pregnancy Testing

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

Contraception

Females
REBLOZYL may 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 REBLOZYL and for at least 3 months after the last dose.

Infertility

Females
Based on findings in animals, REBLOZYL may impair female fertility *[see Nonclinical Toxicology (13.1)]*. Adverse effects on fertility in female rats were reversible after a 14-week recovery period.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Based on findings in juvenile animals, REBLOZYL is not recommended for use in pediatric patients *[see Non-Clinical Toxicology (13.1)]*.

8.5 Geriatric Use
Clinical studies of REBLOZYL in beta thalassemia did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients.

Clinical studies of REBLOZYL for treatment of anemia in MDS-RS and MDS/MPN-RS-T included 206 (79%) patients ≥ 65 years of age and 93 (36%) patients ≥ 75 years of age. No differences in safety or effectiveness were observed between older (≥ 65 years) and younger patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity or mutagenicity studies have been conducted with luspatercept-aamt.

In a repeat-dose toxicity study, juvenile rats were administered luspatercept-aamt subcutaneously at 1, 3, or 10 mg/kg once every 2 weeks from postnatal day 7 to 91. Hematologic malignancies (granulocytic leukemia, lymphocytic leukemia, malignant lymphoma) were observed at 10 mg/kg resulting in exposures (based on area under the curve [AUC]) approximately 4.4 times the maximum recommended human dose (MRHD) of 1.75 mg/kg.

In a combined male and female fertility and early embryonic development study in rats, luspatercept-aamt was administered subcutaneously to animals at doses of 1 to 15 mg/kg. There were significant reductions in the average numbers of corpora lutea, implantations, and viable embryos in luspatercept-aamt-treated females. Effects on female fertility were observed at the highest dose with exposures (based on AUC) approximately 7-times the MRHD of 1.75 mg/kg. Adverse effects on fertility in female rats were reversible after a 14-week recovery period. No adverse effects were noted in male rats.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to and during treatment with REBLOZYL.

Thromboembolic Events
Advise beta thalassemia patients of the potential risk of thromboembolic events. Review known risk factors for developing thromboembolic events and advise patients to reduce modifiable risk factors (e.g., smoking, use of oral contraceptives) *[see Warnings and Precautions (5.1)]*.

Effects on Blood Pressure
Caution patients that REBLOZYL may cause an increase in blood pressure *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity
Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving REBLOZYL and for at least 3 months after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with REBLOZYL *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

Lactation
Advise females not to breastfeed during treatment with REBLOZYL and for 3 months after the final dose *[see Use in Specific Populations (8.2)]*.

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ELIZABETH BETTENCOURT, NATASHA OLSON HONORED FOR NCODA ROLES

The recipients of NCODA's 2020 Living the Mission Award were Elizabeth Bettencourt, MSN, RN, OCN, and Natasha Olson, PharmD.

The award is presented each year to a member or members who best exemplify the NCODA Mission to "empower the medically-integrated oncology team to deliver positive, patient-centered outcomes by providing leadership, expertise, quality standards and best practices."

Living the Mission Committee Chair and NCODA Executive Council member Jan Montgomery, PharmD, presented the awards during the NCODA Virtual Fall Summit on Oct. 22, 2020.

The two healthcare professionals were selected from a group of 12 nominees. Each woman received an award plaque, NCODA apparel and a leather portfolio.

ELIZABETH BETTENCOURT

Bettencourt is an Oral Chemotherapy Nurse Navigator at Palo Alto Medical Foundation/Sutter Health in Sunnyvale, California.

She has served as oral oncolytic nurse navigator for the past 12 years. Her position focuses on all facets of oral oncolytic patient care, including coordinating with mail-order pharmacies, insurance companies, copay assistance organizations and drug manufacturer patient support foundations to ensure patients can access their medication. She also works with in-house pharmacists for drug interaction checks and dose checks.

"I work to ensure that patients on oral oncolytics receive the same dedicated care that patients receiving intravenous/in-house chemo receive," Bettencourt said.

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Above: Elizabeth Bettencourt, MSN, RN, OCN, is an oral chemotherapy nurse navigator at Palo Alto Medical Foundation/Sutter Health in Sunnyvale, California.

Left: Natasha Olson, PharmD, (right) who is now NCODA's Manager of Clinical Initiatives, formerly was an oncology pharmacist at Summit Cancer Centers in Spokane, Washington.

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Her professional focus has been tempered by personal experience.

"My husband was on four different oral oncolytics from 2006 to 2008," Bettencourt explained. "We received little, if any, education or support while on treatment; hence my passion for dedicated quality care for these patients."

Bettencourt joined NCODA in 2016, and has co-chaired the NCDOA Nursing Committee since late 2017. In 2018, she presented at the NCODA Fall Summit with Executive Council member Mary Anderson.

She has been involved in several NCODA initiatives, including the Oral Oncolytic Welcome Letter, First Fill/After First Fill Tracking Forms and Oral Therapy Patient Follow-up Templates. She also authored two nursing articles in *Oncolytics Today*.

Bettencourt's nomination paper noted that she, along with Anderson, "helped grow the NCODA Nursing Committee into a great community of nurses who have developed many resources to help oncology practice nurses better improve the care of their patients." She began leading the group in early 2019 and has since grown it to more than 50-plus nursing members who appreciate the support the nursing committee has provided to their practices.

NATASHA OLSON

Olson, named Manager of Clinical Initiatives at NCODA in January 2021, was formerly an oncology pharmacist at Summit Cancer Centers in Spokane, Washington.

In her previous role, she was responsible for overseeing medication fills, initiation and completion of prior authorizations, procurment of funding, medication ordering, inventory maintenance, oral medication counseling, managment of pricing and rebates for both oral and IV medications, and chart reviews.

"My goal was a $0 copay and a 24-hour turnaround on all Medically Integrated Dispensing (MID) prescriptions," Olson said.

Olson joined NCODA as a member in 2017.

"I was recommended to join by another member, Jen Hasiak," Olson said. "Being in a similar practice setting, she told me she used NCODA and its members to ask questions and bounce ideas off others who do the same things we do. This was exactly what I needed! Being new to oncology, I felt that I really needed support from others for advice, answers to random questions and to develop best practices."

Olson has served in a wide variety of positions, including 2018 Fall Summit Cost Avoidance and Waste Tracker workshop leader, 2019 Fall Summit Planning Committee member, 2019 Fall Summit presenter ("The Value in Treatment Support Kits and Oral Chemotherapy Education Sheets"), 2019 Practice in Focus presenter, Immunotherapy-related Rash PQI author, Vaccination in Chemotherapy Patients PQI co-author, Treatment Support Kit Committee Chair, PQI Committee Chair, 2019 Fall Summit Meeting Chair, 2020 Fall Summit Meeting Chair, Inrebic Clinical Corner presenter, Ovarian Cancer EMR Resource presenter and 2021 Spring Forum Meeting Chair.

She also served as NCODA's Region 1 leader, a region that has seen the highest percentage of member recruitment based on region size.

Olson has served as a speaker at numerous national meetings and seminars, and has authored several articles for *Oncolytics Today*.

She also served as NCODA's ambassador to the Washington State University Professional Student Organization chapter and hosted a Student Educational Talks (SETs) webinar in June 2020.

Olson's nomination paper stated that she "has greatly helped in various NCODA initiatives to further our Mission and lead others by example," making note of her participation in numerous committees and initiatives.

"The NCODA team also highly values her great responsiveness and receptiveness to helping wherever she can," Olson's nomination paper concluded.

ABOUT THE LIVING THE MISSION AWARD

NCODA's Living the Mission Award recognizes members who exemplify the Mission "to empower the medically integrated oncology team to deliver positive, patient-centered outcomes by providing leadership, expertise, quality standards and best practices."

NCODA members wishing to highlight the accomplishments of their colleagues submit nominations for the award.

Past award winners include Julie Watson, PharmD, Southeast Nebraska Cancer Center, in 2017; Neal Dave, PharmD, Texas Oncology, in 2018; Britny Rogala, PharmD, BCOP, Women & Infants Hospital, Providence, Rhode Island, and Nora Hansen, CPhT, Illinois Cancer Specialists, in 2019.

Nominations for the 2021 Living the Mission Award will begin in May. For more information or to download a nomination form, go to ncoda.org/awards.

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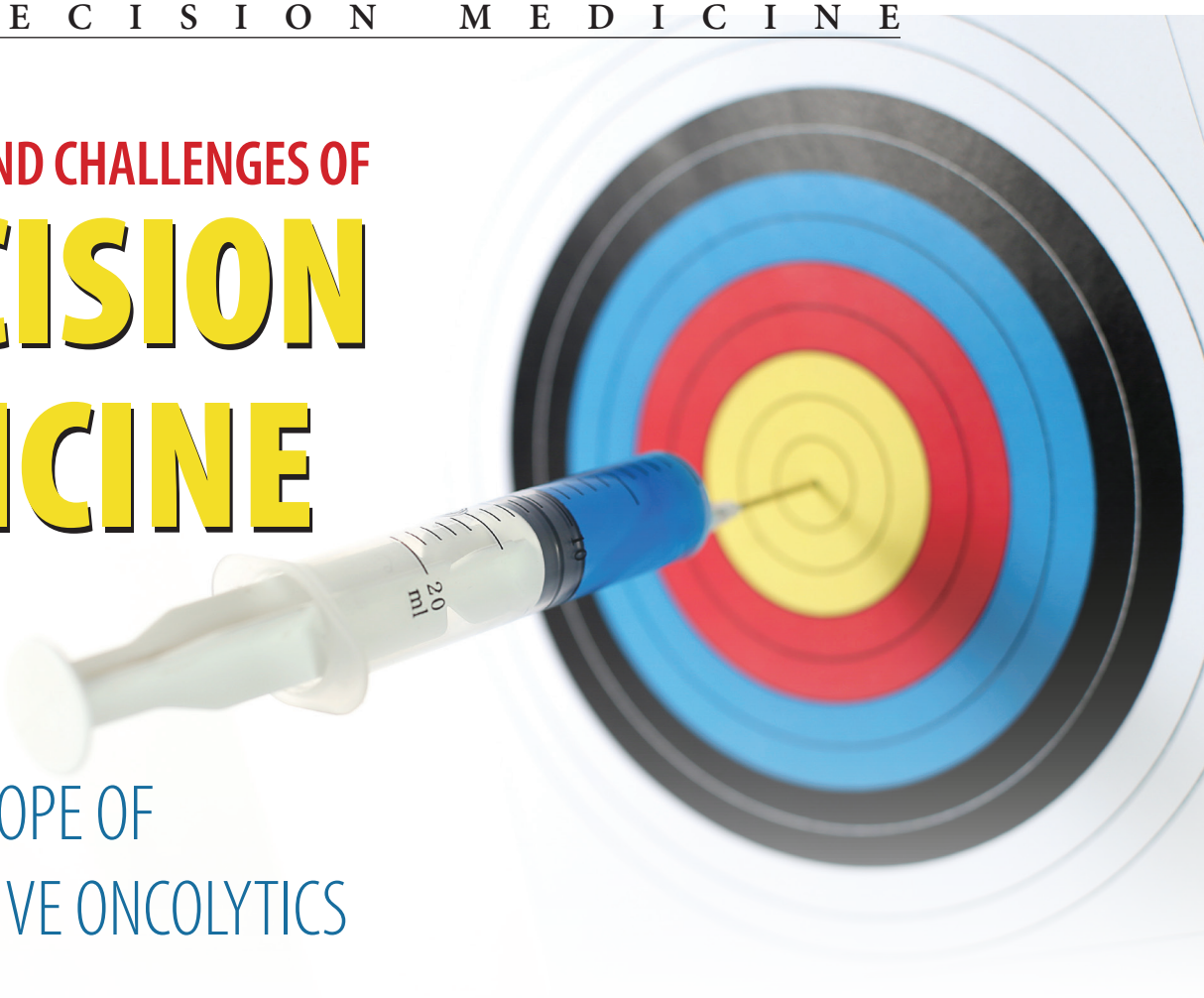

THE PROMISE AND CHALLENGES OF PRECISION MEDICINE

INFORMATION INTEGRATION OFFERS THE HOPE OF MORE EFFECTIVE ONCOLYTICS

By Anna O. Williford, PhD, Trey L. Schuchart, BS, & Lorraine C. Brisbin, MS

Precision medicine is a relatively new and rapidly evolving approach in healthcare that considers differences in patients' individual characteristics to identify the most effective disease prevention, detection and treatment strategies.

Broadly defined, precision medicine includes the integration of information from a wide variety of sources — including genetic and molecular profiles, imaging data, records from wearable health-tracking devices and lifestyle choices — to provide increasingly personalized healthcare.

This is the approach taken by an ambitious national research program, "All Of Us," that aims to enroll one million participants from all backgrounds in order to investigate how differences between individuals can guide disease prevention, detection and treatment.[1]

Here, we focus on precision medicine understood in a narrower and more practical sense: an approach to treating patients with therapies that are guided by the presence of alterations in patients' molecular profiles.

The need for a shift in healthcare toward precision medicine is made evident by the low efficacy of drugs designed for the "average" patient. For example, among people taking one of the 10 top-selling drugs in the US, only 4-25% see their condition improve.[2]

When drug effectiveness is examined by drug category, the highest effectiveness is seen for anti-depressants, with close to 60% of patients improving, while anti-cancer drugs are the least effective, with health benefits seen in only 25% of patients, on average.[3]

The underlying cause of this variation in drug response is likely a combination of genetic and environmental factors. Scrutinizing the mechanisms of action and relative contribution of each factor is the key to improving the treatment response rate.

Precision medicine emerged as a result of a better understanding of the genetic bases of the disease, and it offers treatments that utilize patients' genetic profiles in addition to clinical and demographic factors that have guided medical care up to now.

The first precision medicine drug, Herceptin (trastuzumab), was approved by the FDA in 1998 for treatment of breast cancer with overexpression of HER2 protein.[3,4] Since then, the FDA has approved more than 300 precision medicine drugs.[3,5]

The share of precision drugs also is

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growing: in 2005, 5% of FDA-approved drugs were classified as precision medicine; in 2020 this fraction grew to more than 25%.[3]

A large portion of precision medicine drugs are anti-cancer drugs. As of 2020, there were 160 targeted anti-cancer therapies for 30 cancer types.[6]

One of the most impressive examples of a targeted therapy is Gleevec® (imatinib), approved by the FDA in 2001. It took more than 40 years from the initial discovery of the Philadelphia chromosome (an abnormal chromosome that results from genetic translocation) to FDA approval of the drug.

Imatinib is a kinase inhibitor developed to treat a rare blood cancer, chronic myeloid leukemia (CML). The molecular alteration that imatinib targets is a BCR-ABL fusion protein, an overactive tyrosine kinase produced by a translocation-induced gene fusion, that stimulates cell division.[7]

Imatinib has the highest response rate of all genome-guided treatments, with 98% of patients showing a complete response. This early remarkable success of targeted therapy generated a lot of enthusiasm for precision medicine among members of the research community, physicians and patients alike.

The list of FDA-approved precision medicine drugs also includes three therapies that point to the success of tumor-agnostic treatments. These are therapies that are informed by genetic alterations shared by different tumor types.

The first tumor-agnostic drug that lifts the inhibition of anti-tumor immune response, pembrolizumab (Keytruda), was approved in 2017 for treatment of solid tumors with high microsatellite instability or deficiency in mismatch repair system. The other two tumor-agnostic drugs, larotrectinib and entrectinib, were approved for treatment of solid tumors with NTRK gene fusions.

The approval of these drugs was possible due to a novel clinical trial design, the so-called "basket" trials, where patients are enrolled based on the presence of genetic alteration rather than primary tumor site. This approach accelerates drug development for rare cancers and rare biomarkers for which standard clinical trials are not feasible. At least eight additional tumor-agnostic therapies are currently in development.[8]

One of the most impressive examples of a targeted therapy is Gleevec® (imatinib), approved by the FDA in 2001. It took more than 40 years from the initial discovery of the Philadelphia chromosome (an abnormal chromosome that results from genetic translocation) to FDA approval of the drug.

In addition to detection of actionable mutations or genetic signatures that can guide targeted therapies, molecular profiles can be utilized for disease prevention and early cancer detection. For example, mutations in BRCA1 or BRCA2 genes greatly increase chances of developing breast and ovarian cancer (among others) and evaluation for these mutations gives physicians and patients an opportunity to discuss and decide on preventative and treatment measures before symptoms develop.[3]

For cancer screening and early detection, much research has focused on the analysis of blood samples to detect presence of molecular biomarkers shed by tumor cells. In 2016, the FDA approved the first blood-based detection of methylated SEPT9 gene for colorectal cancer screening.[9]

The use of liquid biopsy for multi-cancer detection faces many challenges,[10] but recent studies report encouraging results, detecting cancer using a mixture of DNA and protein biomarkers[11] or detecting both tumor presence and its location, using methylation patterns in cell-free DNA.[12]

Development of reliable multi-cancer blood-based screening tests is expected to result in reduction in cancer-related deaths due to more effective treatments in early stages of the disease. It is estimated that cancer detection at stage III instead of stage IV can reduces cancer-related death by 15%, with further reductions in deaths if cancer is detected in earlier stages.[13]

These few examples illustrate the potential of precision medicine — better disease prevention and detection, more effective and more targeted treatment, faster drug development and approval, and overall reduction in healthcare costs as a result of abandoning ineffective treatments and improvements in early cancer detection.

Although the success of precision medicine can be reflected in the increasing number of targeted drug approvals, the overall benefit to cancer patients remains sub-optimal. It is estimated that between 2006 and 2018, the percentage of patients with metastatic cancer benefiting from genome-guided therapy increased from 1.3% to 6.62%.[14]

In 2018, 15% of patients were estimated to have an actionable mutation that could be treated by an FDA-approved drugs. Considering the response rate to the targeted treatments, the percentage of patients who benefited fell to ~ 7%.[14]

A similar picture emerges when aggregating the results of multiple studies that included 13,780 patients who were matched to targeted therapies based on the presence of actionable mutations identified

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by genomic profiling of tumors. Targetable mutations were present in 40% of patients, but only 12% were treated with targeted therapy and at the end, only 0.8-3% of patients benefited from treatment.[15]

These results indicate that the field of precision medicine is still in its early stages and point to research areas where further advances are needed to bring the benefit of targeted therapy to a larger patient population.

First, the number of drugs that target known driver mutations is low. Recent analysis of mutations in nearly 10,000 tumor samples across 33 cancer types identified 299 cancer driver genes with ~3,400 driver mutations.[16] Currently, available drugs work against only a handful of these mutations; many more mutations need to be investigated as potential drug targets. The discovery of genes playing a driver role in multiple cancer types[16] offers an opportunity to develop additional tumor-agnostic therapies.

Second, multiple genetic studies have documented spatial and temporal tumor heterogeneity within the same patient.[17] Consequently, sequencing results from a single biopsy are unlikely to represent the full spectrum of mutations present in the tumor and thus will miss targetable mutations.

Use of liquid biopsy can reduce the problem of intratumor heterogeneity as circulating tumor DNA contains genetic material from different regions of the tumor. Liquid biopsy also allows for assessment of temporal changes in mutation burden and can guide changes in therapies over time.

Third, the response rate to many targeted therapies is still low. The median overall response rate for 31 FDA-approved cancer drugs through 2018 is 54%.[14] This means that many patients still do not respond to treatment despite having molecular alterations that therapy is designed to target.

Tumor heterogeneity can explain the lack of response to treatment if a subpopulation of tumor cells has mutations that confer resistance to drug or acquires new driver mutations.[15,17] Many other factors can contribute to varied response in treatment, including variation in genes that govern pharmacokinetic and pharmacodynamic properties of the drug.

In general, low success of some treatments indicate that much of individual variation that governs the response to therapy remains unaccounted for. Integration of additional information — such as gene expression data, epigenetic profiles, proteomics and metabolomics — will be required to achieve more effective and more personalized health care.

Even though the field of precision medicine is still very young, approved genome-guided therapies have already improved treatment options for thousands of oncology patients and thousands more are eligible for clinical trials.

However, efforts to bring these treatment options into community practices, where about 85% of all cancer patients are treated,[18] often are accompanied by clinical, financial and technical difficulties.[3,19]

To overcome these hurdles, many community practices have established dedicated precision medicine programs. **In the sidebar below**, we share our experience with the precision medicine program at Texas Oncology.

▲ **Anna O. Williford**, PhD, is Precision Medicine Data Scientist, **Trey L. Schuchart**, BS, is Precision Medicine Laboratory Data Manager, and **Lorraine C. Brisbin**, MS, is Vice President of Precision Medicine at Texas Oncology in Dallas, Texas.

ADOPTION OF PRECISION MEDICINE INTO A COMMUNITY PRACTICE

Texas Oncology is a community oncology practice with more than 480 physicians treating ~70,000 new cancer patients per year at more than 200 sites across Texas.

To keep up with advances in targeted therapy, Texas Oncology implemented a precision medicine program to:

1. Expand appropriate utilization of precision medicine in routine clinical practice, and

2. Increase patient enrollment into clinical trials. **(see Figure 1 on Page 29)**

Expansion of precision medicine utilization in routine clinical practice.

We already mentioned that the estimated fraction of cancer patients benefiting from targeted therapy is low, within 0.3-7%.[14,15] This estimate assumes that every patient gets a molecular profile.

In practice, however, only a fraction of cancer patients have their tumor sequenced for identification of biomarkers for which either FDA-approved drugs or clinical trials are available. In order to bring the full potential of targeted therapy into practice, we had to overcome several challenges that hindered efficient implementation of genetic testing in our practice.

CLINICAL CHALLENGES

The first challenge was to maximize the appropriate use of precision medicine in our practice by implementing diagnostic pathways and standard operating procedures for test orders. With so many tests on the market that differ in the set of biomarkers and detection methods, it is often difficult to select the right test for a given tumor type. Additional challenges are introduced by frequently changing guidelines for biomarker testing.

To address these problems, we developed a diagnostic pathway tool that guides clinicians in selection of appropriate tests from the set of specified laboratories. The application includes

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functionality for updating NCCN, FDA and ASCO guidelines on daily bases, ensuring relevant up-to-date test choices.

The application also allows for the addition of biomarkers of interest for patient enrollment in clinic trials to allow for a proactive versus reactive interrogation for actionable mutations. We introduced a diagnostic pathway tool in August 2019 with 24 participating physicians and currently have more than 250 physicians and medical oncologists utilizing the tool for ordering precision medicine tests.

Our team also includes dedicated laboratory liaisons who provide full support for placing and tracking all precision medicine orders, freeing nurses and other clinicians from this time-consuming task. The liaisons also work closely with outside reference laboratories to make sure that the specimen and all required information are received by the laboratory, eliminating potential delays in testing.

FINANCIAL CHALLENGES

The financial burden of genetic tests is another common problem, with costs ranging somewhere between $200-$5,000 and sometimes even higher.

As there is no guarantee that actionable mutations will be identified in a patient's tumor, it is understandable that without reimbursement, patients might decide to decline testing. There is currently no consistent reimbursement coverage of precision medicine tests amongst both government and commercial payors.

In addition, inconsistent claims processing requirements often result in delays in testing and ultimately may adversely affect the ability to use targeted therapies. For example, insurance companies often require prior authorization, or permission to perform testing. Without it, reimbursement is more likely to be denied, and laboratories may refuse testing.

But even when prior authorization is granted, reimbursement is not guaranteed. And when coverage is denied, there is an appeal process in place that requires collection of additional medical documentation.

Our laboratory liaisons collaborate with the performing laboratories and payors to meet the reimbursement requirements while reducing the time and effort required from the treatment team to perform these administrative duties.

TECHNICAL CHALLENGES

As we continue to expand our partnerships with reference labs performing molecular profile testing, it is imperative to improve, standardize and streamline the ordering/resulting process taken on by our physicians, nurses, clinical staff and laboratory liaisons.

In addition to our adoption of the diagnostic pathway tool, we developed and continue to develop bidirectional HL7 interfaces with each reference lab, which can be used for the electronic transmission of orders and results. Doing this eliminates the need to manually complete paper order forms and/or manual entry via an online ordering portal.

In addition, the electronic transmission of results (both discrete data and PDF reports) are delivered in real-time, directly into our Electronic Medical Records sytem (EMR) for physicians to review, which eliminates the need for personnel to search for completed results via an online portal or from a fax machine. This mean less passwords to remember, less paper and more secure transmission of confidential patient information.

Bidirectional electronic interfaces create a seamless ordering/resulting process, freeing up hours in the day of our clinical staff and lab liaisons.

One challenge we continue to face is the technical capabilities of our internal systems and our collaborating reference laboratories. As healthcare information technology continues to improve and expand around the globe, not all laboratories' information systems are at the same level of technical advancement.

To adapt, we must tackle each interface independently, with the goal of continuing to standardize the ordering and resulting process within our internal systems. For some, this means we can create a complete bidirectional

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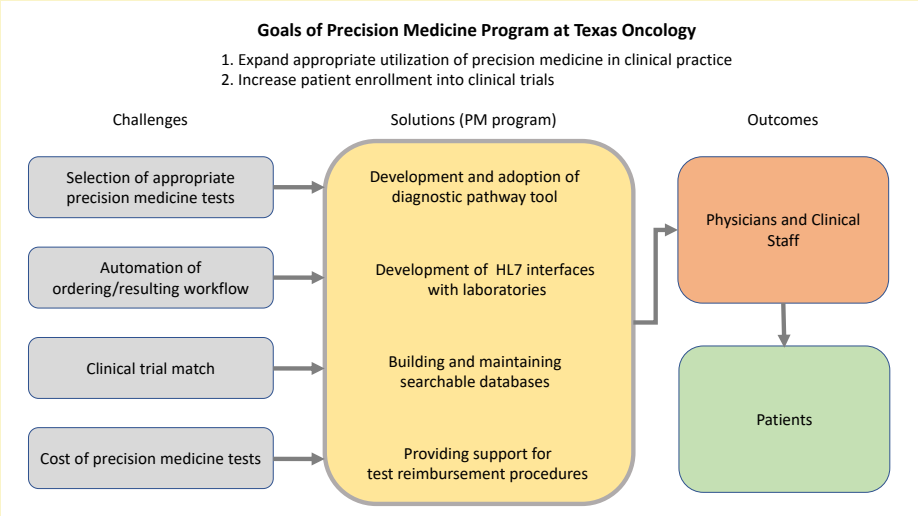
FIGURE 1 | INCREASE PATIENT ENROLLMENT INTO CLINICAL TRIALS



COMMUNITY PRACTICE

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HL7 interface with transmission of both discrete data and PDF embedded documents for both orders and results.

Although this is the ideal solution, it is not always the available solution. For others, we create customized order forms, generated by our Electronic Medical Record (EMR), which can be used in lieu of a paper order form. We also utilize secure file transfer protocols for the transmission of the order forms, pathology reports, insurance cards, etc., and for the retrieval of the complete PDF reports and discrete data. We then peruse automated workflows for the movement of files within our system so that our lab liaisons are not tasked with this otherwise manual and tedious process.

FACILITATING PATIENT ENROLLMENT INTO CLINICAL TRIALS

The advances in cancer prevention and treatment are driven by patients' participation in clinical trials. And yet, recent estimates indicate that only 8% of adult cancer patients in US enroll into clinical trials.[18] The top two reasons for this include trial unavailability at treatment location and patient's ineligibility for a trial, resulting in non-participation rate of ~77%.

The low rate of enrollment leads to delays and even failures in clinical trials,[18] reducing treatment options available to patients. Increasing patient participation in clinical trials has always been an important goal for Texas Oncology.

More than 2,500 patients are enrolled every year and clinical trials are offered in 56 of Texas Oncology locations. So far, patient participation from our practice contributed to the development of over 90 cancer therapies.[20]

To increase patient participation in clinical trials that investigate genome-guided therapies, precision medicine program has invested heavily into creation of molecular data warehouse, a searchable database that contains patients' molecular profiles.

The biggest challenge of this project was to standardize genetic data provided by different testing laboratories. Not only there are differences in data formats, but biomarker names, mutation nomenclature and annotation are not always consistent between laboratories.

The database is live and undergoes continuous updates and data curation for any changes that can be introduced with the addition of new tests.

We also have a database that contains information included in the EMR. With these resources, we can quickly identify patients that satisfy inclusion/exclusion criteria for ongoing and upcoming clinical trials.

The successful implementation of the precision medicine into practice can be greatly facilitated by the integration of clinical and genomic data. This is the most exciting and challenging next step for our team, requiring large efforts to ensure complete and accurate data extraction from electronic health records.

Such real-world data can serve as a knowledge base for physicians, providing an easy access to data on treatments and clinical outcomes across the entire practice and assisting with selecting most effective treatment options.

In addition, real-world data can be used to study how different patient populations respond to treatments outside clinical trials, monitor long-term adverse effects, evaluate the cost effectiveness of alternative treatments and more.[3,21,22,23]

Building such integrated database is an ambitious task, but the insights that can be gained from the analysis of these data will greatly benefit our patients.

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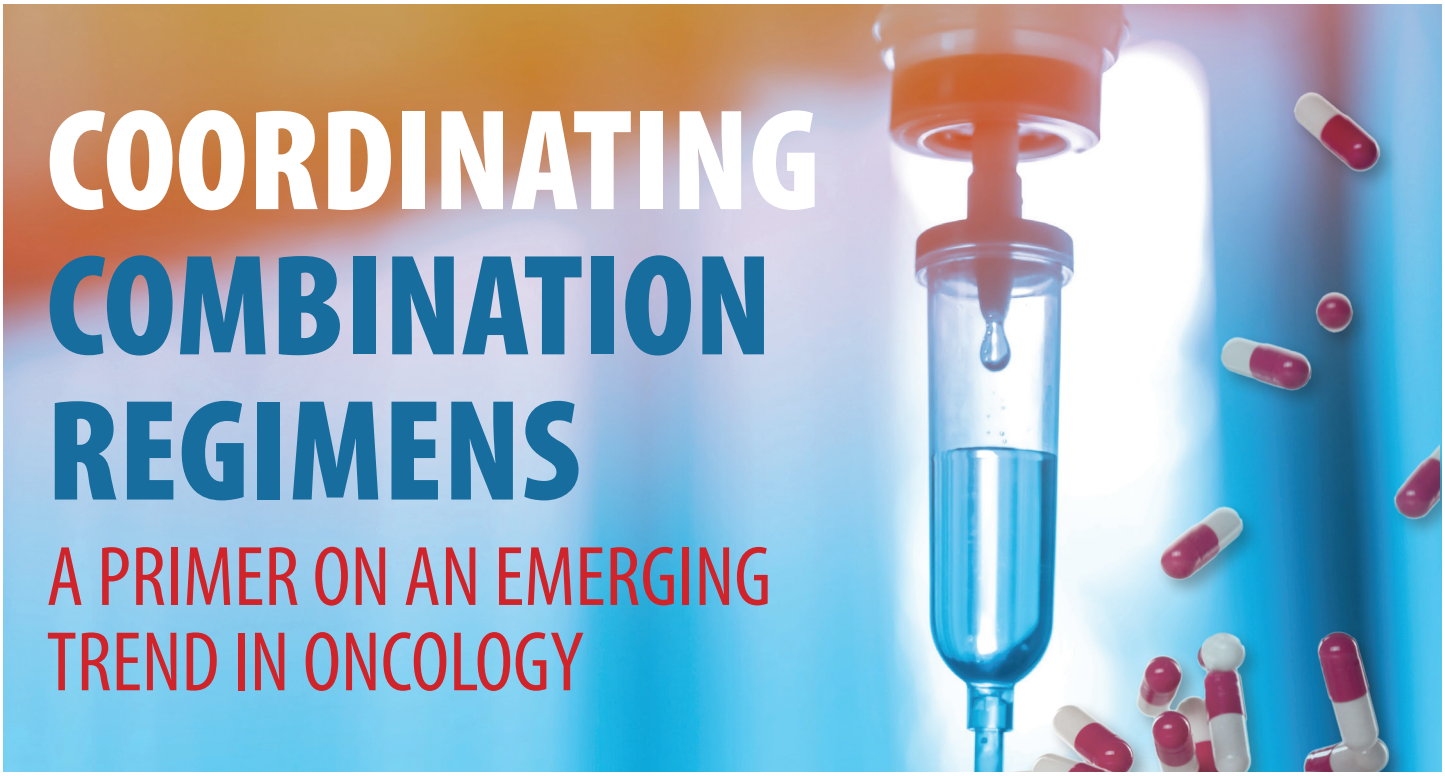

COORDINATING COMBINATION REGIMENS

A PRIMER ON AN EMERGING TREND IN ONCOLOGY

By Bijoy P. Telivala, MD

The modern-day oncology clinic is vastly different from what it was a decade ago. Ten years ago, the majority of treatments were parenteral and were given in the office or hospital setting.

Bijoy Telivala

In the last decade, there has been an explosion in the discovery and approval of cancer drugs and many of them have been oral oncolytics. In the first six months of 2020, amid a pandemic, the FDA approved 21 precision oncology drugs with the majority being orals.

Oral oncolytics are here to stay and will form a backbone of various cancer regimens. We, as the oncology community, will have to be creative and resourceful as we incorporate them into our treatment landscape.

ORAL ONCOLYTICS

Oral oncolytics have multiple advantages but also carry some unique challenges which need to be addressed quickly.

Patients do not have to come to the clinic to take them. This is particularly important during the ongoing COVID-19 pandemic.

Making fewer clinic visits means patients can spend more time doing what they like, and families don't have to take time off for their visits. Patients often prefer oral medications.

The biggest challenge with oral oncolytics is the perceived notion that pills are less toxic than IV medications. Many times that is not true. Compliance can also become a big issue when patients miss their treatment doses.

Access to oral oncolytics is not always easy and often times patients have large co-pays. Certain oral oncolytics are required to be filled with designated mail-order pharmacies, which takes a lot of time and effort. Also, the dosing schedule of oral oncolytics can be very confusing for patients.

COMBINATION REGIMENS

As we move forward, we will see more and more combination regimens. Newer regimens have a combination of an oral and parenteral medicine **(see Table 1)**.

TABLE 1: COMBINATION REGIMEN EXAMPLES

Disease	Medicines
Multiple Myeloma Velcade	RVD (Revlimid, & Dexamethasone)
Breast Cancer	Faslodex & Ibrance
CLL	Gazyva & Venclexta
Colon Cancer	Xeloda & Oxaliplatin
Kidney Cancer	Keytruda & Axitinib
AML	Vidaza & Venclexta
Marginal Zone Lymphoma	Rituxan & Revlimid

This carries its own distinctive challenges. Combining two different routes of medicine is not as easy as it sounds. Strategies for improvement should focus on the following areas: compliance, errors, authorizations, scheduling and Electronic Medical Records (EMR).

COMPLIANCE

The best medicine is one which the patient can afford and take reliably for the prescribed duration. It is very

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COMBINATION

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common for patients to forget their oral medicines. Studies have shown an oral adherence rate anywhere between 15-97 percent.[1]

To improve compliance, especially in combination regimens, we should consider various approaches. We need synergy between the patient and various stakeholders in the clinic **(see Table 2)**.

ERRORS

Oral oncolytics have a much higher rate of mistakes from both patients and providers. Chemotherapy errors occur at the rate of 1-4 per 1,000 orders. Oral drugs carry significant risk.[2]

Polypharmacy leads to substantial burden and mistakes all across the board. Errors are both of omission and oversight and can be reduced by team effort.

The healthcare provider (HCP) must make sure correct doses of both IV and oral drugs are documented in the EMR.

Oral dose adjustment and reasons for the same should be documented in the EMR. The dosing of the oral drugs should be readdressed every clinic visit.

Illustration 1 is an example demonstrating the wrong dose of Capecitabine in the care plan. The pharmacy cannot get to a 1,875 mg dose with currently available tablet sizes.

TABLE 2: COMPLIANCE STRATEGIES

Strategy	Role Players
Medicine list reconciliation	Starts with MA but doctor should double-check
Pill bottles	Very important: patient brings pill bottle to visit
Reminders	Pharmacy staff to put automated text reminders
Written calendar	Made by the doctor/team during office visit
IV vs. Oral	Chemo nurse/pharmacist educates patient about importance of both IV and PO meds

AUTHORIZATIONS

Authorizations are a huge challenge and can lead to a lot of frustration for both providers and patients.

Oral oncolytics are authorized in a different way than parenteral medications. Often times the parenteral medication gets approved quickly, but the oral medication is delayed because of higher copays or issues with Pharmacy Benefit Managers (PBM), etc.

Combination regimens can have additive effects or synergy between the various medications. Many times starting one without the other can be futile or even harmful to the patient.

Harmony between the entire clinic is an excellent solution to this challenge **(see Illustration 2)**.

The patient can feel lost in the process. There should be one contact person the patient can turn to in the clinic. Good old human touch can play a big role in smoothing feathers and helping the patient navigate this labyrinth.

The IV and oral authorization teams have to communicate with each other. The office staff has to get together at least once a week to review all new treatments and have a game plan ready.

On a macro level, lobbying Congress to pass legislation allowing oral oncolytics to be filled at a local pharmacy rather than a PBM mail-order pharmacy will help dramatically.

ILLUSTRATION 2: COORDINATED CARE

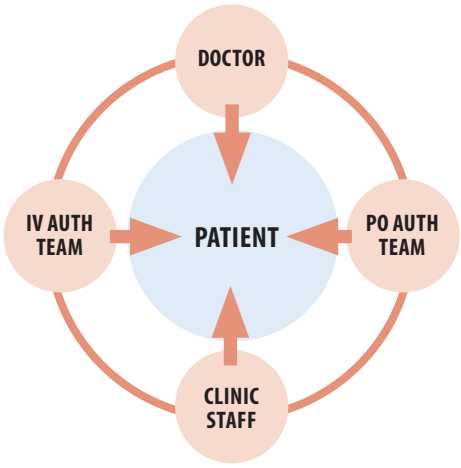

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ILLUSTRATION 1: DOSING ERROR EXAMPLE

Hide NCCN_COL17: Capecitabine						1:1
Fosaprepitant IV						150 mg
Palonosetron (Aloxi) IV						250 mcg
Dexamethasone IV						12 mg
BMP						*
Capecitabine (Xeloda) PO BID D1				DOSING ERROR		1875 mgX2
CBC with Auto Diff						*
CMP						
Magnesium						*
OXALIplatin (Eloxatin) IV						260 mg
Business Office						Required

COMBINATION

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SCHEDULING

All of us miss medication doses. The most common reason is forgetting the dose, followed by side effects.

Now, imagine asking a 78-year-old man with six other comorbidities to take a pill three times a day, but only on four days a week, for two weeks on and two weeks off. There is a very high chance that he will make a mistake and multiple studies have shown that complicated regimens are very difficult to follow.

Illustration 3 offers an example of patient-centered coordinated scheduling by various stakeholders.

In the big picture, pharmaceutical companies have to look at dosing and scheduling of medicines when they are under development. Clinical trial investigators and Key Opinion Leaders (KOLs) should be vocal about this salient issue. The FDA should look closely at this problem when evaluating drug approval.

ELECTRONIC MEDICAL RECORDS

We spend millions of dollars on EMR systems but all of them can fall short when it comes to patient care. One of the most popular EMR systems has its own Twitter parody account, which is followed by many physicians and patients.

Many of them were designed and built in the era when IV treatments dominated, and oral medications have historically been given inferior treatment. We need care plans to be built taking into account the unique circumstances for both classes of medications.

The quest for a smart, intuitive EMR which doesn't cause "click fatigue" still continues. The medical community has been promised the moon but so far the rocket hasn't left earth's atmosphere.

We need the ability to track authorization and adherence to oral oncolytics. As healthcare workers, we also have to do our duty and enter appropriate data in the EMR.

ILLUSTRATION 4: DREAM TEAM FLOW CHART

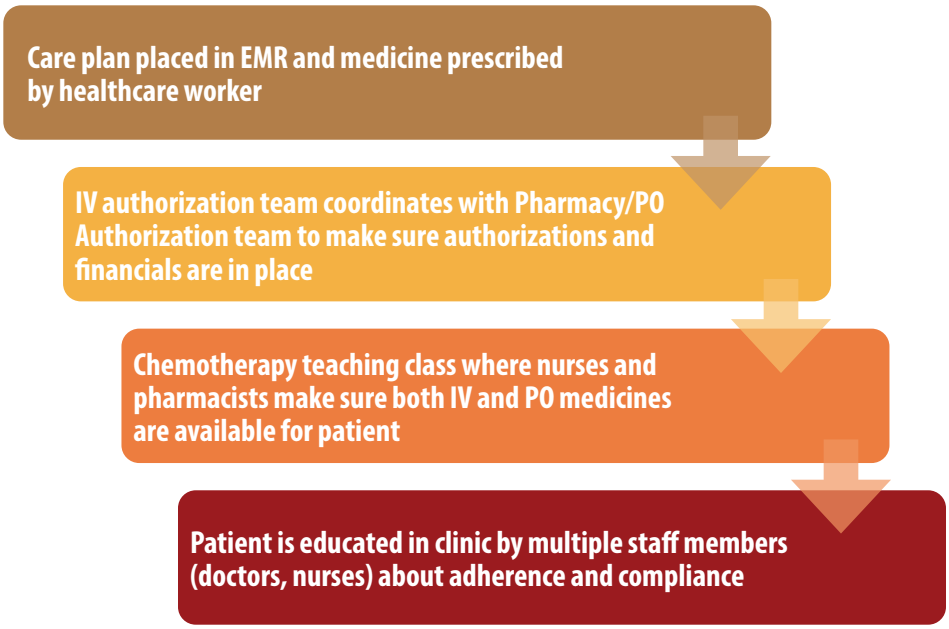
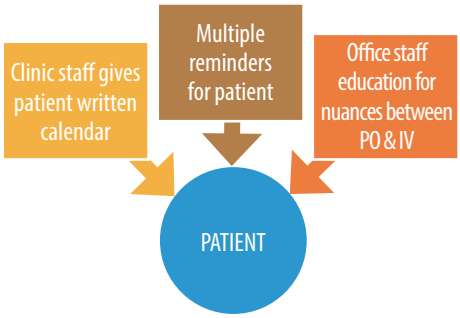


ILLUSTRATION 3: COORDINATED SCHEDULING



DREAM TEAM COORDINATION

In a utopia, everything would be perfect, and everything would run smoothly. We however live on earth and mistakes are common. No one is perfect and all systems have flaws. The goal is to find an arrangement that works for the patient, doctor, pharmacists, nurses and clinic staff.

Illustration 4 is a possible flow which can help everyone and most importantly get the patient the care he/she deserves. By no means is it perfect — it is a work in progress. It is at best a scaffolding to build a better apparatus for patient-centered care.

SUMMARY

The world of oncology is becoming more complex and challenging. There are multiple hoops the patient has to jump through to get the care he/she deserves. The patient is already going through many emotional, physical and financial challenges and we as a team have to help them in a coordinated manner.

This is a gigantic task with many pot holes on the road ahead. As William James said, "it is our attitude at the beginning of a difficult task which more than anything else, will affect its successful attempt."

Teamwork, common sense and a patient-centered model will help us navigate the challenges and improve patient care and experience.

▲ **Bijoy P Telivala**, MD, is a Partner Physician at Cancer Specialists of North Florida in Jacksonville, Florida.

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CONSIDERATIONS FOR INITIATION OF ^{177}LU-DOTATATE THERAPY AT A LARGE ACADEMIC MEDICAL CENTER

By Jennifer Collins, PharmD, BCOP, Lianna Serbas, PharmD, BCOP, & Sandeep Parsad, PharmD, MBA, BCOP

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies with variable presentation and histology. They are grouped together solely based upon their expression of neuroendocrine markers.[1]

Despite the broad tumor types included, NETs only account for approximately 0.5% of all new cancer diagnoses. The incidence is approximately 6.98 cases per 100,000 people and is on the rise due to improved awareness and diagnosis.[2] There are an estimated 170,000 cases in the United States, thus qualifying for orphan disease status.[3,4]

Most NETs occur sporadically and risk factors are poorly understood but may involve inherited genetic syndromes (e.g., MEN1/2).[5]

The neuroendocrine system spans from the thymus to the rectum, so presentation varies based on tumor location. The most common primary sites include the gastrointestinal tract and lung.[1]

Diagnosis is often facilitated by the presence of carcinoid syndrome due to hypersecretion of amines and peptides. Symptoms of carcinoid syndrome include flushing, watery diarrhea and hypotension.[6]


Jennifer Collins


Lianna Serbas


Sandeep Parsad

The mainstay of treatment is surgery for all types of NETs.[5] If surgery is not feasible due to comorbidities or extent of disease, then the use of systemic therapy may be considered. Currently, there is not a well-established role for systemic treatment, but somatostatin analogs (e.g., octreotide, lanreotide) are common first-line agents for locoregionally advanced or metastatic tumors given the frequent expression of somatostatin receptors by majority of NETs.

Unfortunately, due to limited clinical data, optimal management after progression on somatostatin analogs is not well-determined and may vary based on the tumor type.[1]

Evidence has identified aberrant signaling in the mTOR pathway as involved in the development of NETs as well, making it a promising therapeutic target.[7] Everolimus has demonstrated synergistic anti-tumor activity when used in addition to octreotide as well as monotherapy, but in low-intermediate grade or well-differentiated disease.[8,9]

Since NETs also express VEGF, sunitinib has received approval for metastatic pancreatic NETs. However, the response rate was only 9.3% in the phase III trial leading to FDA approval and patients experienced severe diarrhea, nausea and fatigue.[10]

Cytotoxic agents including 5-FU, capecitabine,

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NEUROENDOCRINE

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dacarbazine, oxaliplatin, streptozocin, and temozolomide have demonstrated response rates of 35-70% in pancreatic and gastrointestinal tumors, but also result in significant toxicity.[1] There is no consensus on which regimen is the most effective.

Bronchial and thymic tumors are treated with platinum-based doublets given their pathologic similarities to small-cell lung cancer, but are associated with poor responses.

Given the variable response rates and poor tolerability, chemotherapy should be reserved for patients without other treatment options.[5]

The scarcity of effective systemic therapy options makes these tumor types very difficult to treat, especially in the advanced or metastatic stage. ^{177}Lu-Dotatate offers a promising new therapy option by combining the mechanism of somatostatin analogs with radiation.

^{177}Lu-Dotatate binds to somatostastin receptors and emits beta radiation to induce cellular damage to somatostatin receptor-positive and neighboring cells.[11] Due to this radioactive component, successful administration of ^{177}Lu-Dotatate will require extensive multidisciplinary preparation.

CLINICAL TRIAL SUMMARY

^{177}Lu-Dotatate was granted fast track status in April 2015 and subsequent accelerated approval in January 2018.

The FDA developed this process in 1992 in order to expedite approval for drugs treating "serious conditions that fill an unmet medical need" by allowing for approval based on a surrogate endpoint.

These drug companies are then required to continue with phase 4 studies to confirm that the benefit in the surrogate endpoint indeed results in clinical benefit.

For cancer drugs, progression-free survival is often used as a surrogate endpoint for overall survival.[12]

The pivotal trial leading to accelerated FDA approval of this orphan drug compared ^{177}Lu-Dotatate with high-dose octreotide long-acting repeatable (LAR) for midgut neuroendocrine tumors in an open-label phase 3 trial (NETTER-1).[13] Eligible patients were required to have tumors that had metastasized or were locally advanced, inoperable and progressing on octreotide treatment.

Between 2012 and 2016, 229 patients were randomized to receive either ^{177}Lu-Dotatate 7.4 GBq followed by standard-dose octreotide LAR (30 mg) administered every eight weeks for a total of four doses, or high-dose octreotide LAR (60 mg) every four weeks.

^{177}Lu-Dotatate offers a promising new therapy option by combining the mechanism of somatostatin analogs with radiation.

The treatment groups were well-balanced in regards to tumor grade, somatostatin radiotracer uptake and chromogranin A levels. Approximately 80% of the patients had undergone surgical resection, and nearly half had undergone a previous form of systemic therapy other than a somatostatin analog.

Progression-free survival (PFS) at month 20 was significantly higher with ^{177}Lu-Dotatate at 65.2% vs. 10.8% in the control group (HR 0.21, $p < 0.001$).

The median PFS had not yet been reached in the experimental group and was 8.4 months in the control group. This benefit was demonstrated across subgroup analyses stratified according to tumor markers, tumor grade, sex and age.

At the planned interim analysis for overall survival (OS), a total of 14 deaths in the ^{177}Lu-Dotatate group and 26 deaths in the control group were observed, representing a 60% lower risk of death (HR 0.40, $p = 0.004$).

Of 201 patients who could be evaluated for tumor response, the experimental group was also associated with a significantly higher response rate (18% vs. 3%, $p < 0.001$).

The ^{177}Lu-Dotatate group demonstrated one complete response and 17 partial responses whereas the control group demonstrated no complete responses and only three partial responses. Updated supplemental analysis resulted in a median OS of 27.4 months in the control group and not reached in the experimental group (HR 0.52, 95% CI 0.32-0.84).[11,15]

Treatment-related side effects were reported more commonly in the experimental group (85%) than the control group (31%).

The most frequently reported adverse effects were nausea, vomiting, fatigue, abdominal pain and diarrhea amongst the ^{177}Lu-Dotatate group.

Despite the increased grade 1 and 2 adverse effects in the experimental group, grade 3 and 4 adverse effects were similar between the two groups with the exception of slightly more neutropenia, lymphopenia and thrombocytopenia (1%, 2%, and 9% respectively) with ^{177}Lu-Dotatate.

Analysis of time to relevant deterioration (TTD) of health-related quality of life (HRQoL) completed a year later showed overall significantly longer TTD HRQoL in global health status, physical functioning, role functioning, fatigue, pain, diarrhea, disease related worries and body image in patients receiving ^{177}Lu-Dotate.[15]

Long-term efficacy and safety were also demonstrated in a single-center study of more than 1,200 patients with somatostatin receptor-positive tumors in the Netherlands, including patients with gastroenteropancreatic (GEP) and bronchial NETs.[16]

Median OS in the overall population

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was found to be 63 months (95% CI, 55-72) with a median PFS of 29 months (95% CI, 26-22). In the subset of 360 patients with GEP-NETs, 16% were found to have complete or partial tumor shrinkage.[14,16]

It should be noted that there were incidences of acute leukemia and myelodysplastic syndrome (MDS) that occurred in four patients (0.7%) and nine patients (1.5%), respectively, during the follow-up period after their first ^{177}Lu-Dotate therapy.

Renal failure also occurred in about six patients (1%), but was likely not related to their therapy. There were no incidences of hepatic failure observed during or after therapy.

PLANNING

Successful administration of ^{177}Lu-Dotatate requires interdisciplinary teamwork. The first step in preparing for administration should include a meeting with representatives from Medical Oncology, Nuclear Medicine, Radiation Safety, Pharmacy and Nursing to coordinate responsibilities. **Table 1** depicts an example of potential roles for each discipline.

Figure 1 displays a proposed timeline for preparing an institution for the administration of ^{177}Lu-Dotatate.

The multidisciplinary meeting should determine what logistical steps are required by the manufacturer and assign tasks to the appropriate disciplines. After consideration of each discipline's own processes, the establishment of a workflow should involve all parties to determine the process for ordering, preparing, administering, and educating on the product.

Once a workflow is established, an order set should be created to include the necessary supportive care agents.It is also important to include Information Systems in this step to coordinate the billing associated with each order.

The representative from each discipline will be responsible for providing appropriate education to their colleagues in order to obtain a smooth workflow.

For example, the nursing lead should arrange for radiation training for any nurse that may be participating in the care of one of these patients. Before the first patient arrives, a multidisciplinary run-through should be held to ensure that all involved feel comfortable with their responsibilities.

After treatment with ^{177}Lu-Dotatate has commended, meetings should be held as needed to reflect on cases and assess areas for improvement.

ORDERING

When planning for the day of

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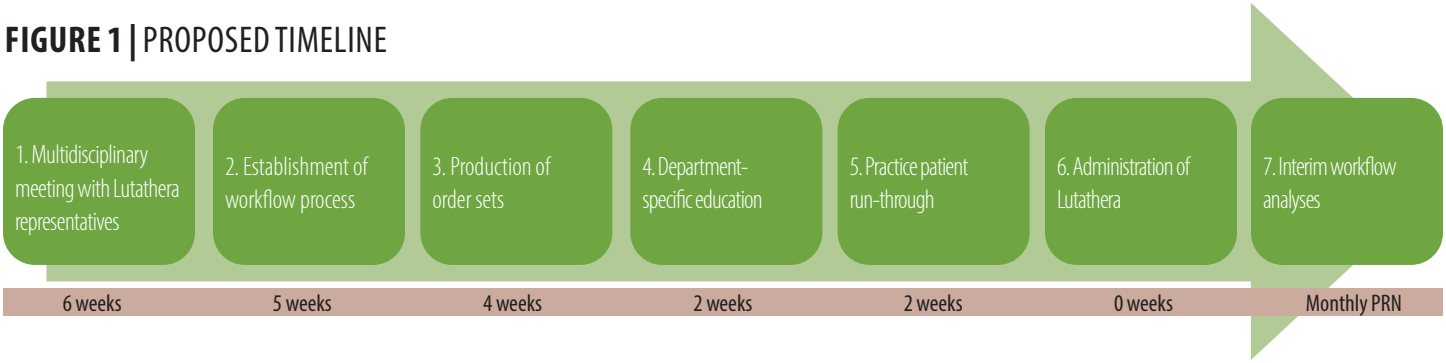
TABLE 1 | INTERDISCIPLINARY ROLES

NUCLEAR MEDICINE	• Place order for ^{177}Lu-Dotatate from manufacturer • Receive and store ^{177}Lu-Dotatate • Prepare and administer ^{177}Lu-Dotatate
RADIATION SAFETY	• Set-up isolation precautions for the patient's room and restroom • Provide patient education regarding radiation safety
MEDICAL ONCOLOGY	• Provide patient education regarding drug response and side effects • Apply and sign order set
PHARMACY	• Compose order set • Obtain formulary approval • Place order for amino acid infusion from compounding pharmacy (if not produced in-house) • Receive and store amino acid infusion • Dispense supportive medications
NURSING	• Alert radiation safety of patient arrival • Administer supportive medications • Ensure compliance with radiation precautions • Oversee administration of ^{177}Lu-Dotatate
CASE MANAGEMENT	• Verify insurance coverage of ^{177}Lu-Dotatate • Assist in enrollment in patient assistance when needed

FIGURE 1 | PROPOSED TIMELINE



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administration, it is important to note that orders must be placed at least two weeks in advance to Advanced Accelerator Applications. The product will only be delivered on Wednesday, Thursday, or Friday given its short stability of 72 hours and transportation from Italy.

Ordering should be done by the Nuclear Medicine department, which will receive, store and prepare the product.

Given these tight ordering restrictions, the manufacturer does allow for full refunds if canceled at least 10 days prior to administration or if the product is not delivered on time.

^{177}Lu-Dotatate also requires prehydration with amino acid solution for nephroprotection. This amino acid infusion is not provided with the radiopharmaceutical and must contain 18-24 g of lysine and 18-24 g of arginine in 1.5-2.5 L of saline or sterile water.

Commercially available amino acid solutions that may be used per manufacturer are included in **Table 2**.

The choice of amino acid product will depend largely on the availability from manufacturer.

For institutions that do not have an internal compounding pharmacy, these solutions must be obtained through an outside 503b pharmacy. Establishing a relationship with a new pharmacy can require significant preparation, so each institution should determine its own preference on how to obtain an appropriate amino acid solution.

These commercial products may also contain various other amino acids and are highly emetogenic. As an alternative to reduce emetogenicity, an amino acid solution containing only lysine and arginine may be compounded **(see Appendix 1)**.

TO VIEW APPENDIX 1, SCAN THE QR CODE BELOW

This product requires high-risk compounding procedures due the use of lysine and arginine powders for reconstitution. Thus, samples must be tested for sterility.

The feasibility of this method is challenged by the requirement for an experienced compounding staff, appropriate compounding facility and supplies, sterility testing process, and availability of lysine and arginine powder.

Given the potential for nausea/vomiting with the amino acid infusion, pre-medication should include a 5HT3 antagonist, steroid and NK1 antagonist, at the minimum. An order for octreotide should be available to use as needed in the event of a neurohormonal crisis.

See **Appendix 2** for an example order set that incorporates hydration, supportive care medications, laboratory tests and vital sign monitoring.

TO VIEW APPENDIX 2, SCAN THE QR CODE BELOW

ADMINISTRATION

Unlike most intravenous infusions, ^{177}Lu-Dotatate should not be administered via a port; peripheral administration is preferred. If unable to obtain peripheral access, then a PICC line may be used as an alternative.

Although no reports of extravasation have been reported, staff should be educated on proper management; the area should be aspirated within six hours of administration and Radiation Safety should be contacted immediately.

The most significant obstacle with administration is limiting radiation exposure. Nuclear Medicine will be responsible for administration, but Nursing should be educated on the following points:

- Radiation safety should be alerted upon the patient's arrival.
- The patient should be kept in radiation isolation for a period of 4 to 5 hours following administration.
- A separate bathroom should be reserved for the patient only to use.
- The patient must void at least once after administration to be cleared for discharge by Nuclear Medicine.
- Any pregnant staff members should not be involved in the direct care of this patient.

PATIENT EDUCATION

Given both the novel mechanism and risk for radiation exposure, patient education is an important component that should be reinforced by multiple disciplines.

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TABLE 2 | COMMERCIALLY AVAILABLE AMINO ACID SOLUTIONS

	Lysine	Arginine	Solvent
Aminosyn II 10%	21 g	20.4 g	2 L
Aminosyn II 15%	23.6 g	22.9 g	1.5 L (diluted to 2 L)
Clinisol 15%	18 g	18 g	1.6 L (diluted to 2 L)
Plenamine 15%	18.8 g	23.5 g	1.6 L (diluted to 2 L)
Trophamine 10%	18 g	26 g*	2.2 L
Amino Acid 5%	25 g	25 g	1 L (total 2 L given)

**Content is slightly higher than recommended and therefore may be associated with increased adverse events.*

NEUROENDOCRINE

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The primary physician should review the curative expectations as well as potential side effects with the patient prior to starting treatment.

Nuclear Medicine should inform the patient on proper methods to limit exposure to radiation before the patient receives the infusion.

Nursing should also be knowledgeable on these points to ensure compliance while receiving the infusion.

See **Appendix 3** and **Appendix 4** for a sample consent form and patient education handout.

TO VIEW APPENDIX 3 & 4, SCAN THE QR CODE BELOW

Patients should also be advised regarding what processes to follow when visiting another healthcare facility, given the potential for radiation exposure from bodily fluids.They should also be provided a contact number to call with questions.

CONCLUSION

Because ^{177}Lu-Dotatate is a novel radioactive therapy that requires unique management that differs from most therapies, there are many procedural and operational considerations involved.

Addressing these considerations by utilizing a multidisciplinary approach will allow for successful therapy. The experiences described here may serve as a guide to assist institutions with the incorporation of ^{177}Lu-Dotatate into clinical practice.

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Because ^{177}Lu-Dotatate is a novel radioactive therapy that requires unique management that differs from most therapies, there are many procedural and operational considerations involved. Addressing these considerations by utilizing a multidisciplinary approach will allow for successful therapy.

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PANDEMIC FALLOUT A KEY CONCERN DURING NCODA 2020 FALL SUMMIT

The threat of COVID-19 and its chilling effect on healthcare was a major theme at the 2020 NCODA Virtual Fall Summit.

More than 600 oncology care professionals, industry experts and key opinion leaders participated in the Oct. 22-23 event, which featured nearly 30 presentations on diverse topics that included practice management, copay accumulators, the evolving role of pharmacy technicians and biosimilars, as well new treatments for advanced renal cell carcinoma, HER2+ metastatic breast cancer, chronic lymphocytic leukemia, non-small cell lung cancer, multiple myeloma and other disease states.

COVID-19: INTERNATIONAL UPDATE

David M. Allen, MD, one of the foremost infectious disease experts in the world, kicked off the meeting with a comprehensive clinical primer on COVID-19, current treatment practices and the outlook for a vaccine. He also focused on the need for open communication and international cooperation.

David Allen

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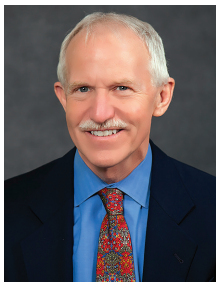
"Countries don't live in a silo; we depend on workers from other countries," said Allen, Associate Vice President (Health Innovation and Translation) | National University of Singapore, Associate Professor | NUS — Yong Loo Lin School of Medicine and Senior Consultant — Infectious Diseases Division | National University Hospital. "We don't live in a closed world. Nationalism is not a productive strategy."

Allen also stressed the need for science literacy, especially among lay people, journalists and politicians. "If we don't agree on a common language for science, we're not going to be able to communicate," Allen said, noting that the challenge won't end with the eradication of COVID-19. "This isn't a 100-year pandemic; there is another one coming, Pandemic X. We have to be prepared. We can't whistle in the graveyard."

COVID-19: NATIONAL UPDATE

Jay C. Butler, MD, FAAP, MACP, FIDSA, Deputy Director for Infectious Diseases | Centers for Disease Control and Prevention, gave a national update on the pandemic, focusing on epidemiology, transmission and prevention.



Jay Butler

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Butler noted that one challenge of talking about COVID-19 was the novel and ever-evolving nature of the disease: "It's basically a disease that none of us knew existed only 10 months ago; SARS-CoV-2 may not have even existed a year ago. It's very possible that a recombination event led to its ability to jump from the species host … and adaptation to human infection may have been very recent, causing human disease with a great enough frequency with transmission from person to person that was not recognized until last December (2019)."

Other presenters focused on the challenge the virus imposed on medical practices and society in general.

Barbara McAneny

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PRACTICE MANAGEMENT IN CHANGING TIMES

Barbara McAneny, MD, MACP, FASCO, Chief Executive Officer | New Mexico Cancer Center and a former president of the American Medical Association, talked about managing a healthcare practice

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SUMMIT

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in times of unpredictability and offered strategies for coping with change.

McAneny said COVID-19 is only the latest challenge providers face in an industry already beset by aging demographics, social inequity, workforce shortages, predatory insurance company practices, high drug prices, Medicare shortages and other issues.

And while the United States far outspends any other country on health per capita, "we are looking at increasing expense of healthcare to the point it is looking to become unaffordable," McAneny said. And despite the investment, the U.S. still "ranks lower than most industrialized countries on nearly every metric of healthcare," she noted.

COPAY ACCUMULATORS AND MAXIMIZERS

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While dealing with the pandemic was probably foremost in many particpants' minds, COVID-19 was far from the only topic discussed during the Fall Summit.

Michael Ybarra, MD, Vice President and Chief of Medical Affairs | PhRMA, moderated a panel discussion on financial preparations for providers and patients for dealing with copay accumulators and maximizers. This panel featured **Barry Brooks**, MD, Medical Director of Oral Oncolytics | Texas Oncology and NCODA Executive Council member, **Ben Jones**, Vice President of Government Relations & Public Policy | McKesson, and **Brian Morrissey**, Vice President, Oncology National Customer Group | Pfizer.

Copay accumulator programs, which deny patients the ability to count manufacturer subsidies as part of their insurance deductible, are becoming more prevalent in the healthcare industry, and with them a growing level of financial toxicity.

"We've all seen the growth of these programs," Jones said. "We all know there has been significant change in insurance design, there's been a growth of high-deductible plans and there's been constant pressure to drive down costs. You couple that with the fact that about 42% of specialty medication is supported through some sort of patient-assistance program to avoid patient abandonment — patients truly are suffering."

Copay Accumulator Case Study for Single Tablet Regimen

- Plan annual OOP maximum: $6,000
- Drug cost sharing for preferred brand: $50 after deductible
- WAC monthly drug price: $3,090
- Deductible (combined medical and Rx): $3,000
- Manufacturer co-pay assistance program (CAP) annual maximum: $6,000

Medication Costs without Co-pay Accumulator

	Consumer	Manufacturer Co-pay Card
January	$0	$3,050
February	$0	$50
March	$0	$50
April - December	$0	$450
Total	$0	$3,600
Total collected by Insurance Plan		$3,600

Medication Costs with Co-pay Accumulator

	Consumer	Manufacturer Co-pay Card
January	$0	$3,090
February	$180	$2,910
March	$2,870	$0
April - December	$450	$0
Total	$3,500	$6,000
Total collected by Insurance Plan		$9,500

The NCODA Fall Summit session on copay accumulators featured a case study of the potential for financial toxicity in what is becoming a more common industry practice.

Brooks offered several patient perspectives on copay accumulators, including a patient with chronic myelogenous leukemia whose $50 copay for oral treatment was suddenly increased to $3,800.

"She told me, 'I'm a single mom with two children and I can't pay for this. What am I going to do? Am I going to die?'" Brooks said. "She's seeing what happens with these copay programs. For a few months, everything seems 'normal,' until the manufacturer's coupon runs out or hits its limit and then, all of a sudden, the patient is hit with a big spike in the bill. She was stuck four or five months into her course with a multi-thousand-dollar bill that she literally didn't have any money to pay for."

COORDINATING COMBINATION THERAPY

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James Gilmore, PharmD, Executive Vice President | Georgia Cancer Specialists and NCODA Executive Council Member, moderated a panel discussion on strategies for coordinating the complexities of combined oral and infusion regimens. This panel featured **Melissa Leaman**, BSN, RN, OCN, Nurse | Lancaster Cancer Center, and **Bijoy Telivala**, MD, Partner Physician | Cancer Specialists of North Florida.

The panel looked at several challenges of providing regimens in tandem, including ordering combination therapy in the electronic medical record, staffing for oral dispensing vs. the need for IV teams, coordinating starting dates with prior authorization and financial assistance, synching IV and oral cycles, adherence, insurance coordination, financial concerns and other issues.

"Can we have a seamless process (for combination regimens)?" asked Telivala. "Yes, but it takes teamwork, and it requires everyone to be on the same page. We need the right hand to know what the left hand is doing."

Some common combination regimens include RVD (Revlimid+Velcade+Dex) for multiple myeloma, Keytruda+Axitinib for kidney cancer, CapeOx (Xeloda+Oxaliplatin) for multiple GI cancers, Faslodex+Ibrance for breast cancer and Gazyva+Venclexta for CLL.

Telivala stressed the need for efficient coordination. "We don't want

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the patients to have side effects or feel that their cancer is not treated or feel frustrated, which leads to anxiety and anger," he said. "If we can coordinate our care and give it as a full dish rather than piecemeal, it makes a big difference for the patients."

Poor coordination of combined regimens, he warned, "is a recipe for disaster." Compliance is essential. Doctors, nurses and pharmacists must be on the same page, Telivala said.

From a nurse's perspective, Leaman identified the three key challenges in combination therapy as communication, documentation and care coordination.

Nurses often are "out of the loop" when patients begin oral chemotherapy, Leaman noted, and sometimes have to rely on office notes or verbal instructions given to the patient for documentation.

With multiple personnel involved in each case, each with their own documentation, nurses are often left wondering "where are we in this process?" she said. This situation has led to the development of an oral adherence flowsheet and an oral adherence nursing role at her practice to document drugs, doses, frequency, authorization, prescribing pharmacy, labs, side effects, education, adherence and compliance, Leaman said.

PQI IN ACTION

NCODA Manager **Ginger Blackmon**, PharmD, led a panel discussion on "Putting Positive Quality Interventions into Action: Consistent Clinical Standards for Medically Integrated Teams." Panel participants included **Thomas Butler**, MD, and **Brittney Carden**, PharmD | University of South Alabama – Mitchell Cancer Institute, **Chara Reid**, PharmD | Illinois Cancer Specialists, **Ernestine Wigelsworth**, PharmD | Cancer Specialists of North Florida, **Tamara Weinberg**, RN, BSN, OCN, ONN-CG | AON Pharmacy, LLC, and **Alicia Barnes**, CPhT | Summit Cancer Centers. All these panelists participate in Medically Integrated Dispensing (MID) teams.

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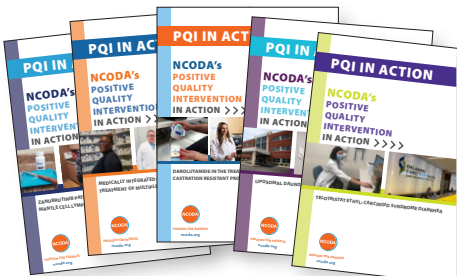

Panel members discussed their experience utilitzing three new PQI In Action resources.

Panel members discussed their experience utilizing Positive Quality Interventions (PQIs) written on the topics of Ixazomib (Ninlaro®) in the treatment of multiple myeloma, Zanubrutinib (Brukinsa™) patient selection and management in mantle cell lymphoma and Liposomal Daunorubicin-Cytarabine (Vyxeos®) management — NCODA's first intravenous (IV) PQI in Action.

PQIs are peer-reviewed clinical guidance documents published by NCODA to promote higher quality patient care and they are designed to standardize practices to achieve positive clinical outcomes.

PQI In Action articles incorporate opinions and experiences from oncology experts within medically integrated teams at leading cancer care organizations.

Carden said her team utilizes PQIs in the pharmacy, for staff education, and they provide them to the nurse practitioners and new fellows.

Wigelsworth said her practice also use PQIs for staff education, especially with pharmacists and technicians new to oncology.

"It's a very concise and clear tool that they can use and it's easily digestible without being immediately overwhelming," Wigelsworth said.

Butler said PQIs have become an invaluable aid to MID practices.

"Oncology is becoming more and more complex and there are more folks being hands-on with the oncology patient," Butler noted. "I think for us to have a template to follow makes it easier."

EFFECTIVE LEADERSHIP

NCODA closed the 2020 Fall Summit with an interview with Pulitzer Prize-winning presidential historian **Doris Kearns Goodwin**, who spoke on "Leadership in Turbulent Times."

Doris Kearns Goodwin

Goodwin highlighted the leadership experiences of such presidents as Abraham Lincoln, Theodore Roosevelt, Franklin Delano Roosevelt, John F. Kennedy and Lyndon B. Johnson as examples of leaders who persevered through hard times. All, she said, shared values of humility, empathy, resilience, hard work, an ambition for greatness outside themselves and a capacity to gather a team willing to question the leader's decisions.

Anyone enduring this time of COVID-19 can take heart from their example, she said.

"I think that the most important lesson that history can impart is that now that we are living through a very tough time, we have lived through a lot of tough times before and somehow we got through them," Goodwin said.

She compared the country's current challenge of dealing with COVID-19 to that of people living during the early days of the Revolutionary War, Civil War, Great Depression and World War II.

"It wasn't clear what the ending would be," Goodwin said. "That's the thing about history: We know the revolution was won, we know the Civil War ended with the Union restored and emancipation intact, we know that the Allies won WWII. But they, like us, were living in the midst of tumultuous times and weren't sure how the story would end. So, history does give us perspective, it does give us hope and it does give us lessons."

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HELPING OUR WORDS TRAVEL THE WORLD

NCODA AND PARTNERS LAUNCH FOREIGN LANGUAGE INITIATIVE FOR OCE SHEETS

The Oral Chemotherapy Education (OCE) platform has been a growing success within the international oncology community.

The OCE website is viewed more than 30,000 times each month in the United States and around the world. From Brazil to China to Australia, the OCE platform is being used as a template for furthering the education on oncology medications worldwide. Yet with this success comes various obstacles, most notably the language barrier.

Healthcare providers all know the importance of communicating with patients and properly discussing details in a common language. As Nelson Mandela once said, "If you talk to a man in a language he understands, that goes to his head. If you talk to him in his language, that goes to his heart."

Mandela's philosophy of language also resonates in the world of oncology: clearer communication leads to better patient outcomes.

This need for clear communication has become even more important in the current world of COVID-19 healthcare, now that virtual learning and telemedicine have become the new norms.

And while virtual translation services are available for non-English speakers, they are by no means perfect. Much work needs to be done to close the communication gap within the United States and across the globe.

NCODA has received many requests for OCE sheets in languages besides English from both consistent users and the core leadership of the OCE platform [which includes representatives of NCODA, the Association of Community Cancer Centers (ACCC), the Oncology Nursing Society (ONS) and the Hematology/Oncology Pharmacy Association (HOPA)].

Based on this feedback, NCODA has decided to push forward with translating its already well-received OCE patient-friendly documents into other languages.

NCODA's OCE committee recently launched an initiative to create OCE sheets in additional languages. A new group, the Language Support Committee, was dedicated for this endeavor.

Spanish was chosen as the first OCE translation language.

Bilingual nurses, pharmacists and health professional students from the ACCC, HOPA, NCODA and ONS were assembled and tasked with providing accurate translation of side effects and counseling points.

The Language Support Committee also was directed to account for the colloquial differences between different regions of the United States.

It was paramount that the medical terminology not only remain at a standard patient literacy level — which is already an obstacle within oncology itself — but also remain universally comprehensible for all users.

Now that the first prototype sheets have been completed, the committee has begun the process of translating all OCE sheets currently online from English to Spanish.

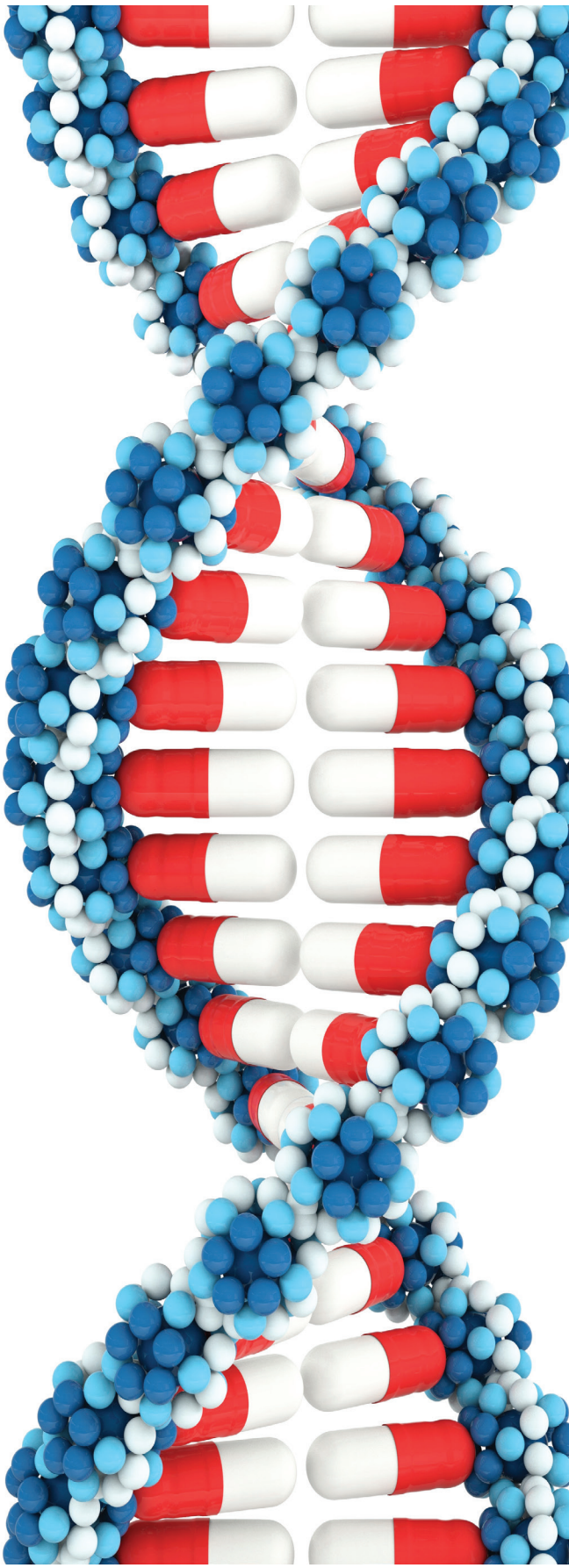
SCAN QR CODE TO VIEW THE OCE WEBSITE

Translation services for future OCE sheets are being evaluated as well, but the benefit of having healthcare professionals providing early input has proved to be invaluable.

The ins and outs of oncology can be difficult to explain, but with the help of the Language Support Committee, NCODA hopes to expand its OCE initiative and share patient guidelines worldwide.

HARVESTING THE HELIX

HOW PHARMACOGENOMICS TESTING EMPOWERS ONCOLOGY PHARMACY



By Michael J. Schuh, PharmD, MBA, FAPhA

Medicine and medication therapy are increasingly becoming individualized to better improve overall patient care and avoid medication adverse drug reactions (ADRs) or other medication-related problems (MRPs).

Michael J. Schuh

In the past, much of medication selection and dosing was a matter of trial and error. Trial-and-error prescribing resulted in multiple provider visits and communications. This, in turn, led to increased labor costs, increased medication costs from medications that either did not work or caused MRPs, and more downstream overall patient costs due to lost work productivity and wages.[1-2]

Trial-and-error prescribing also has increased medical costs through additional emergency room visits for treatment of ADRs or other MRPs,[3] with the possible added ripple effect of lower medication adherence for the aforementioned reasons.

Yet the rise of pharmacogenomics (PGx) lab testing is now changing the paradigm of trial-and-error prescribing. Costs for PGx panel tests have decreased greatly over the past five years. Where once a single gene test by a Clinical Laboratory Improvement Amendments (CLIA) certified lab in the not-too-distant past could have cost hundreds of dollars, a panel of more than a score of genes can now be accomplished for the same cost.[4-5]

PGx testing can now help with initial medication treatment and help predict a starting dose, guide dosing changes, or eliminate a medication altogether that may be predicted to either perform suboptimally in an individual or that may have an increased risk of interaction, ADR or other MRP.

PGx panels may be predictive of serious, sensitivity reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome conditions such as Stevens-Johnson syndrome in the case of HLA tested genes, and predict irinotecan or nilotinib toxicities in Gilbert's syndrome patients who

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have inherited a UGT1A1*28 gene from both parents.

Other genes tested with oncology applications are TPMT for potential thiopurine toxicities and DPYD for potential fluoropyrimidine toxicities.[6]

TERMINOLOGY

Common PGx terminology may be unfamiliar to some. As a review, one should remember from genetics class that phenotype is how a person expresses a gene (i.e., blue eyes), genotype is how one is made up genetically that may or may not be expressed (i.e., a BRCA carrier who may exhibit no breast cancer disease).

Gene phenotype terminology refers to a spectrum of gene and consequently enzyme activity from Poor, Intermediate, Normal (or Extensive), Rapid and Ultrarapid. Terminology is now more uniform than in the past, so it has become easier to understand and apply clinically. Alleles, represented as an (*) then a number (*28), as a letter (G) or as a letter and number (rs123456) are alternative forms of a gene found at the same location on a chromosome.

Some genes have many variants (e.g., CYP2D6) and others (e.g. CYP3A4) have few. It should be kept in mind, however, that gene activity can be regulated up or down by foods, supplements and other drugs. If this up-or-down regulation is great enough, it can actually change the phenotype. This is referred to as phenoconversion.

ANALGESIC, ANTIDEPRESSANT EFFECTS

Many oncology patients take antidepressants and pain medications. Standard CYP2D6 testing can help predict efficacy of tramadol or codeine as a pain reliever or even if tamoxifen should or should not considered for breast cancer prophylaxis and substituted with an aromatase inhibitor such as exemestane or letrozole.

An example case study at Mayo Clinic in Florida demonstrated the benefit of PGx testing in a 60-year-old male ER/PR+, HER2-, breast cancer patient.[7]

The patient was placed on tamoxifen prophylaxis therapy post breast cancer treatment before PGx panel testing was less expensive and more easily available. He had a recurrence of the cancer while taking the tamoxifen, so his physician ordered PGx panel testing that included testing the CYP2D6 gene. The CYP2D6 gene is responsible for converting the less active tamoxifen to the potent, active endoxifen.

As a result of the PGx panel testing, the patient was found to be a phenotypically poor metabolizer of CYP2D6, rendering tamoxifen as an ineffective therapy in his case. The PGx pharmacist recommended the use of aromatase inhibitor therapy and the patient was started on letrozole with an added gonadotropin-releasing hormone agonist (GnRHa) leuprolide to suppress testicular production of estrogen which is not inhibited by letrozole therapy.[8]

OTHER CONCERNS

In addition to single drug-gene interactions, polypharmacy oncology patients may benefit from PGx testing as well. Patients on pain or psychiatric medications may be taking other classes of medications or nutritional and dietary supplements that could influence CYP enzymes produced by CYP genes via inhibition or induction of the enzymes to increase or decrease functionality.

For example, a patient taking a medication they would genetically metabolize "normally," could take another drug or supplement that might inhibit that CYP enzyme's functionality to "phenoconvert" that patient from a normal metabolizer to possibly an intermediate or poor metabolizer and therefore increase ADR risk or ineffective medication risk, depending on whether a drug is a prodrug or not.[9]

In the case of the male breast cancer patient, consider the patient taking a strong CYP2D6 inhibitor for depression, such as bupropion. In theory, bupropion could render tamoxifen ineffective, even if the patient is a phenotypical normal metabolizer with CYP2D6 since the bupropion would strongly inhibit or suppress the enzyme from converting tamoxifen to the active endoxifen.

PGx testing and its application can be important tools anywhere medications are used across the continuum of medical specialties, including oncology. Simple gene-drug interactions can be taken into account for initial dosing of some oncolytic drugs now with the

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possibility of applications to more of the newer drug therapies.

Metabolism of some newer drugs with regard to polypharmacy must now be taken into account as well. For example, pazopanib is a tyrosine kinase-inhibiting, CYP3A4 substrate that one should avoid giving concomitantly with any strong CYP3A4 inhibitors or inducers.

We are just now scratching the surface of possible PGx applications. There is great potential for this science in the future. So much so that colleges of pharmacy, continuing education providers and other educational entities are routinely including PGx in their academic curricula.

PGx testing and its application can be important tools anywhere medications are used across the continuum of medical specialties, including oncology.

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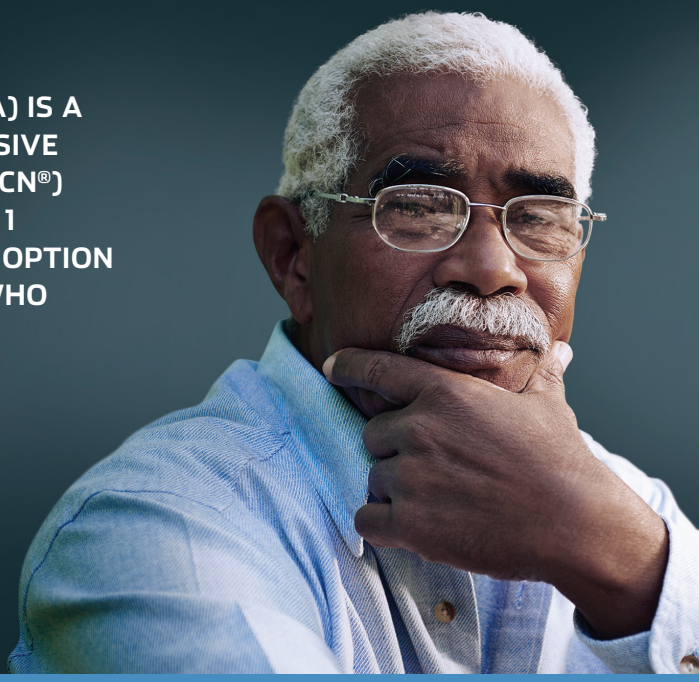
JEVTANA® (cabazitaxel) injection

CABAZITAXEL (JEVTANA) IS A NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) DESIGNATED CATEGORY 1 SECOND-LINE THERAPY OPTION FOR mCRPC PATIENTS WHO PREVIOUSLY RECEIVED DOCETAXEL†



TROPIC[1] Study (n=755)

Validated JEVTANA as a treatment in mCRPC after docetaxel

A randomized, open-label, international, multicenter study of JEVTANA 25 mg/m^2 (n=378) vs mitoxantrone 12 mg/m^2 (n=377) in patients with mCRPC previously treated with a docetaxel-containing regimen.

Primary endpoint: overall survival

PROSELICA[1] Study (n=1200)

Established JEVTANA 20 mg/m^2 as the recommended dose

25 mg/m^2 can be used in select patients at HCP discretion

A noninferioriy, randomized, open-label, multicenter study of JEVTANA 20 mg/m^2 (n=598) vs 25 mg/m^2 (n=602) in patients with mCRPC previously treated with a docetaxel-containing regimen.

Primary endpoint: overall survival

JEVTANA is the only microtubule inhibitor approved in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing 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/mm^3. 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/m^2.

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/mm^3, 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 ≥65 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 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.

What's next... what's possible.

Discover the possibilities for your metastatic castration-resistant prostate cancer (mCRPC) patients when prescribed JEVTANA early post docetaxel

Prescribed to over 40,000 men*

The efficacy and safety of JEVTANA were evaluated in the TROPIC and PROSELICA trials. Most recently, results from the CARD study were published in the *New England Journal of Medicine* and presented at the 2020 ASCO GU symposium. Data from the TROPIC, PROSELICA and CARD studies are included in the US Prescribing Information.

*Estimate based on US sales & use data. 01/2010-10/2019

CARD[2] Study (n=255)

The first comparative, prospective, phase 4 trial evaluating JEVTANA versus abiraterone or enzalutamide

A randomized, open-label, multicenter study of JEVTANA 25 mg/m^2 vs an androgen receptor (AR)-targeted agent (abiraterone or enzalutamide) in patients with mCRPC who had previously received docetaxel and had disease progression within 12 months on an alternative AR-targeted agent.

Primary endpoint: radiographic progression free survival

SEE CARD RESULTS AT:
JEVTANApro.com/results

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 x ULN or AST >1.5 x ULN) and moderate (total bilirubin >1.5 to ≤3.0 x ULN and any AST) hepatic impairment, based on tolerability data in these patients. Administer JEVTANA 20 mg/m^2 for mild hepatic impairment. Administer JEVTANA 15 mg/m^2 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 (≥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 full Prescribing Information, including Boxed WARNING on following pages.

† Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed March 11, 2020. 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.

1. JEVTANA Prescribing Information. Bridgewater, NJ: sanofi-aventis U.S. LLC **2.** 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. doi: 10.1056/NEJMoa1911206.

 MAT-US-2100733-v1.0-02/2021

SANOFI GENZYME

JEVTANA® **Rx Only**
(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/mm^3. 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/m^2 *[see Contraindications (4) and Warnings and Precautions (5.1, 5.2)]*.

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)]*.

1 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

2.1 Dosing Information

The recommended dose of JEVTANA is based on calculation of the Body Surface Area (BSA), and is 20 mg/m^2 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/m^2 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/m^2 *[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),
- H_2 antagonist (ranitidine 50 mg or equivalent H_2 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 1.

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/mm^3, 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/mm^3, 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/m^2 dose who require dose reduction should decrease dosage of JEVTANA to 15 mg/m^2 *[see Adverse Reactions (6.1)]*.

Patients at a 25 mg/m^2 dose who require dose reduction should decrease dosage of JEVTANA to 20 mg/m^2. One additional dose reduction to 15 mg/m^2 may be considered *[see Adverse Reactions (6.1)]*.

2.3 Dose Modifications for Hepatic Impairment

- Mild hepatic impairment (total bilirubin >1 to ≤1.5 × Upper Limit of Normal (ULN) or AST >1.5 × ULN): Administer JEVTANA at a dose of 20 mg/m^2.
- Moderate hepatic impairment (total bilirubin >1.5 to ≤3 × ULN and AST = any): Administer JEVTANA at a dose of 15 mg/m^2 based on tolerability data in these patients; however, the efficacy of this dose is unknown.
- Severe hepatic impairment (total bilirubin >3 × 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]*.

2.4 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.

4 CONTRAINDICATIONS

JEVTANA is contraindicated in patients with:

- neutrophil counts of ≤1,500/mm^3 *[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 × ULN) *[see Warnings and Precautions (5.8)]*

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

JEVTANA is contraindicated in patients with neutrophils ≤1,500/mm^3 *[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.

TROPIC Trial (JEVTANA 25 mg/m^2)

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/m^2 versus 25 mg/m^2)

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/m^2 arm and 15 patients (3%) on the 25 mg/m^2 arm died from infection; of these, 4 deaths on the 20 mg/m^2 arm and 8 deaths on the 25 mg/m^2 arm occurred within the first 30 days of treatment. Clinically important neutropenia-related events occurred and included febrile neutropenia (2.1% on 20 mg/m^2 arm and 9.2% on 25 mg/m^2 arm), neutropenic infection/sepsis (2.1% on 20 mg/m^2 arm and 6.4% on 25 mg/m^2 arm), and neutropenic deaths (0.3% on 20 mg/m^2 arm and 0.7% on 25 mg/m^2 arm).

Fewer patients receiving JEVTANA 20 mg/m^2 were reported to have infectious adverse reactions. Grade 1–4 infections were experienced by 160 patients (28%) on the 20 mg/m^2 arm and 227 patients (38%) on the 25 mg/m^2 arm. Grade 3–4 infections were experienced by 57 patients (10%) on the 20 mg/m^2 arm and 120 patients (20%) on the 25 mg/m^2 arm. Noninferiority for overall survival was demonstrated between these two arms *[see Adverse Reactions (6.1)]*.

CARD Trial (JEVTANA 25 mg/m^2 + primary prophylaxis G-CSF)

In the CARD trial where JEVTANA 25 mg/m^2 was administered with primary prophylaxis of G-CSF, 1 patient (0.8%) died from sepsis within the first 30 days of 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/m^2.

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/m^2 arm and 1.3% (8/595) patients on the 25 mg/m^2 arm; all of these patients were >60 years of age.

In PROSELICA, on the 20 mg/m^2 arm, 3% (5/178) of patients <65 years of age and 2% (9/402) ≥65 years of age died of causes other than disease progression within 30 days of the last JEVTANA dose. On the 25 mg/m^2 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 bronchospasm.

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 bleeding.

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/m^2 arm reported diarrhea, compared to patients on the 20 mg/m^2 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 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 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 tolerability 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)]*.

6 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/m^2 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 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, fatigue, 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

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 %
Blood and Lymphatic System Disorders				
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 Disorders				
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 and Administration Site Conditions				
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

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 %
Renal and Urinary Tract Disorders				
Hematuria	17	2	4	<1
Dysuria	7	0	1	0
Musculoskeletal and Connective Tissue Disorders				
Back Pain	16	4	12	3
Arthralgia	11	1	8	1
Muscle Spasms	7	0	3	0
Metabolism and Nutrition Disorders				
Anorexia	16	<1	11	<1
Dehydration	5	2	3	<1
Nervous System Disorders				
Peripheral Neuropathy¶	13	<1	3	<1
Dysgeusia	11	0	4	0
Dizziness	8	0	6	<1
Headache	8	0	5	0
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	12	1	4	<1
Cough	11	0	6	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	10	0	5	0
Investigations				
Weight Decreased	9	0	8	<1
Infections and Infestations				
Urinary Tract Infection#	8	2	3	1
Cardiac Disorders				
Arrhythmiaᵇ	5	1	2	<1
Vascular Disorders				
Hypotension	5	<1	2	<1

*Graded using NCI CTCAE version 3.
†Based on laboratory values, JEVTANA: n=369, mitoxantrone: n=370.
‡Includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and GI pain.
§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.
ᵇIncludes 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 mg/m^2 (n=595) or the 20 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/m^2 and 32 (5.4%) patients in the 25 mg/m^2 arm. The most common fatal adverse reactions in JEVTANA-treated patients were related to infections, and these occurred more commonly on the 25 mg/m^2 arm (n=15) than on the 20 mg/m^2 arm (n=8). Other fatal adverse reactions in JEVTANA-treated patients included 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/m^2 versus 20 mg/m^2 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/m^2 versus 20 mg/m^2 arms were leukopenia, neutropenia, and febrile neutropenia.

Treatment discontinuations due to adverse reactions occurred in 17% of patients in the 20 mg/m^2 group and 20% of patients in the 25 mg/m^2 group. The most common adverse reactions leading to treatment discontinuation were fatigue and hematuria. The patients in the 20 mg/m^2 group received a median of 6 cycles (median duration of 18 weeks), while patients in the 25 mg/m^2 group received a median of 7 cycles (median duration of 21 weeks). In the 25 mg/m^2 group, 128 patients (22%) had a dose reduced from 25 to 20 mg/m^2, 19 patients (3%) had a dose reduced from 20 to 15 mg/m^2 and 1 patient (0.2%) had a dose reduced from 15 to 12 mg/m^2. In the 20 mg/m^2 group, 58 patients (10%) had a dose reduced from 20 to 15 mg/m^2, and 9 patients (2%) had a dose reduced from 15 to 12 mg/m^2.

Table 3: Adverse Reactions* and Hematologic Abnormalities in ≥5% of Patients in PROSELICA

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 %
Blood and Lymphatic System Disorders				
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 Disorders				
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 and Administration Site Conditions				
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 Disorders				
Hematuria	14	2	21	4
Dysuria	5	0.3	4	0
Metabolism and Nutrition Disorders				
Decreased appetite	13	0.7	19	1
Musculoskeletal and Connective Tissue Disorders				
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 Disorders				
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

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 %
Infections and Infestations				
Urinary tract infection‡	7	2	11	2
Neutropenic infection§	3	2	7	6
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	5	0.9	8	0.7
Cough	6	0	6	0
Investigations				
Weight decreased	4	0.2	7	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	3	0	6.1	0
Injury, Poisoning and Procedural Complications				
Wrong technique in drug usage process	0.3	0	5	0

*Grade from NCI CTCAE version 4.03.

†Based on laboratory values, JEVTANA 20 mg/m^2: n=577, JEVTANA 25 mg/m^2: n=590.

‡Includes urinary tract infection staphylococcal, urinary tract infection bacterial, urinary tract infection fungal, and urosepsis.

§Includes neutropenic sepsis.

CARD Trial (JEVTANA 25 mg/m^2 + primary prophylaxis with G-CSF)

The safety of JEVTANA 25 mg/m^2 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/m^2 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 ≥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 25 mg/m² + prednisone/prednisolone + G-CSF (N=126)		Abiraterone + prednisone/prednisolone or Enzalutamide (N=124)	
	Grades 1–4 %	Grade 3–4 %	Grades 1–4 %	Grade 3–4 %
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
General disorders and administration site conditions				
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 disorders				
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 tissue disorders				
Musculoskeletal painÞ	27	1.6	40	6
Pain in extremity	4.8	0	11	2.4
Bone fractureß	3.2	1.6	8	2.4
Infections and infestations				
Infectionsà	19	4	14	6
Nervous system disorders				
Peripheral neuropathyè	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 disorders				
Hematuriað	16	0.8	6	1.6
Lower urinary tract symptomsø	10	0	9	0
Acute kidney injuryý	5	2.4	10	4
Metabolism and nutrition disorders				
Decreased appetite	14	0.8	15	2.4
Hypokalemia	3.2	0	6	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Cancer pain	8	1.6	9	2.4
Cardiac disorders£	6	0.8	6	3.2
Respiratory, thoracic and mediastinal disorders				
Pneumonia¥	6	1.6	3.2	0.8

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)		Abiraterone + prednisone/prednisolone or Enzalutamide (N=124)	
	Grades 1–4 %	Grade 3–4 %	Grades 1–4 %	Grade 3–4 %
Dyspnea	6	0	2.4	0
Skin and subcutaneous tissue disorders				
Alopecia	6	0	0	0
Injury, poisoning and procedural complications				
Fall	4.8	0	0	0
Vascular disorders				
HypertensionŒ	4	2.4	8	2.4
Investigations				
Weight decreased	4	0	6	0
Psychiatric disorders				
Insomnia	3.2	0	4.8	0

*Grade from NCI CTC version 4.0.

†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.

§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.

Þincludes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, noncardiac chest pain.

ßincudes 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, pyelonephritis, 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 INTERACTIONS

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 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

8.1 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).
In an embryo-fetal developmental toxicity study in rats, cabazitaxel caused maternal and embryo-fetal toxicity consisting of increased postimplantation loss, embryolethality, 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.

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
Males
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
Males
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 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 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 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 m^2), 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 ≤1.5 × ULN or AST >1.5 × ULN) should have JEVTANA dose of 20 mg/m^2. 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 ≤3.0 × ULN and AST = any) was 15 mg/m^2, 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 appropriate symptomatic measures should be taken, as needed.

Manufactured by:
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A SANOFI COMPANY

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GEOGRAPHIC PRESCRIPTION RATES OF ABIRATERONE AND ENZALUTAMIDE IN THE 2016 MEDICARE PART D POPULACE

By Eric P. Borrelli, PhD, PharmD, MBA, & Conor G. McGladrigan, PharmD, JD, BCSCP

Prostate cancer is the leading cause of cancer for males in the United States with a prevalence of almost 900,000 individuals and a yearly incidence of approximately 165,000 individuals.[1]

The median age at diagnosis for prostate cancer is 66 years.[1] Approximately 10% to 20% of prostate cancers progress to castration-resistant prostate cancer (CRPC) within five years of diagnosis.[2]

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Two oral medications, abiraterone and enzalutamide, were recommended first-line therapy for CRPC in 2016. Both were considered to have similar efficacy and provide a net health benefit in comparison to anti-androgen therapy alone.[3,4]

Abiraterone is a cytochrome P450 17α-hydroxy/17,20-lyase (CYP 17) enzyme inhibitor that was first approved in 2012, whereas enzalutamide is an androgen receptor antagonist, also first approved in 2012.[5,6]

With both oral agents coming to market around the same time and having similar efficacy, it is important to assess their utilization in clinical practice.

A cross-sectional analysis of the 2016 Medicare Provider Utilization and Payment Data Public Use File was conducted to assess the geographic prescribing rates of abiraterone and enzalutamide dispenses in the Medicare Part D population.[7]

The 2016 United States Census Bureau was used to estimate the population of males 65 years of age or older in each state and geographic division.[8,9] Patients under the age of 65 were excluded from the analysis.

Geographic division was categorized into nine regions.[8] The annual prescription rate (PR) of each drug is the number of prescriptions divided by the estimated population of males 65 years and older (M65Y) and multiplied by 100,000. Enzalutamide/abiraterone (E/A) rates were defined as the number of prescriptions of abiraterone or enzalutamide per 100,000 M65Y in 2016.

There were 63,613 prescriptions for abiraterone in 2016 for Medicare Part D M65Y, comprising an aggregate cost of $540,215,315 (standard deviation (SD): $57,508,420). There were 65,244 prescriptions for enzalutamide, comprising an aggregate cost of $586,037,981 (SD $66,767,447).

The PR nationally in Medicare Part D in 2016 for enzalutamide was 333.9 prescriptions per 100,000 M65Y, whereas the rate for abiraterone was 325.6 prescriptions per 100,000 M65Y **[Table 1]**.

The five states with the highest E/A rates were North Dakota (1,147.7),

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TABLE 1: STATE PRESCRIBING RATES

State	Enzalutamide Rate	Abiraterone Rate	E/A Rate
Alaska	0.0	61.8	61.8
Alabama	339.1	307.8	646.9
Arkansas	354.3	258.5	612.9
Arizona	312.8	333.5	646.3
California	434.9	380.2	815.1
Colorado	315.2	303.2	618.4
Connecticut	398.5	398.1	796.6
Wash. DC	546.5	573.5	1,120.0
Delaware	167.2	438.8	606.1
Florida	305.7	351.1	656.0
Georgia	439.5	345.9	785.4
Hawaii	106.2	292.2	398.4
Iowa	461.7	255.5	717.1
Idaho	179.1	372.6	551.7
Illinois	354.1	250.5	604.6
Indiana	396.0	372.7	768.7
Kansas	242.1	384.8	626.9
Kentucky	174.0	235.6	409.5
Louisiana	383.9	383.5	767.4
Massachusetts	253.3	441.3	694.6
Maryland	228.5	355.6	584.1
Maine	197.8	290.1	487.9
Michigan	427.8	334.8	762.6
Minnesota	304.0	515.6	819.6
Missouri	301.0	286.3	587.4
Mississippi	243.4	239.4	482.8
Montana	301.4	219.0	520.4
North Carolina	389.3	238.1	627.4
North Dakota	387.7	760.0	1,147.7
Nebraska	591.0	322.2	913.3
N. Hampshire	147.4	428.0	575.4
New Jersey	300.3	242.9	543.2
New Mexico	223.8	110.5	334.3
Nevada	264.1	310.9	575.0
New York	339.6	311.6	651.3
Ohio	367.1	333.7	700.8
Oklahoma	229.9	225.4	455.3
Oregon	441.8	410.9	852.7
Pennsylvania	373.0	266.7	639.7
Rhode Island	354.6	341.5	696.1
South Carolina	330.6	284.3	614.9
South Dakota	263.7	486.8	750.5
Tennessee	326.7	236.9	563.6
Texas	246.8	347.9	594.7
Utah	218.0	322.0	540.0
Virginia	400.4	253.0	653.5
Vermont	243.9	505.2	749.1
Washington	279.8	334.7	614.5
Wisconsin	226.3	335.9	562.2
West Virgina	177.7	337.9	515.6
Wyoming	122.6	0.0	122.6
OVERALL	**333.9**	**325.6**	**659.5**

PRESCRIPTION RATES

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Washington, D.C., (1,120.0), Nebraska (913.3), Oregon (852.7) and Minnesota (819.6) **[Figure 1]**.

The five states with the lowest E/A rates were Alaska (61.8), Wyoming (122.6), New Mexico (334.3), Hawaii (398.4) and Kentucky (409.5). The geographic division with the highest E/A rate was the Pacific (767.2) and the division with the lowest was East South Central (537.2) **[Table 2]**.

Although the national prescribing rates between enzalutamide and abiraterone were similar, these rates varied greatly between individual states and geographic regions.

Of the 10 states with the highest E/A prescribing rates, only three were within the 10 states with the highest rates of prostate cancer — (North Dakota [1 vs. 4], Georgia [8 vs.10] and Louisiana [10 vs. 3]).[1]

Of the 10 states with the lowest E/A prescribing rates, only two were within the 10 states with the lowest rates of prostate cancer — (New Mexico [48 vs. 48], and Alaska [50 vs. 50]).1 States with the greatest variation between E/A prescribing rates and prostate cancer rates were Oregon (4 vs 43), California (6 vs 41) and New Jersey (40 vs 1).[1]

Some possible reasons for these substantial differences may be the result of varying practice standards at academic and medical institutions, as well as affordability of the medication for the patient population.

Oral oncolytics are estimated to cost more than $10,000 out-of-pocket per year for Medicare Part D patients without financial assistance.[10] With the differences in patient cost-sharing structure between Medicare Part B (for infusion therapy) and Medicare Part D (for self-administered agents) and the rise in cost of oral oncolytics in recent years,[11,12] the potential high cost of these oral oncolytics for CRPC may result in patients receiving less efficacious therapy due to the possibility of financial toxicity.

FIGURE 1: E/A PRESCRIPTION RATE PER STATE

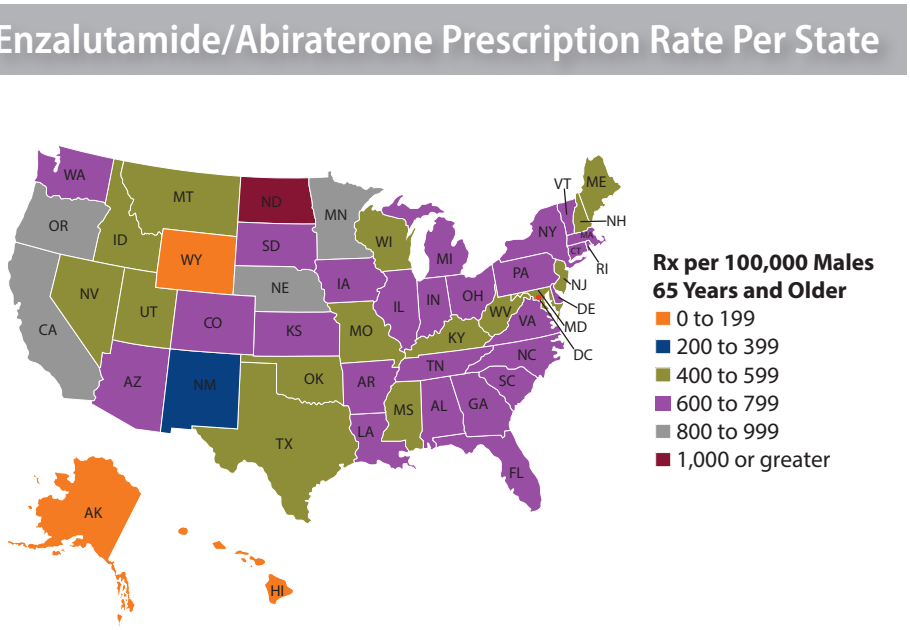

TABLE 2: GEOGRAPHIC DIVISION PRESCRIBING RATES

Region	Enzalutamide Rate	Abiraterone Rate	E/A Rate
New England	279.0	425.2	704.2
Middle Atlantic	342.9	282.2	625.0
East North Central	363.1	318.3	681.4
West North Central	345.7	379.9	725.7
South Atlantic	336.4	320.2	656.6
East South Central	281.6	255.6	537.2
West South Central	273.5	329.0	602.5
Mountain	274.5	289.7	564.2
Pacific	397.2	370.0	767.2

With respect to the limitations of our findings, we calculated prescriptions per 100,000 males ≥65 years for enzalutamide and abiraterone that may not be representative of the number of patients receiving these medications.

Standardizing rates by U.S. Census data provides an approximate age-adjustment, yet may not accurately reflect differences in patient demographics within the Medicare population.

Due to the potential difference in day supplies of prescriptions (partial fills less than 30-days or fills of 90-day supplies), prescription rates may not accurately represent patients receiving therapy for the same length of time.

However, when expenditure rates were assessed as a sub-analysis, there were not substantial differences in state and/or geographic division rankings between the two rates.

Availability of abiraterone as a generic in 2019, along with additional indications received by enzalutamide may affect their utilization in the future as well.

The total Medicare Part D spend for abiraterone and enzalutamide exceeded $1.1 billion in 2016. Although nationally the total number of prescriptions and overall costs were similar for the two medications, prescribing rates varied significantly between certain states.

Further research is needed to determine if these differences reflect variation in either quality of care or medication access.

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NEW (& FAMILIAR) FDA APPROVALS FOR PROSTATE CANCER TREATMENT

By Melissa Ruter, PharmD

Prostate cancer remains one of the leading causes of cancer-related deaths in the U.S., where 3,087,800 new cases were diagnosed from 2003-2017.

Melissa Ruter

While longitudinal data from the CDC shows that the overall incidence of prostate cancer has decreased over this time, the incidence of distant disease has actually increased.[1]

The advent and adoption of advanced imaging modalities has driven earlier detection of advanced prostate cancer and, along with it, the demand for novel oral therapeutic agents. From new targets to new dosage forms, here are a few notable examples that emerged from 2020:

RELUGOLIX (ORGOVYX®)

Approved: 12/18/20

Relugolix (Myovant) is the first oral drug in its class to receive FDA approval for the treatment of advanced prostate cancer. This once-daily tablet offers patients an alternative to the standard injectable GnRH agents used to achieve androgen deprivation.

Approval is based on the phase III HERO trial that showed 96.7% of patients randomly assigned to receive relugolix reached and maintained castrate-level testosterone from day 29 through 48 weeks of treatment, versus 88.8% of patients treated with leuprolide.[2]

A gonadotropin-releasing hormone (GnRH) receptor antagonist, the mechanism of action mimics that of the injectable degarelix (Firmagon®), competitively binding to pituitary GnRH receptors to reduce the release of LH and FSH resulting in reduced testosterone production. Leuprolide, the study's control drug, is a GnRH receptor agonist that also causes reduced testosterone production after a brief spike upon initiation, leading to a longer interval to castration than antagonists.

A potential advantage of relugolix to leuprolide is the quick testosterone recovery upon discontinuation. In a subgroup of 184 patients, testosterone levels recovered to the lower limit of normal or higher within 90 days of treatment discontinuation in 54% of patients in the relugolix group and 3% in the leuprolide group.[2] This may be preferential for patients on androgen deprivation treatment intermittently or short-term surrounding radiation therapy.

However, the quick testosterone recovery could be disadvantageous for non-compliant patients. Notably, the safety analysis found the incidence of major adverse cardiac events (MACE) in the relugolix arm to be 2.9%, as compared to 6.2%, in the leuprolide arm. Though MACE incidence was not an endpoint, history of MACE could be a compelling indication for selection of relugolix.

Other adverse effects include hot flash (54.3% in the treatment arm vs. 51.6% in the control arm), fatigue (21.5% vs. 18.5%), constipation (12.2% vs. 9.7%), arthralgia (12.1% vs 9.1%) and diarrhea (12.2% vs. 6.8%).[2]

While relugolix' oral dosage form will appeal to injection-weary patients, a careful assessment of patient compliance is a critical component of the treatment decision.

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PROSTATE DRUGS

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ENZALUTAMIDE (XTANDI®)

Approved: 8/4/20

Astellas' enzalutamide (Xtandi®) is now available in 40 mg and 80 mg tablets. The oral androgen receptor inhibitor has been on the market in the U.S. as a 40 mg capsule since its first FDA approval in 2012 for treatment of men with metastatic castrate-resistant prostate cancer (CRPC) post-chemotherapy.[3]

Following its debut, enzalutamide received indication for non-metastatic CRPC based on its PROSPER trial and , last quarter, for metastatic hormone-sensitive prostate cancer based on data from the ARCHES trial.[3,4]

This latest approval is based on the same efficacy data and alleviates the pill burden of the original capsules. The tablet itself is smaller than the capsule, and the new 80 mg strength cuts the recommended dose in half to two tablets. All enzalutamide can be taken with or without food and patients should be advised not to crush or chew either dosage form.[5]

RUCAPARIB (RUBRACA®), OLAPARIB (LYNPARZA®)

Approved: 5/15/20, 5/19/20

Established years ago as ovarian and breast cancer treatments, poly ADP ribose polymerase (PARP) inhibitors breached the prostate cancer domain with the approval of rucaparib (Rubraca®) and olaparib (Lynparza®) last year. They are indicated for the treatment of men with mCRPC who have a deleterious somatic and/or germline mutation of certain homologous recombination repair (HRR) genes, including BRCA.[5,6]

PARP enzymes are recruited to repair single stranded breaks in DNA, but when PARP inhibitors are given they prevent this repair and cause the generation of double strand breaks. In the presence of an HRR mutation, there is insufficient DNA repair and the accumulation of breaks leads to cell death. Such mutations have shown demonstrated induced lethality in ovarian, breast, pancreatic and now, prostate cancer.[7]

Olaparib was approved based on the results of the PROFOUND trial, which enrolled men with mCRPC and a confirmed mutation of a DNA repair gene who had progressed on either abiraterone or enzalutamide.

The men were divided into two cohorts then randomized to receive olaparib or their physician's choice of enzalutamide or abiraterone. Cohort A included men with a mutation of

BRCA1, BRCA2 or ATM genes and Cohort B included men with one of 12 other HHR genes. In the treatment arm, median radiographic progression-free survival (rPFS) and median overall survival (OS) were 7.4 months and 19.1 months, respectively (vs. 3.6 and 14.7, respectively). Cohort B saw a less profound response, though olaparib received approval for all but one of these additional mutations.[8]

Rucaparib's phase II TRITON2 trial earned it an accelerated approval for BRCA1 and/or BRCA2 mutation-associated mCRPC that progressed after taxane-based chemotherapy. The trial enrolled 115 patients with the characteristics described in the indication, all of whom received rucaparib. At the time of approval, 43.5% of men experienced a confirmed response and 56% of those men had a duration of response > 6 months. The mean duration of response was not estimable. The phase III TRITION3 trial to verify these results is ongoing.[9]

Safety and tolerability are relatively similar between the two agents, both of which are associated with significant toxicities that require close monitoring of patients. Anemia, fatigue, nausea, appetite loss, diarrhea and constipation are among the most common side effects.[8,9] Pharmacists can play a critical role in the management of these side effects through education and interventions to promote treatment continuation at optimal doses.

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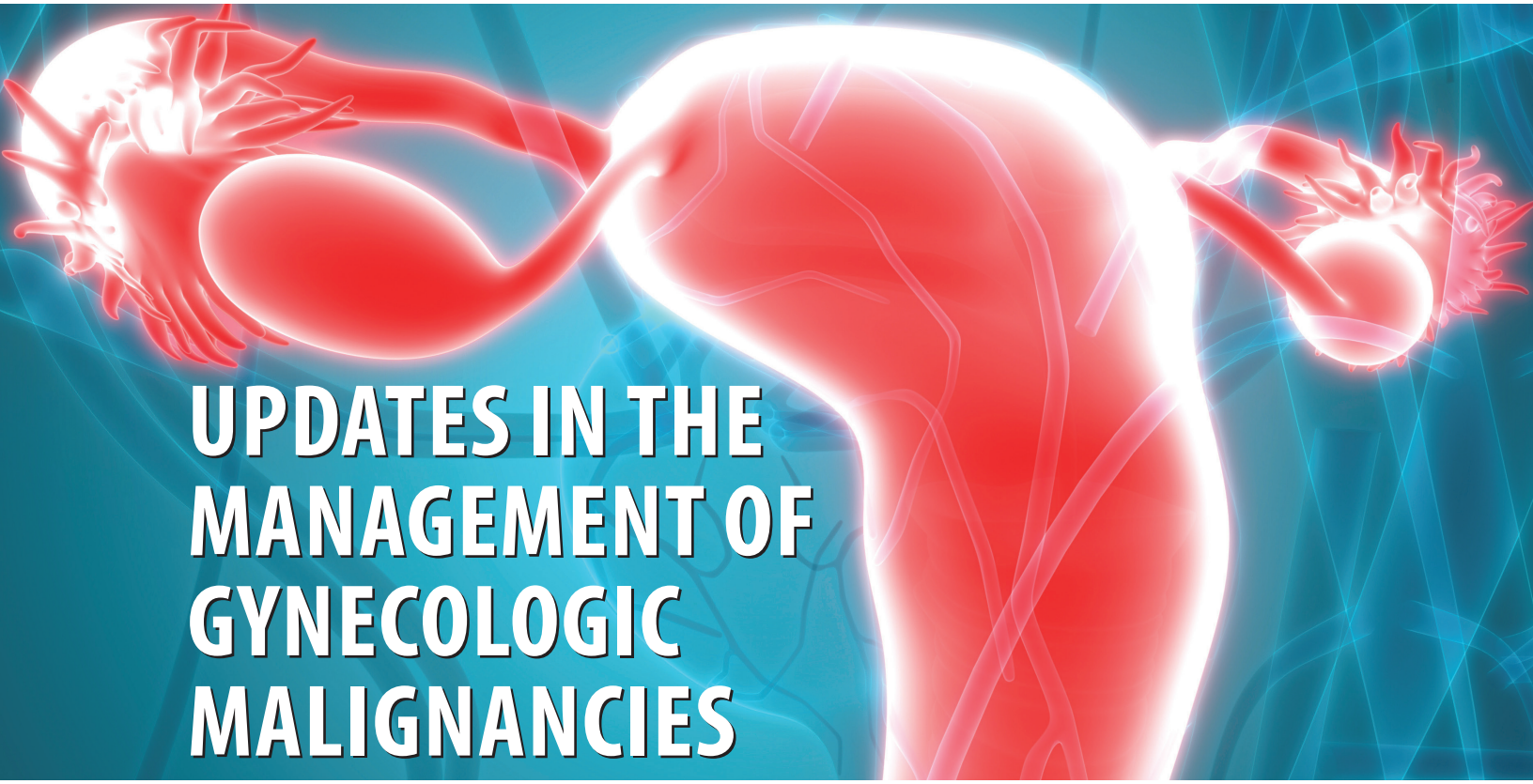

UPDATES IN THE MANAGEMENT OF GYNECOLOGIC MALIGNANCIES

By Colleen Bohnenkamp, PharmD, BCOP, BCPS, & Olivia Fahey, PharmD, BCOP

Ovarian cancer is the fifth most common cause of cancer deaths among women and the leading cause of death from a gynecologic malignancy.

An estimated 22,410 new cases will be diagnosed in 2021 with a resultant 13,770 deaths.[1] Most patients present with advanced stage disease.

The initial treatment of advanced ovarian cancer includes surgical cytoreduction and platinum-based combination chemotherapy — typically carboplatin and paclitaxel.[2]

Response rates to surgery and chemotherapy are roughly 80%, but an estimated 70-90% of patients will relapse within three years of diagnosis.[3,4]

Strategies to prevent relapse and increase progression-free survival (PFS) are therefore paramount to improving outcomes for women with advanced ovarian cancer. Particular interest exists in maintenance therapies to prevent or extend time to recurrence.

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Olivia Fahey

In the last several years, significant advances have emerged in the maintenance treatment of ovarian cancer. Poly ADP-ribose polymerase (PARP) inhibitors induce their effects by blocking the PARP enzymes which are involved in DNA transcription and repair.[5]

Many patients with ovarian cancers have gene mutations and alterations which lead to what is termed homologous recombination deficiency (HRD). BRCA genes are most commonly associated with this phenomenon, but other mutations and deficiencies can also lead to HRD. Mutations in BRCA genes — which are involved in DNA repair via the homologous recombination repair pathway — confer sensitivity to PARP inhibitors. HRD positive tumors are also susceptible to the effects of PARP inhibition.

Several FDA-approved medications have received expanded indications to include use in the frontline maintenance setting. In addition, genetic testing is now recommended for all patients with newly diagnosed ovarian cancer.

OLAPARIB

Olaparib gained FDA approval on Dec. 29, 2018, for use in patients with BRCA-mutated advanced ovarian, fallopian tube or primary peritoneal cancer for frontline maintenance treatment after a complete response (CR) or partial response (PR) to platinum-based chemotherapy.

Olaparib was approved based on the findings from the phase III SOLO-1 trial[6,7] in which 391 patients were randomized 2:1 to receive olaparib 300 mg by mouth twice per day or placebo for up to two years.

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Patients had newly diagnosed, stage III-IV high grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer, and achieved a CR or PR to platinum-based therapy within 12 weeks of randomization. Patients also had to have a confirmed BRCA1 and/or BRCA2 mutation.

After a five-year follow-up, the primary endpoint of median progression-free survival (PFS) was 56 months in the olaparib arm compared to 13.8 months in the placebo arm. This resulted in a 63% reduction in the risk of disease progression or death in the olaparib group. Overall survival data are not yet mature.

Anemia was the most common grade 3 toxicity observed in 22% of patients, followed by neutropenia (9%). Nausea (77%), fatigue (63%), vomiting (40%) and anemia (39%) occurred more frequently among patients receiving olaparib than placebo.

It is estimated that only 15-20% of patients with advanced ovarian cancer harbor BRCA mutations,[8] therefore maintenance treatment options for the remaining 80-85% of patients are needed.

NIRAPARIB

On April 29, 2020, niraparib was FDA-approved for the frontline maintenance treatment of women with advanced ovarian, fallopian tube or primary peritoneal cancer, after a complete or partial response to platinum-based chemotherapy based on data from the PRIMA trial.[9] Approval is irrespective of BRCA mutational status.

In the phase III PRIMA trial, 733 patients were randomized 2:1 to receive niraparib 300 mg by mouth daily or placebo for up to three years. The protocol was amended partway through the trial to reduce the starting dose of niraparib to 200 mg by mouth daily in patients with a baseline body weight less than 77 kg and/or a platelet count of less than 150,000 per cubic millimeter. This is the current FDA-approved dosing strategy.

Maintenance treatment strategies are at the forefront of advances in the treatment of ovarian cancer. The emergence of several new treatment options requires clinicians to be familiar with the details of the approvals as well as the anticipated adverse effects.

The study met its primary endpoint of PFS in the overall population and in the subgroup of patients with HRD. The median PFS was significantly longer at 13.8 months with niraparib, compared to 8.2 months with placebo in the overall population. In patients with HRD, the median PFS was 21.9 months with niraparib versus 10.4 months with placebo. Overall survival data are not sufficiently mature.

The most common grade 3 or higher adverse events in patients receiving niraparib were anemia (31%), thrombocytopenia (28.7%), and neutropenia (12.8%).

More patients in the niraparib than the placebo group discontinued therapy due to adverse events, 12% versus 2.5%. Dose reduction occurred in 70.9% of patients in the niraparib group.

The most common adverse events in patients receiving niraparib were anemia (63.4%), nausea (57.4%), thrombocytopenia (45.9%) and constipation (39%).

Owing to the high rate of dose reductions and propensity for hematologic toxicities, pharmacists can play a critical role in assisting providers in the management of PARP Inhibitor toxicities to ensure patients can safely remain on therapy.

OLAPARIB + BEVACIZUMAB

The combination of olaparib plus bevacizumab was FDA-approved on May 8, 2020, for frontline maintenance treatment of patients with advanced ovarian, fallopian tube or primary peritoneal cancer after a CR or PR to platinum-based chemotherapy.

Patients must have a cancer that is considered HRD-positive. Results from the phase III, PAOLA-1 trial[10] led to the FDA approval.

Patients were eligible for the study regardless of BRCA mutation status and were randomized 2:1 to receive olaparib 300 mg by mouth twice per day or placebo for up to two years. All patients received bevacizumab (bev) 15 mg/kg intravenously every three weeks for up to 15 months. Eligible patients achieved a CR or PR to frontline chemotherapy in combination with bev.

In the overall patient population, the median PFS was significantly longer in the olaparib + bev arm compared to the placebo + bev arm (22.1 months versus 16.6 months).

Approximately 48% of patients in the study were considered HRD-positive, and the median PFS benefit was largest in this subgroup, 37.2 months in the olaparib + bev arm versus 17.7 months in the placebo + bev arm.

In patients that were considered HRD negative or unknown, there was not a statistically significant benefit to the combination of olaparib + bev (16.9 months versus 16 months).

The most common grade 3 or higher adverse events in the olaparib + bev arm were hypertension (19%) and anemia (17%).

The most common any grade adverse events in the combination arm were fatigue (53%), nausea (53%), hypertension (46%) and anemia (41%). Any grade hypertension occurred more frequently in the placebo + bev arm (60%).

Dose reduction and discontinuation occurred in 41% and 20% of patients in the olaparib + bev arm, respectively.

In summary, maintenance treatment

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strategies are at the forefront of advances in the treatment of ovarian cancer.

The emergence of several new treatment options requires clinicians to be familiar with the details of the approvals as well as the anticipated adverse effects.

Pharmacists play a critical role in appropriate patient selection for use of therapy, monitoring and management of toxicities.

ENDOMETRIAL CANCER

In comparison, endometrial cancer is the most commonly diagnosed gynecologic malignancy. However, a majority of patients are diagnosed with early stage disease that has greater than 95% five-year survival.[11-13]

The American Cancer Society estimates that there will be 66,570 new diagnoses of endometrial cancer or uterine sarcoma, resulting 12,940 deaths in 2021. Unfortunately, the incidence and mortality of endometrial cancer is currently increasing.[11]

The management of early stage endometrial cancer primarily consists of surgical resection and thorough staging with the addition of adjuvant radiation with or without chemotherapy recommended in patients at higher risk of relapse.[12]

For advanced or recurrent endometrial cancer, standard of care adjuvant therapy consists of carboplatin and paclitaxel-based chemotherapy.[12-13]

Hormonal agents such as progesterone or aromatase inhibitors are an option for patients with limited performance status or in the second-line and beyond setting. However, there is an overall scarcity of treatment options in this setting.

The newest treatment update in this disease state was the approval of an immunotherapy and targeted therapy combination for the second line and beyond treatment of advanced endometrial cancer.

PEMBROLIZUMAB + LENVATINIB

While single-agent pembrolizumab has been approved for the treatment of microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) endometrial cancer ever since pembrolizumab was granted that tissue-agnostic solid tumor indication, on September 19, 2019, the FDA granted accelerated approval to the combination of pembrolizumab and lenvatinib.

The combination of pembrolizumab with lenvatinib represents a new treatment option for patients with recurrent or advanced endometrial cancer who have progressed after receipt of first-line systemic therapy.

The combination is indicated for the treatment of patients who have advanced endometrial carcinoma that is not MSI-H or dMMR, with disease progression following prior systemic therapy.

The accelerated approval was granted based upon the primary efficacy analysis of the advanced endometrial cancer cohort of the open-label, single-arm, phase II KEYNOTE-146/Study 111 study.[13] Patients were eligible for study inclusion if they had metastatic endometrial cancer with measurable disease and had received no more than two previous lines of systemic treatment.

A total of 108 previously treated patients received lenvatinib 20 mg by mouth once daily continuously as well as pembrolizumab 200 mg intravenously every 21 days until disease progression or unacceptable toxicity. Patients could only receive a maximum of 35 pembrolizumab treatments.

In total, 94 (87%) of the tumors were determined to be microsatellite stable (MSS) or proficient in mismatch repair (pMMR). However, 11 patients (10%) had tumors that were classified as MSI-H/dMMR.

The primary endpoint evaluated the proportion of patients who had achieved an objective response, defined as a complete or partial response, at 24 weeks. Out of the 108 total patients included in the primary analysis, an objective response per investigator review occurred in 41 patients (38%).

After a median follow-up of 11.9 months, median progression-free survival was 7.4 months and median overall survival was 16.7 months. A post hoc exploratory analysis of the 94 patients with MSS/pMMR tumors found an objective response in 35 patients (37%).

Hypertension was the most common side effect and was observed in 61% of patients, including 32% who experienced grade 3 or 4 blood pressure elevations. Diarrhea was reported in more than half (53%) of patients followed by fatigue (52%), decreased appetite (47%) and hypothyroidism (44%). Seventy patients experienced pre-specified, immune-related adverse events from pembrolizumab.

Twenty-two patients (18%) ended up discontinuing one or both of the study medications due to treatment related adverse effects, and dose interruptions occurred in 87 (70%) of patients. Seventy-eight (63%) of patients required a dose reduction in lenvatinib.

In summary, the combination of pembrolizumab with lenvatinib represents a new treatment option for patients with recurrent or advanced endometrial cancer who have progressed after receipt of first-line systemic therapy.

▲ **Colleen Bohnenkamp**, PharmD, BCOP, BCPS, and **Olivia Fahey**, PharmD, BCOP, are Oncology Clinical Pharmacists at the University of Kansas Cancer Center.

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GYNECOLOGIC UPDATES

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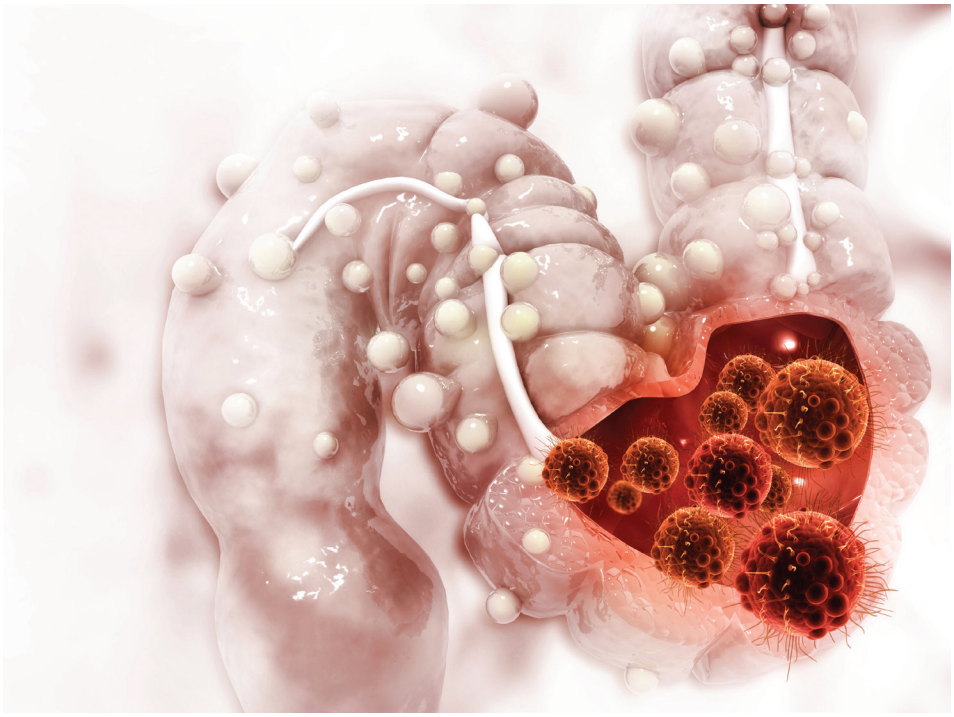
A CHEMOTHERAPY ALTERNATIVE

UPDATE: FIRST-LINE IMMUNOTHERAPY FOR DMMR/MSI-H COLORECTAL CANCER

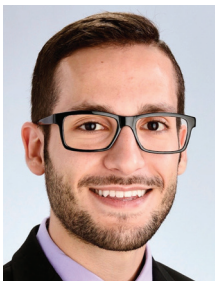
By Kelly Brunk, PharmD, BCOP, & Vincent Cascone, PharmD, BCOP



Over the past 10 years, immune checkpoint inhibitor (ICI) therapy has revolutionized cancer care.

ICI activity in solid tumors often corresponds with the presence of highly mutated tumors, such as those with deficient mismatch repair (dMMR) mechanisms and a high degree of microsatellite instability (MSI-H).[1]

Kelly Brunk



Vincent Cascone

Studies in patients with dMMR/MSI-H tumors have shown promising results, and in 2017, the U.S. Food and Drug Administration (FDA) granted pembrolizumab the first tumor-type–agnostic approval for use as salvage therapy in patients with advanced dMMR/MSI-H tumors.[2]

In metastatic colorectal cancer (mCRC), tumors with dMMR/MSI-H are seen in about 3.5% to 5% of patients.[3,4] The prevalence is greater in tumors that originate on the right side of the colon, in tumors with a BRAF V600E-mutation, and in female patients.

In later lines of therapy, ICIs have demonstrated remarkable durability in dMMR/MSI-H mCRC, with response rates of 30-40% for single-agent pembrolizumab or nivolumab and 40-50% for the combination of nivolumab and ipilimumab.[5,6,7]

Based on these results, the FDA approved both pembrolizumab and nivolumab — alone or in combination with ipilimumab — in 2017 and 2018, respectively, for treatment of dMMR/MSI-H mCRC beyond first-line therapy.[2,8]

Recently, studies have shown promise for utilizing ICIs in the first-line setting for dMMR/MSI-H mCRC. In June 2020, the FDA granted pembrolizumab approval for treatment of dMMR/MSI-H mCRC in the first-line setting. Currently, national guidelines recommend either pembrolizumab or nivolumab — alone or in combination with ipilimumab — as a first-line recommendation in this setting.[9,10,11]

In light of these significant changes to the standard of care treatment for the dMMR/MSI-H patient population, we evaluated and summarized the literature supporting these updates. This article discusses the recent publications and reviews key features of microsatellite instability in colorectal cancer (CRC).

UNDERSTANDING MICROSATELLITE INSTABILITY

Malignancies with dMMR mechanisms are extensively mutated, and the phenotype associated with these aberrations is called microsatellite instability (MSI) or MSI-H.[1,12,13] dMMR/MSI-H status is determined by either immunohistochemistry (ICH) or polymerase chain reaction (PCR) testing.[12]

ICH assesses for alterations in four key genes involved in deoxyribonucleic acid (DNA) mismatch repair: MLH1, MSH2, MSH6 and PMS2. PCR testing detects mononucleotide and dinucleotide repeats in the tumor genome, which indicate dMMR/MSI-H status. Both tests are highly concordant in determining dMMR/MSI-H status.[14]

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Tumors that lack these mutations are otherwise termed microsatellite stable (MSS). Microsatellite instability can also be categorized as having intermediate or low instability (MSI-L), but at this time, the clinical relevance of MSI-L status remains nebulous.[15]

The presence of dMMR/MSI-H status has treatment implications in many solid tumors. Somatic mutations that encode for non-self immunogenic antigens are harbored more in MSI-H tumors as compared to MSS tumors. Therefore, immunotherapy — specifically with ICIs — produces impressive treatment efficacy in these dMMR/MSI-H tumors.

In addition to dMMR/MSI-H tumors, ICIs may be indicated in specific tumors with programmed cell death-ligand 1 (PD-L1) positivity. Measurements of PD-L1 positivity include tumor proportion score (TPS) and combined positivity score (CPS).

TPS is the proportion of PD-L1 positive tumor cells stained out of all tumor cells in the sample, whereas CPS is the proportion of PD-L1 positive tumor cells and tumor-associated immune cells out of the total number of tumor cells in the sample.[16]

Tumor mutational burden (TMB) is another measure of the total number of nonsynonymous mutations per coding area of a tumor genome and is expressed as mutations per megabase.[17] Tumors with high tumor mutational burden (TMB-H) are often defined as ≥10 mutations/megabase.

The statuses of dMMR/MSI-H and TMB-H indicate that the tumors have accumulated many mutations that cause various molecular changes. As stated before, these changes increase the expression of neoantigens and subsequently attract tumor-infiltrating lymphocytes to the site of cancer.[18]

It is hypothesized that the aggregation of tumor-infiltrating lymphocytes at the tumor site causes the marked responses seen in this setting.

Germline mutations in DNA mismatch repair genes are a defining feature of Lynch Syndrome (LS).[12] LS is an autosomal dominant genetic disorder that predisposes patients to various cancers, including CRC.[19,20]

Patients with LS have a 50-70% lifetime risk of developing CRC, and the prevalence of LS in CRC is 1 in 35 patients.[20,21]

Interestingly, for patients with undiagnosed LS, positive studies for dMMR/MSI-H status are correlated with establishing the LS diagnosis.[22] Patients with LS benefit from cancer screenings due to their high risk of various cancers.[20]

The role of immunotherapy in the treatment of LS-associated cancers is well established, and without contraindications for immunotherapy, treatment should include an ICI.

TARGETING MICROSATELLITE INSTABILITY IN COLORECTAL CANCER

Immunotherapy indications have grown substantially since the first FDA approval of pembrolizumab in advanced melanoma in 2014.[23]

The most sweeping of these indications came from the 2017 tissue-site-agnostic approval of pembrolizumab for unresectable or metastatic, dMMR/MSI-H solid tumors that have progressed after first-line treatment.[2]

More recently, pembrolizumab was approved for the treatment of unresectable or metastatic TMB-H solid tumors after first-line treatment.[24]

These approvals illustrate the growing evidence of immunotherapy in dMMR/MSI-H and TMB-H malignancies.[18]

The role of dMMR/MSI-H status has treatment implications in the advanced cancer setting and can influence clinical decisions in earlier stages. In stage II colon cancer, adjuvant fluoropyrimidine-based chemotherapy can be considered.[10]

However, in patients with dMMR/MSI-H disease, the overall survival (OS) benefit with adjuvant chemotherapy is not seen.[25]

Moreover, some evidence shows a reduced OS in patients with dMMR/MSI-H stage II colon cancer who receive adjuvant chemotherapy.[26]

Unlike stage II colon cancer, MSI status does not factor into the appropriateness of adjuvant therapy in stage III disease.[27]

Notably, patients with dMMR/MSI-H stage III colon cancer are less likely to recur than those with MSS status. Regarding rectal cancer, the standard of care management of non-stage IV disease remains largely unaffected by dMMR/MSI-H status.

In mCRC, several treatment options are available for dMMR/MSI-H tumors, including pembrolizumab and nivolumab – alone or in combination with ipilimumab.[6,28]

PEMBROLIZUMAB

The FDA approved pembrolizumab in June 2020 for the first-line treatment of unresectable or metastatic dMMR/MSI-H CRC based on the phase 3, randomized, open-label KEYNOTE-177 trial.[9]

In the trial, 307 patients received either pembrolizumab 200 mg every three weeks (n=153) or investigator's choice of doublet chemotherapy, with or without the addition of another targeted monoclonal antibody (n=154).[28]

At a median follow up of 32.4 months, median progression-free survival (PFS) was more than twice as long for the pembrolizumab group as compared to the chemotherapy group (16.5 vs. 8.2 months; hazard ratio, 0.60; 95% confidence interval, 0.45-0.8; p=0.0002).[28]

Crossover from the chemotherapy group to the pembrolizumab group occurred in 59% of patients. Although OS data are maturing, the high crossover rate may make it challenging to show a significantly improved OS with pembrolizumab despite the dramatic improvement in PFS.

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Pembrolizumab also led to a higher overall response rate as compared to chemotherapy (43.8% vs. 33.1%; complete response rate, 11.1% vs. 3.9%) and showed a remarkable durability of response (11 vs. 5.7 months).[28]

Treatment-related adverse events of grade 3 or higher occurred more often in the chemotherapy group (22% vs. 66%). Treatment discontinuation due to treatment adverse effects occurred in 14% of patients in the pembrolizumab group and 12% in the chemotherapy group.

The most common toxicities were diarrhea, fatigue, nausea and abdominal pain.

A notable finding of the KEYNOTE-177 trial was that patients harboring RAS-mutated cancers did not appear to have the same benefit from pembrolizumab as seen with the group overall. Previous non-randomized studies have yet to elucidate this association of RAS mutations with decreased activity of ICIs, and this remains a clinical question for future studies to explore.[6,7]

NIVOLUMAB ± IPILIMUMAB

In 2018, the FDA approved nivolumab — alone or in combination with ipilimumab — for dMMR/MSI-H mCRC in the subsequent-line setting.[8]

Use in the first-line setting is currently being investigated in a cohort of the phase 2 CheckMate-142 trial.[29] In the trial, 45 patients received nivolumab 3 mg/kg every two weeks with low-dose ipilimumab at 1 mg/kg every six weeks until disease progression or unacceptable toxicity.

At a median follow up of 29 months, the overall response rate was 69% (complete response rate, 13%).[29] Median PFS and OS were not yet reached, however, the rates of these outcomes at 24-months were 74% and 79%, respectively.[29]

Treatment-related grade 3 or higher toxicities occurred in 20% of patients (11% reported as grade 4-5), and only two patients (4%) discontinued therapy due to a treatment-related adverse event.[29]

The most common toxicities were pruritus, hypothyroidism, arthralgia and asthenia. The combination was well tolerated, potentially due to the use of a six-week dosing interval for ipilimumab rather than the historically used three-week dosing interval.

FUTURE DIRECTIONS

The expansion of immunotherapy into a wide variety of cancers represents a promising treatment option for both treatment-naive and relapsed/refractory diseases. Studies are underway in various cancers to evaluate the role of immunotherapy as monotherapy or in combination with cytotoxic or other targeted therapy.[30]

While the benefit of immunotherapy is well established in dMMR/MSI-H mCRC, data is growing for its use in MSS disease.

Unfortunately, not all CRC patients respond equally, and ongoing studies are exploring predictive biomarkers to help identify those most likely to respond to immunotherapy.

Other challenges involve clarifying the role of immunotherapy for the subset of patients with MSI-L disease, which represents up to 95% of all CRC cases.[30] Response to immunotherapy in this MSI-L group has been inconsistent and needs further study.

ICI therapy is also being explored in non-stage IV cancers. For example, the phase 3 ATOMIC trial is assessing the addition of the anti–PD-L1 monoclonal antibody atezolizumab to adjuvant FOLFOX (fluorouracil, leucovorin and oxaliplatin) chemotherapy in dMMR/MSI-H, stage III colon cancer.[31]

Additionally, the COMMIT trial is currently recruiting patients with dMMR/MSI-H mCRC to evaluate the combination of FOLFOX, bevacizumab and atezolizumab compared to atezolizumab monotherapy in first-line treatment.[32]

Future directions in managing CRC within the realm of immunotherapy may include cancer vaccines, adoptive cell transfer technology and bispecific monoclonal antibodies. Currently, 70 trials result on **clinicaltrials.gov** when the search terms "colorectal cancer" and "immunotherapy" are used.[33]

Indeed, new agents, combinations, and modalities are on the horizon and may soon find their way into standard-of-care practice.

CONCLUSION

For patients with dMMR/MSI-H mCRC, first-line use of ICIs is preferred over chemotherapy due to its improved durability of response, better safety profile, and improved quality of life. Trials are currently underway to further clarify the role of immunotherapy in CRC.

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FDA APPROVALS FOR Q4 2020 & Q1 2021

By Derek Gyori, PharmD, BCOP

During Q4 2020 and Q1 2021, the U.S. Food & Drug Administration (FDA) approved nine oral oncology agents through Feb. 25, 2021.

In the charts 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.

▲ **Derek Gyori**, PharmD, BCOP, is a Clinical Assistant Lecturer at the University of Toledo College of Pharmacy and Pharmaceutical Sciences and a Clinical Pharmacist Specialist at the Eleanor N. Dana Cancer Center at the University of Toledo Medical Center.

Drug	Approval Date	Indication & Dosing	Clinical Trial Outcomes	Clinical Trial Adverse Effects	Clinical Pearls
Onureg™ (azacitadine)[1-3]	9/1/2020+	Acute Myeloid Leukemia maintenance therapy: 300 mg once daily on days 1 to 14 of a 28-day treatment cycle Initiation of oral therapy if complete remission occurs following induction therapy and unable to complete intensive curative therapy	**QUAZAR TRIAL** *Randomization in a 1:1 ratio (azacitadine or placebo)* • Median Overall Survival (OS): Onureg 24.7 months versus 14.8 months in placebo (HR 0.69; 95% CI: 0.55 to 0.86; p=0.0009) • Median Relapse-Free Survival (RFS): 10.2 months for Onureg and 4.8 months for placebo, P<0.001	≥ 10%: nausea, vomiting, diarrhea, fatigue/asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness and pain in extremities	Taken with or without food at the same time each day If ANC is <500/mm^3 prior to the start of a cycle, delay the treatment cycle until ANC is ≥500/mm^3 During the first two cycles, administer an antiemetic 30 minutes prior to each dose; antiemetic prophylaxis may be omitted after two cycles if there has been no nausea and vomiting
Gavreto™ (pralsetinib)[1,4]	9/4/2020+ 12/1/2020*	Metastatic RET-fusion positive Non-Small Cell Lung Cancer: 400 mg by mouth once daily until disease progression or unacceptable toxicity Advanced or Metastatic RET-mutant medullary thyroid cancer (MTC)*: 400 mg by mouth once daily until disease until disease progression or unacceptable toxicity	**ARROW (NSCLC) TRIAL** *Open-label cohort study* Previously treated (N= 87) • Objective Response Rate (ORR): 57% (95% CI: 46% to 68%) • 80% of patients had responses longer than six months Treatment-naïve (N= 27) • ORR: 70 % (95% CI: 50%-86%) • 58% of patients had responses longer than six months **ARROW (MTC) TRIAL** Previously treated (N= 55) • Objective Response Rate (ORR): 60% (95%) • CI: 46%-73%) • 79% of patients had responses longer than six months Treatment-naïve (N= 29) • ORR: 66% (95% CI: 46% to 2%) • 84% of patients had responses longer than six months	≥25%: increased aspartate aminotransferase (AST), decreased hemoglobin, decreased lymphocytes, decreased neutrophils, increased alanine aminotransferase (ALT), increased creatinine, increased alkaline phosphatase, fatigue, constipation, musculoskeletal pain, decreased calcium, hypertension, decreased sodium, decreased phosphate and decreased platelets	Take on an empty stomach (no food for at least two hours before and at least one hour after taking) Hold five days prior to elective procedure Available as a 100 mg capsule

Drug	Approval Date	Indication & Dosing	Clinical Trial Outcomes	Clinical Trial Adverse Effects	Clinical Pearls
Venclexta® (venetoclax)[1,5-9]	10/16/2020*	Newly diagnosed acute myeloid leukemia in adults 75 years or older: Dose based on agent being used in combination with Azacitadine or Decitabine: Day 1: 100 mg daily Day 2: 200 mg daily Day 3 and beyond : 400 mg daily LDAC: Day 1: 100 mg daily Day 2: 200 mg daily Day 3: 300 mg daily Day 4 and beyond: 600 mg daily	**VIALE-A TRIAL** *Randomized in a 2:1 Ratio* Venetoclax + Azacitadine or Azacitadine Alone • Median Overall Survival (OS): • Venetoclax plus azacitidine — 14.7 months (95% CI: 11.9 to 18.7) • Azacitadine — 9.6 months (95% CI: 7.4, 12.7) • HR 0.66; 95% CI: 0.52 to 0.85; p<0.001 **VIALE-C TRIAL** *Randomized in a 2:1 Ratio* • Venetoclax plus LDAC did not significantly improve OS versus placebo plus LDAC (HR 0.75; 95% CI 0.52 to 1.07; p=0.114) • Complete Response (CR): Venetoclax plus LDAC — 27% (95% CI: 20% to 35%) • LDAC — 7.4% (95% CI: 2.4%, 16%)	≥ 30%: nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, musculoskeletal pain, dizziness, cough, oropharyngeal pain and hypotension	Taken with a low-fat meal and water at the same time each day Assess risk for tumor lysis syndrome and administer appropriate hydration or anti- hyperuricemic agents. Available as 10 mg, 50 mg, and 100 mg tablet
Xpovio® (selinexor)[1,10-11]	12/18/2020*	Relapsed or refractory multiple myeloma who have received at least one prior therapy: 100 mg once weekly on day 1 of each week (incombination with bortezomib and dexamethasone) until disease progression or unacceptable toxicity	**BOSTON TRIAL** *Randomization in a 1:1 ratio (SVd vs Vd)* • Progression-Free Survival (PFS): SVd — 13.9 months (95% CI: 11.7 to NE) vs. Vd — 9.5 months (95% CI: 7.6 to 10.8) • Estimated Hazard Ratio (HR): 0.70; 95% CI: 0.53 to 0.93	≥20%: nausea, fatigue, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection decreased weight, cataract and vomiting	Take with a full glass of water on the scheduled day and at approximately the same time Antiemetics are recommended to prevent nausea and vomiting Available as 20 mg tablets in therapy packs
Orgovyx® (relugolix)[1,12-13]	12/18/2020+	Advanced prostate cancer: 360 mg on day 1 followed by 120 mg daily thereafter	**HERO TRIAL** *Randomization in a 2:1 ratio (relugolix to leuprolide)* Sustained testosterone suppression below castrate levels (<50 ng/dL) from day 29 through 48 weeks: • Relugolix: 96.78% • Leuprolide: 88.8% Relugolix was found to be noninferior based on between group difference (between-group difference, 7.9 percentage points; 95% CI, 4.1 to 11.8)	≥10%: hot flush, musculoskeletal pain, fatigue, diarrhea and constipation Lab abnormalities ≥ 15%: increased glucose, triglycerides, alanine aminotransferase and aspartate aminotransferase	With or without food Used in patients with recurrence after surgery, radiation, or newly diagnosed castration-sensitive advanced prostate cancer Available as 120 mg tablet Mean drop in testosterone below 50 was seen on day 4

Drug	Approval Date	Indication & Dosing	Clinical Trial Outcomes	Clinical Trial Adverse Effects	Clinical Pearls
Tagrisso® (osimertinib)[1,14-15]	12/18/2020*	EGFR exon 19 deletion- or exon 21 L858R mutation-positive NSCLC adjuvant therapy: 80 mg once daily until disease progression or unacceptable tolerability for up to three years	**ADAURA TRIAL** *Randomization in a 1:1 ratio (osimertinib or placebo)* • Disease-Free Survival (DFS): Median DFS not reached in patients on osimertinib; 19.6 months (16.6 to 24.5) on the placebo arm (HR 0.17 95% CI: 0.12 to 0.23; <0.0001) • OS data is immature at this time	>20%: lymphopenia, leukopenia, thrombocytopenia, diarrhea, anemia, rash, musculoskeletal pain, nail toxicity, neutropenia, dry skin, stomatitis, fatigue and cough	Stage IB to IIIA Taken with or without food Adjuvant therapy for up to three years
Xalkori® (crizotinib)[1,16-18]	1/14/2021*	Relapsed/refractory ALK-positive systemic anaplastic large cell lymphoma (ALCL) for patients ≤21 years of age: 280 mg/m^2 twice daily until disease progression or unacceptable toxicity	**STUDY ADVL0912** *Single-arm open-label trial* (N=26) • Objective Response Rate (ORR): 88% (95% CI: 71 to 96) • CR Rate: 81% • Duration of Response (DoR): 39% for at least six months, 22% for at least 12 months	Ocular toxicity occurred in 65% of patients with ALCL, gastrointestinal toxicity occurred in 92%, and serious adverse reactions (mostly neutropenia or infection) occurred in 35% of subjects ≥35%: diarrhea, vomiting, nausea, vision disorder, headache, musculoskeletal pain, stomatitis, fatigue, decreased appetite, pyrexia, abdominal pain, cough and pruritus	Taken with or without food Antiemetics are recommended to prevent nausea and vomiting Avoid grapefruit and grapefruit juice
Tepmetko® (tepotinib)[1,19-20]	2/3/2021+	MET exon 14 skipping alteration Metastatic NSCLC: 450 mg by mouth once daily until progression or unacceptable toxicity	**VISION TRIAL** *Open-label Multicohort Study* (N=152) **Treatment-naïve** (N=69) • ORR: 43% (95% CI: 32% to 56%) • DoR: 10.8 months (95% CI: 6.9 to not estimable) **Treatment-experienced** (N=83) • ORR: 43% (95% CI: 33% to 55%) • DoR: 11.1 months (95% CI: 9.5 to 18.5)	≥20%: edema, fatigue, nausea, diarrhea, musculoskeletal pain and dyspnea Tepotinib can also cause interstitial lung disease, hepatotoxicity and embryo-fetal toxicity	Taken with food Available as a 225 mg tablet
Ukoniq™ (umbralisib)[1,21]	2/5/2021+	Relapsed or refractory marginal zone lymphoma: 800 mg by mouth once daily until disease progression or toxicity Relapsed or refractory follicular lymphoma: 800 mg by mouth once daily until disease progression or toxicity	**Marginal zone lymphoma** (N=69) • ORR: 49% • (95% CI: 37.0 to 61.6) • CR: 16% • DoR: Not Reached (95% CI: 9.3 to NE) **Follicular lymphoma** (N=117) • ORR: 43% • (95% CI: 33.6 to 52.2) • CR: 3% • DoR: 11.1 months (95% CI: 8.3 to 16.4)	≥15%: increased creatinine, diarrhea-colitis, fatigue, nausea, neutropenia, transaminase elevation, musculoskeletal pain, anemia, thrombocytopenia, upper respiratory tract infection, vomiting, abdominal pain, decreased appetite and rash	Taken with food at the same time each day Administer P. jirovecii pneumonia (PCP) prophylaxis during therapy; consider antiviral prophylaxis to prevent cytomegalovirus (CMV) infection, including CMV reactivation Available as 200 mg tablets

FDA APPROVALS

CONTINUED FROM PREVIOUS PAGE

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A UNIQUE EXPERIENCE IN UNPRECEDENTED TIMES

By Tahsin Imam & Raisa Nishat

As members of the inagural pharmacy program at Binghamton University School of Pharmacy and Pharmaceutical Sciences, we've been through a unique experience enriched with an excellent opportunity to help shape the program to what it is today.

Tahsin Imam

Raisa Nishat

With only one available slot for completing a non-patient care-related advanced pharmacy practice experience (APPE), it was difficult to decide upon what the most valuable experience would be.

As a new program, there weren't many options available in terms of unique APPE rotations. Especially with the COVID-19 pandemic, many of our APPE sites canceled their rotations due to safety concerns.

Fortunately, Binghamton was able to establish a relationship with NCODA to take APPE students. This rotation worked out perfectly for both of us, given our interests in pursuing a non-traditional route within the pharmacy field.

Neither of us knew much about NCODA prior to starting. However, thanks to the assignments we were given about what NCODA is and what makes it unique, we soon came to realize the tremendous value NCODA brings in optimizing health care outcomes for cancer patients.

Our first APPE assignment was to deliver an elevator speech about what NCODA is and what makes it unique. This gave us a thorough understanding of NCODA's Mission, vision, guiding values, resources and initiatives.

We presented on medically integrated dispensing (MID). Through this, we learned about the benefits of having an MID team involved in the care of cancer patients.

The experience not only taught us more about oncology and NCODA, it also honed our presentation skills. We also presented on a variety of topics, including:

▲ **Financial assistance programs available to oncology patients:** Tahsin presented on AFINITOR® (everolimus). Raisa presented on Arimidex (anastrazole). The project required extensive research via the NCODA and pharmaceutical manufacturer websites to obtain relevant information.

▲ **Molecules on the pipeline:** Raisa presented on LARTRUVO™ (olaratumab) and Tahsin on IBRANCE® (palbocicilb). The project allowed us to grasp the competitive landscape of pipeline oncolytics.

▲ **Research on cardiovascular considerations in cancer:** Our final project involved a research paper and a 45-minute presentation to several members of the NCODA team. Our topic choice was unanimous since we both also have an interest in cardiology.

Our other APPE projects involved participating in weekly oncology discussions, reviewing Positive Quality Interventions (PQIs) for accuracy, and discussing ORGOVYX™ (relugolix) at an Oncology Pharmacy Technician Association (OPTA) meeting.

We would like to thank NCODA for giving us the opportunity to be involved with such an innovative and unique APPE experience. Given the issues that we've all faced during the global pandemic, it is amazing to be able to engage in a robust learning experience remotely which definitely contributed to our professional development.

This non-traditional APPE taught us more about how versatile the PharmD truly is, and we will surely convey our experience to future cohorts within our school.

▲ **Tahsin Imam** and **Raisa Nishat** are PharmD Candidates (Class of 2021) at Binghamton University School of Pharmacy and Pharmaceutical Sciences in Johnson City, New York.

THE NCODA APPE IN ONCOLOGY

A 4- to 6-week Advanced Pharmacy Practice Experience offered year-round

Current affiliations

- Albany College of Pharmacy & Health Sciences
- Binghamton University
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- Regis University
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- Shenandoah University
- The Ohio State University
- The University of Rhode Island
- University of Arizona
- University of Minnesota
- University of South Florida

Scan QR code to learn more about NCODA's APPE rotation

NCODA PROFESSIONAL STUDENT ORGANIZATION

Empowering Your Education

NCODA is collaborating with universities and colleges worldwide to offer pharmacy students membership into a professional organization that is centered on advancing NCODA's Mission of improving patient care.

The **NCODA Professional Student Organization** was established for students interested in oncology pharmacy, association management & industry leadership.

BENEFITS

- Opportunities to attend NCODA international meetings & present research
- Increased networking opportunities with clinical & industry professionals
- Participation in community service events through NCODA-led initiatives & partnerships
- Opportunities to help create new educational materials that will aid cancer patients worldwide

ESTABLISHED CHAPTERS

- Albany College of Pharmacy and Health Sciences (Albany, NY)
- Auburn University (Auburn, AL)
- Belmont University College of Pharmacy (Nashville, TN)
- Binghamton University (Johnson City, NY)
- Howard University (Washington DC)
- Lake Erie College of Osteopathic Medicine (Bradenton, FL)
- Massachusetts College of Pharmacy and Health Sciences University (Boston, MA)
- Midwestern University (Downers Grove, IL)
- Nova Southeastern University (Davie, FL)
- Oregon State University College of Pharmacy (Corvallis, OR)
- Purdue University (West Lafayette, IN)
- Shenandoah University Bernard J Dunn School of Pharmacy (Winchester, VA)
- South University (Columbia, SC & Savannah, GA)
- Temple University (Philadelphia, PA)
- Texas Tech University (Abilene, Amarillo, Dallas, Lubbock, TX)
- University of Florida College of Pharmacy (Gainesville, Jacksonville, Orlando, FL)
- University of Iowa (Iowa City, IA)
- University of Minnesota (Duluth, Minneapolis, MN)
- University of Missouri-Kansas City (Kansas City, MO)
- University of New Mexico (Albuquerque, NM)
- University of North Texas (Fort Worth, TX)
- University of Rhode Island (Kingston, RI)
- University of Toledo (Toledo, OH)
- University of Toronto (Toronto, Canada)
- University of Utah College of Pharmacy (Salt Lake City, UT)
- Washington State University (Spokane, WA)
- Wingate University (Wingate, NC)

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**

GAS CARDS HELP DRIVE CANCER SUPPORT

By Heather Young, BS

The Professional Student Organization chapter at South University School of Pharmacy (SUSOP) in Columbia, South Carolina, has found a unique way to drive home our mission of community outreach to those in need. And it's been a real gas!

In February 2020, our PSO chapter met with the South Carolina Oncology Associates (SCOA) *Supporting Sisters*, a support group for women diagnosed with cancer, undergoing cancer treatment or currently in remission, or who are long-term survivors of cancer. Its main objective is to provide support to help these women cope with the array of emotions and fears that come with cancer treatment.

During the meeting, students heard personal experiences and stories from group members. Many women dealt with the same burdens when first diagnosed or about to begin treatment. But one issue stood out: money.

The financial aspect of cancer treatment goes beyond just the cost of the medication and testing itself. Many patients are unemployed or facing significant pay cuts, forcing them to seek outside help from family and friends to alleviate the cost of care. Those without such support have to push through the pain, exhaustion and emotional toll of cancer in order to provide for themselves.

One member told us that she and many other cancer patients were even willing to engage in drug trials that had no proven efficacy at the time of trial just to obtain treatment as soon as possible and to avoid the costs.

Transportation was another major issue. Finding a ride to chemotherapy and regularly scheduled appointments was a major and costly setback for many of the patients. Because of this challenge, our PSO chapter decided that pooling our resources to obtain gas cards was the best way we could help *Supporting Sisters*.

During the meeting, it was also brought to our attention that patients travel from all different parts of South Carolina and North Carolina for treatment at SCOA.

Yet not all have the finances or support system to continue getting the treatment at the oncology clinic of their choice.

Because of this situation, PSO members Tiffiny Sandrapaty, Ly Tran, Alisha Blackman, Emily Barrett, Lilian Ndianefo, Armelle Njinguet, Shivani Patel, Nishi Patel and I launched the group's new "Sponsor a Gas Card" initiative on June 17, 2020, for patients in need.

Our PSO sent an email with a link allowing voluntary donations of at least $10 to the entire student body at SUSOP. Donors also had the option to include a personal message with words of encouragement handwritten by members. This message would be included along with the gas card.

Gas cards were purchased from Circle K, the most abundant and accessible gas station chain in the region. Patients who receive the cards can use them themselves or provide them to those who are driving them to appointments.

In July 2020, we raised a total of $680, allowing us to sponsor 60 gas cards for those in need. This is only the beginning and we plan to continue this initiative.

Our meeting at SCOA was an astounding opportunity for our NCODA chapter and gave us the opportunity to contribute to patients who need financial assistance while battling cancer.

▲ **Heather Young**, BS, is a PharmD/MBA Candidate at South University School of Pharmacy in Columbia, South Carolina, and president of its NCODA Professional Student Organization chapter.

A PARTNERSHIP IN EDUCATION

COLLABORATIVE EFFORT BETWEEN **GENENTECH** AND **NCODA** FOCUSES ON FUTURE HEALTHCARE PROFESSIONALS

A collaborative effort between NCODA and the biotechnology company Genentech is helping educate the next wave of healthcare professionals.

Genentech, a longtime partner of NCODA's, has agreed to provide both speakers and content for a portion of NCODA's Student Education Talks (SETs) webinars throughout 2021.

"As a company, we have invested a lot of time and energy developing educational resources and building expertise across our teams," Genentech Senior Marketing Manager Doug Beeman, PharmD, said. "It is terrific working with NCODA to provide a forum where that information and expertise can be shared with those who may most benefit from it."

Doug Beeman

Genentech, a San Francisco-based biotechnology company, started featuring 20-minute presentations during the SETs webinars in 2021.

Peter Finlayson

"NCODA's vision is very much aligned with Genentech's," explained Peter Finlayson, National Account Executive for the company. "We are grateful to be able to work with NCODA to help bring this vision to life in pharmacy schools across the country."

Because Genentech studies disease states and develops groundbreaking pharmaceuticals to treat them, the company is in a unique position.

In January, for instance, a Genentech team member presented on "Emerging Perspectives in Breast Cancer." In February, Genentech followed up with an update on TECENTRIQ® (atezolizumab), the company's cancer immunotherapy treatment for triple negative breast cancer.

Lina Lazore

"It is exciting to have found a way to work with local pharmacy schools and a national organization like NCODA in support of better patient care," said Lina Lazore, Therapeutic Area Manager with Genentech's NY Ecosystem.

The Professional Student Organization (PSO) SETs webinars, which NCODA began hosting at the end of 2019, are hour-long educational programs held at 8 p.m. Eastern on the final Wednesday of each month. Talks focus on oncology topics meant to help students gain more exposure, education and experience in the field of oncology.

Two to three different topics are covered each month. SETs webinars take place in a Zoom format. Each webinar is recorded and uploaded to NCODA's website for students to watch at a later time.

Past sessions have focused on a variety of topics, including renal cell carcinoma, brain cancer epidemiology, antineoplastics, lymphoma and cervical cancer.

Students have the opportunity to present on a clinical topic of their choice if they wish. Students also are encouraged to ask topical questions during each webinar.

The series has proved to be quite popular with students, and typically numerous PSO members attend each session.

SCAN QR CODE BELOW TO VIEW SETs WEBINARS

"SETs provide an amazing opportunity to learn from both peers and experts about the field of oncology," said Jonathan Rivera, a PharmD candidate at The University of North Texas Health Science Center, and Vice President of the NCODA Professional Student Organization Chapter there.

"Every session provides great insight into oncology pharmacy and I am fortunate to be a part of this organization, especially since these unique experiences will help me become a better pharmacist in the future.," he said.

"SETs provide an amazing opportunity to learn from both peers and experts about the field of oncology."

Jonathan Rivera, PharmD Candidate
The University of North Texas Health Science Center

NCODA FORMS LEGISLATIVE & POLICY ADVISORY COMMITTEE

By Kevin Scorsone

Coping with the everyday challenges of oncology can be a daunting task for healthcare providers, a task made even more complicated by state and federal legislation that sometimes unwittingly inhibits patient care.

For that reason, NCODA recently created its Legislative & Policy Advisory Committee (LPAC) to provide cancer patients and the practices that serve them with a voice in the halls of the government.

Committee members include a diverse group of well-informed physicians, pharmacists, legislative experts and a nurse, all passionately determined to serve the greater good for patients battling cancer.

Serving on the newly formed Legislative & Policy Advisory Committee are Chair Nancy Egerton, PharmD, BCOP, Director of Pharmacy | New York Oncology Hematology; Holly Books, BSN, RN, OCN, Executive Director of Operational Excellence | Texas Oncology; Barry Brooks, MD, Medical Director of Oral Oncolytics | Texas Oncology; Eric Dallara, RPh, Director of Specialty Practice Solutions Northeast | AmerisourceBergen Specialty Group, Inc.; Ben Jones, Vice President of Government Relations & Public Policy | McKesson Specialty Health & The US Oncology Network; Jessica Nagro, MPA, Senior Director of Advocacy and Strategic Alliances | PhRMA; and Wayne Ormsby, MD, Medical Oncologist/Hematologist | Utah Cancer Specialists.

SCAN QR CODE TO VIEW COPAY ACCUMULATOR RESOURCES

The committee currently meets once a month, supplemented by behind-the-scenes work via Zoom meetings, phone calls and weekly updates.

Although still in its infancy, the committee already is making an impact. The group has written statements on flaws in the most Favored Nation Model, Pharmacy Benefit Managers and Any Willing Provider systems. NCODA believes the negative similarities between all of these systems is the hindrance placed on patients and the healthcare professionals who are treating cancers.

LPAC's Mission as a committee is clear: *patients first, always.* It rejects the obvious, although sometimes buried reality, that well-intentioned government policies can sometimes hinder healthcare for cancer patients and their providers. In such cases, the committee will serve as a voice of reform.

NCODA also has been at the forefront of the Copay Accumulator issue, which has become a growing source of financial toxicity for many cancer patients on private insurance. The committee is currently working on building statements pertaining to the need for relief.

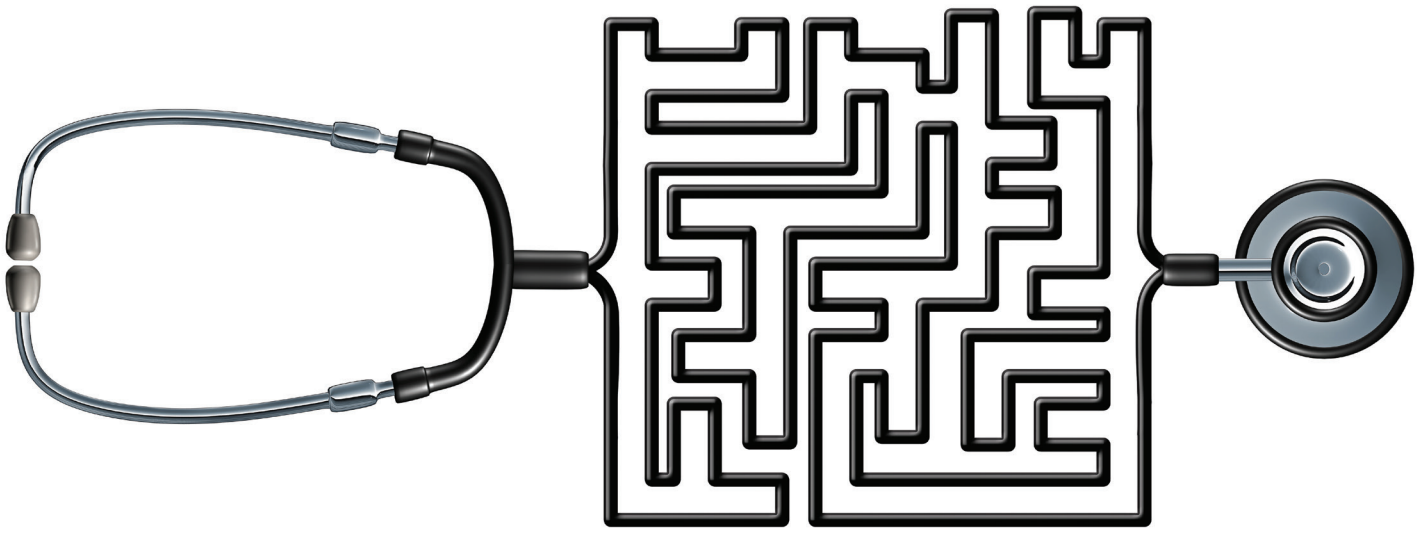
The committee values the role it can play by producing factual information that helps NCODA members understand the issues that are facing them and their patients.

LPAC is not a political or lobbying group; it is focused on advocacy and education without calling out or disparaging lawmakers. The committee hopes to consult, educate and express NCODA's views and opinions on the effects of policy decisions.

The committee plans to continue to release statements on pressing issues. It also will conduct legislative updates updates on National Monthly Webinars and work closely with NCODA's Professional Student Organization (PSO) chapters.

The committee's ultimate goal is for NCODA to become the primary organization for consultation, advice and educational updates for state and federal oncology legislation throughout the United States.

Those interested in assisting the committee in its Mission can contact Kevin Scorsone, Associate Manager of Patient Centered Initiatives, at kevin.scorsone@ncoda.org.



THE DIR LABYRINTH: HOW CONFLICTING ADHERENCE RULES HAMPER MID CLINICS

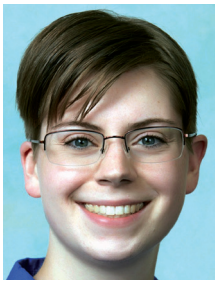
By Brianna Hassett & Darrell Willyard, PharmD

Direct and Indirect Remuneration (DIR) adherence fees have created a frustrating roadblock for Medically Integrated Dispensing (MID) pharmacies and their Medicare patients.

DIRs were originally created by the Centers for Medicaid & Medicare Services (CMS)[1] along with the initiation of Medicare Part D in 2006. DIRs were initiated in an attempt to determine the actual cost of medications after drug manufacturer kickbacks or other allowances were given to Pharmacy Benefit Managers (PBM).

PBMs have since expanded the definition and use of DIRs to ostensibly promote quality.[2] In reality, this strategy has produced a labyrinth of goals from each PBM that makes it almost impossible for small in-house pharmacies to determine the financial penalties that might be retroactively taken back by the PBMs due to performance standings.[3]

Sometimes the goals of one PBM may directly contradict those of another. For example, one may promote 90-day prescription fills while others may penalize for their use.[3]



Brianna Hassett

Darrell Willyard

Most PBMs provide a unique category for in-house oncology clinics, described as a "specialty component."[4] PBMs often choose to focus on specialty drugs dispensed by in-house pharmacies versus broader criteria used by other retail pharmacies for diabetes and statin usage. The PBM determines what is defined as a specialty drug and the respective adherence rate.

A CLOSER LOOK

Oklahoma Cancer Specialists and Research Institute's clinic-based pharmacy (OCS Pharmacy) currently works under DIRs from seven different PBMs. The pharmacy chose to look at specialty drugs and adherence rates from one of the largest PBMs, which will be referred to as XYZ PBM.[4]

Specialty adherence rates reported for the insurance groups XYZ represents were 82.5%, 87%, 89.6%, 89.75% and 92.54%.[4] The adherence rates reported by XYZ do not correspond to rates in previous retroactive reviews performed by the pharmacy, which were between 90% and 94%.[5-6]

XYZ accounted for 26% of the DIR fees recouped from OCS Pharmacy in 2019, making it a good candidate for review.[7]

XYZ provides the pharmacy with an extensive trimester report on the pharmacy's performance, a report both long and confusing to understand. The most recent report was broken down into the five major insurance groups represented by XYZ, and their DIR goals.[4] The total report was 13 pages in length.

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DIR FEES

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INAPPROPRIATE ADHERENCE GUIDELINES

Adherence for specialty drugs was weighted from a low of 25% to a high of 85% (i.e., 25-85% of the final score, which determines the DIR fee to be retroactively taken back, based on adherence to specialty drugs.[4] Therefore, it would make sense that improving adherence would have the largest and most beneficial impact on these trimester pharmacy ratings.

Adherence DIR fees are problematic in this setting because adverse events experienced by oncology medications often call for a temporary discontinuation of therapy until the patient's status returns to an acceptable level. The period during which the drug is held could be perceived by PBMs as a lack of adherence. This may cause the performance rating to decrease and DIR fees to potentially increase.

Cancer drugs are among the top 20 most expensive medications dispensed in the United States and oncology pharmacies often work on very slim margins for brand-name medications.[8] Small changes to the bottom line may cause a large difference in profit margins, especially if part of the expected profit is retroactively taken back by DIR fees imposed by PBMs.[3]

The four most costly oral medications dispensed by OCS Pharmacy are Imbruvica (ibrutinib), Revlimid (lenalidamide), Ibrance (palbociclib) and Zejula (niraparib), which account for 57% of the total drug budget during an average month.[9]

These four medications were investigated to show how their side effects and potential to be held could affect adherence ratings. Information showing the occurrence of each medication's common side effects and how they impact consistency of therapy follows below.

IBRUTINIB

Ibrutinib tends to cause hematologic effects such as neutropenia and thrombocytopenia in mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL).[10] If these adverse events (AE) occur as a grade 3 or greater (neutrophils <1000/mm3 or platelets <50,000/mm3),[11] the medication is held until it drops to a grade ≤ 1 (neutrophils 1500/mm3 to > Lower Limit of Normal (LLN) or platelets 75,000/mm3 to > LLN)[11] and the medication is restarted at the same dose.[10] The dose will be decreased with each following occurrence, unless it has occurred four times, at which point the medication will be discontinued.[10]

TABLE 1: Ibrutinib Grade ¾ AE in MCL & CLL[10]

Adverse Event	Percent of Grade 3 or 4 in MCL	Percent of Grade 3 or 4 in CLL
Neutropenia	29%	26%
Thrombocytopenia	17%	12%

As shown in the trial in **Table 1**, up to 46%* of MCL patients and up to 38%* of CLL patients qualified to have their medication discontinued for a week up to a month. Therefore, it would be expected OCS Pharmacy would experience similar effects and have this percentage of patients on ibrutinib being held at some point during their therapy. This could decrease the pharmacy's specialty adherence rate despite it being a prescribed action to this drug's side effects.

LENALIDOMIDE

Lenalidomide is most commonly used for multiple myeloma (MM), and can cause hematologic toxicities such as neutropenia and thrombocytopenia.[12] When platelets drop below 30,000/mm3 or neutrophils drop below 1,000/mm3, the medication is held until the levels return to a number higher than those aforementioned thresholds.[12]

TABLE 2: Lenalidomide Occurrence of AE[12]

Adverse Event	Percentage of Patients Held on Dosage
Neutropenia	28%
Thrombocytopenia	8%

As shown in **Table 2**, during this trial, up to 36%* of patients qualified to have their medication held during their therapy. This would translate to more than a third of OCS Pharmacy patients on lenalidomide potentially being held at some point during their therapy who should not be counted as non-adherence.

** Study did not indicate patients who might have qualified for both events simultaneously.*

PALBOCICLIB

Palbociclib is used for the treatment of advanced or metastatic breast cancer.[13] The hematologic toxicities that commonly occur on this medication are neutropenia and leukopenia.[13] The numbers below reflect the occurrence of neutropenia and leukopenia with the use of palbociclib in combination with letrozole, which is typical for this medication.

TABLE 3: Palbociclib/Letrozole Grade ¾ AE[13]

Adverse Event	Grade 3†	Grade 4‡
Neutropenia	56%	10%
Leukopenia	24%	1%

† Grade 3:11 neutrophils <1,000-500/mm3 or WBC <2,000-1,000/mm3

‡ Grade 4:11 neutrophils <500/mm3 or WBC <1,000/mm3

As shown in **Table 3**, 66% of patients in this trial experienced neutropenia and 25% of patients experienced leukopenia. These patients qualified to have their medication held during their therapy. A similar number of OCS Pharmacy patients could qualify to have their medication held at some point during therapy which could decrease the pharmacy's adherence score.

NIRAPARIB

Niraparib is used as a maintenance medication for advanced or recurrent ovarian cancer and typically causes neutropenia and thrombocytopenia.[14] When either the neutrophil count is <1000/mm3 or platelet count is <100,000/mm3, the medication is held for 28 days and adjusted accordingly.[14]

TABLE 4: Niraparib Grade3/4AE[14]

Adverse Event	Percentage of Patients Held on Dosage For Grade 3/4
Neutropenia	21%
Thrombocytopenia	39%

• Grade 3:11 neutrophils <1000-500/mm3 or platelets <50,000-25,000/mm3

• Grade 4:11 neutrophils <500/mm3 or platelets <25,000/mm3

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DIR FEES

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Table 4 shows a trial where up to 60%* of niraparib patients qualified to have their medication held during therapy. This would translate to OCS Pharmacy potentially having 60% of patients being held on their medication at some point during therapy which could affect the pharmacy's adherence score.

IN SUMMARY

During the month of July, OCS Pharmacy dispensed specialty medications to 310 patients as seen in **Table 5** (this would vary according to each insurance's definition of specialty). Of that total, 145 patients (46.8%) were on the top four oral medications discussed above and would potentially have their therapies held due to the side effects noted. These examples do not represent all the specialty medications that could cause temporary discontinuations during therapy.

The adherence component is assessed based on the pharmacy's medication possession ratio (MPR), which compares a prescription's written day-supply to the medication day-supply actually dispensed. Previous adherence studies performed by the pharmacy looked in-depth at patient adherence and gave allowances for medications that were held by the physician.[5-6] The disparity between the pharmacy's adherence rate and those reported by the PBM could largely be attributed to the PBM not accounting for the breaks in therapy required for oncology drug side effects during normal treatment.

OCS Pharmacy did not have the means to track each therapy and definitively determine which therapies were held due to side effects. Hopefully, the numbers from the manufacturers indicate that a portion of therapies for their products should be routinely held for side effects.

In-clinic pharmacies are perfectly situated to identify when a patient's therapy should be held for side effects through the performance of medically integrated dispensing.

However, the authors could not find any metrics or documentation processes in place to alert the PBMs that these temporary discontinuations are an important part of managing the success of patient's therapy versus a lack of patient adherence.

These actions should be recognized as appropriate therapy management but currently appear to result in increased DIR fees by the PBMs. Hopefully, this article helps others in identifying possible improper penalizations on oral adherence that are due to justifiable holds in therapy.

TABLE 5: SPECIALTY MEDICATION DISPENSED AT OCS PHARMACY JULY, 2020 (N=310)

	Ibrutinib	Lenalidomide	Palbociclib	Niraparib
# of Patients	50	38	44	13
% of Specialty	50/310 = 16.13%	38/310 = 12.25%	44/310 = 14.19%	13/310 = 4.19%

▲ **Brianna Hassett** is a PharmD Candidate (class of 2021) at Southwestern Oklahoma State University College of Pharmacy. **Darrell Willyard**, PharmD is the Director of Pharmacy Services at Oklahoma Cancer Specialists and Research Institute in Tulsa, Oklahoma.

Hopefully, this article helps others in identifying possible improper penalizations on oral adherence that are due to justifiable holds in therapy.

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ECHELON-1 TRIAL

5-YEAR DATA UPDATE

STAGE III/IV cHL

LASTING REMISSION THE FIRST TIME AROUND

Consistent benefit at 5 years vs ABVD

Get a snapshot of the 5-year data on the following pages

- Primary endpoint: modified PFS per IRF—HR: 0.77 (95% CI: 0.60, 0.98); $P = 0.035$; median follow-up: 24.6 months[1]
- Prespecified exploratory endpoint: PFS per INV at 5 years—HR: 0.68 (95% CI: 0.53, 0.87); not in approved labeling; supportive clinical information only[2]

ECHELON-1 trial design: A randomized, open-label trial of ADCETRIS+AVD vs ABVD in 1334 adult patients with newly diagnosed Stage III/IV cHL. Primary endpoint was modified PFS per IRF, defined as progression, death due to any cause, or receipt of additional anticancer therapy for patients not in complete remission after first-line therapy. Key secondary endpoint was OS. Prespecified exploratory endpoint was 5-year PFS per INV, defined as progression or death due to any cause.[2,3]

Indication

ADCETRIS is indicated for the treatment of adult patients with previously untreated Stage III/IV classical Hodgkin lymphoma (cHL) in combination with doxorubicin, vinblastine, and dacarbazine.

Select Important Safety Information

BOXED WARNING

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML): JC virus infection resulting in PML and death can occur in ADCETRIS-treated patients.

Contraindication

ADCETRIS concomitant with bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

Warnings and Precautions

- Peripheral neuropathy (PN): ADCETRIS causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.
- Anaphylaxis and infusion reactions: Infusion-related reactions (IRR), including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an IRR occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages. Full Prescribing Information is available at adcetrispro.com

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AVD = doxorubicin, vinblastine, dacarbazine; CI = confidence interval; HR = hazard ratio; INV = investigator; IRF = independent review facility; OS = overall survival; PFS = progression-free survival.

CD30-DIRECTED

ADCETRIS®

brentuximab vedotin | for injection

ECHELON-1 PRIMARY ENDPOINT

A+AVD showed superior efficacy over ABVD at 2 years[1]

23% REDUCTION IN EVENT RISK[1]

- Modified PFS per IRF (intent-to-treat population)*
- HR (95% CI): 0.77 (0.60, 0.98); *P* = 0.035; median follow-up: 24.6 months

MOST COMMON AND SERIOUS

adverse reactions with A+AVD in ECHELON-1[1]

- Most common serious adverse reactions: febrile neutropenia (17%), pyrexia (7%), neutropenia (3%), and pneumonia (3%)
- Most common adverse reactions (≥20%): peripheral neuropathy, neutropenia, nausea, constipation, vomiting, fatigue, diarrhea, pyrexia, alopecia, decreased weight, abdominal pain, anemia, and stomatitis

33% REDUCTION

in the need for salvage chemotherapy and transplant[3]

In ECHELON-1, some patients required subsequent therapy:

- Patients requiring salvage chemotherapy: **66 for A+AVD, 99 for ABVD**
- Patients receiving high-dose chemotherapy + HSCT: **36 for A+AVD, 54 for ABVD**

This analysis was evaluated in ECHELON-1 but is not included in the approved product labeling. This analysis was not prespecified. Data are provided as supportive clinical information.

Select Important Safety Information (cont'd)

Warnings and Precautions

- Hematologic toxicities: Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS.

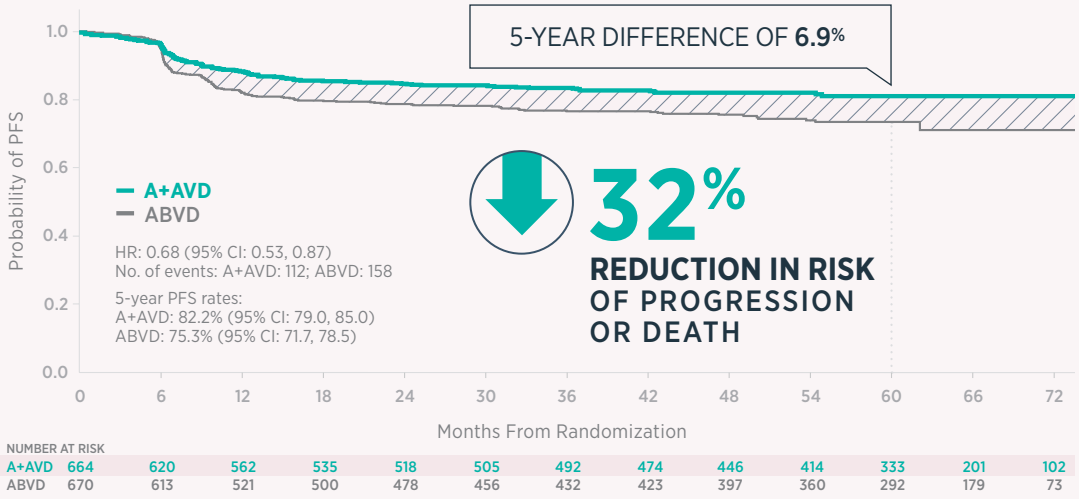
  Administer G-CSF primary prophylaxis beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV cHL or previously untreated PTCL.

  Monitor complete blood counts prior to each ADCETRIS dose. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.
- Serious infections and opportunistic infections: Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in ADCETRIS-treated patients. Closely monitor patients during treatment for bacterial, fungal, or viral infections.
- Tumor lysis syndrome: Closely monitor patients with rapidly proliferating tumor and high tumor burden.
- Increased toxicity in the presence of severe renal impairment: The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Avoid use in patients with severe renal impairment.
- Increased toxicity in the presence of moderate or severe hepatic impairment: The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid use in patients with moderate or severe hepatic impairment.
- Hepatotoxicity: Fatal and serious cases have occurred in ADCETRIS-treated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.
- PML: Fatal cases of JC virus infection resulting in PML have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis in patients with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.
- Pulmonary toxicity: Fatal and serious events of noninfectious pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, have been reported. Monitor patients for signs and symptoms, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.
- Serious dermatologic reactions: Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.
- Gastrointestinal (GI) complications: Fatal and serious cases of acute pancreatitis have been reported. Other fatal and serious GI complications

A+AVD offers the best chance at living relapse-free at 5 years vs ABVD

The 5-year data provided are not contained in the approved product labeling. 5-year PFS per INV was a prespecified exploratory analysis. Data are provided as supportive clinical information.

A+AVD showed an **~7% PFS per INV benefit** over ABVD at 5 years[2]



- OS, a key secondary endpoint, not reached at 5 years†[2]

Discover more data at adcetrispro.com

include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

- Hyperglycemia: Serious cases, such as new-onset hyperglycemia, exacerbation of preexisting diabetes mellitus, and ketoacidosis (including fatal outcomes) have been reported with ADCETRIS. Hyperglycemia occurred more frequently in patients with high body mass index or diabetes. Monitor serum glucose and if hyperglycemia develops, administer anti-hyperglycemic medications as clinically indicated.
- Embryo-fetal toxicity: Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Most Common (≥20% in any study) Adverse Reactions

Peripheral neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, pyrexia, constipation, vomiting, alopecia, decreased weight, abdominal pain, anemia, stomatitis, lymphopenia, and mucositis.

Drug Interactions

Concomitant use of strong CYP3A4 inhibitors or inducers has the potential to affect the exposure to monomethyl auristatin E (MMAE).

Use in Specific Populations

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately and avoid breastfeeding while receiving ADCETRIS.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages. Full Prescribing Information is available at adcetrispro.com

*Patients were randomized 1:1 to A+AVD (n = 664) or ABVD (n = 670) then received treatment on Days 1 and 15 of each 28-day cycle for up to 6 cycles.[1]
†At the time of the modified PFS analysis, an interim OS analysis did not demonstrate a significant difference.[1,3]
A+AVD = ADCETRIS + doxorubicin, vinblastine, dacarbazine; HSCT = hematopoietic stem cell transplantation.

References: 1. ADCETRIS [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc. October 2019. **2.** Straus DJ, Długosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for patients with previously untreated, stage III/IV classical Hodgkin lymphoma: 5-year update of the ECHELON-1 study. Poster presented at: 62nd Annual Meeting of the American Society of Hematology; December 5-8, 2020. **3.** Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med.* 2018;378:331-344.

Seagen®

CD30-DIRECTED
ADCETRIS®
brentuximab vedotin | for injection

ADCETRIS® (brentuximab vedotin) for injection, for intravenous use

Initial U.S. approval: 2011

Brief Summary: see package insert for full prescribing information

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS.

1 INDICATIONS AND USAGE

ADCETRIS is a CD30-directed antibody-drug conjugate indicated for adult patients with previously untreated Stage III/IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

For dosing instructions of combination agents administered with ADCETRIS, see the manufacturer's prescribing information.

Administer ADCETRIS as a 30-minute intravenous infusion.

The recommended dose is 1.2 mg/kg up to a maximum of 120 mg in combination with doxorubicin, vinblastine, and dacarbazine (AVD), administered every 2 weeks until a maximum of 12 doses, disease progression, or unacceptable toxicity. Reduce the dose in patients with mild hepatic impairment (Child-Pugh A) to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks. Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or severe renal impairment (creatinine clearance [CrCL] <30 mL/min). The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

2.2 Recommended Prophylactic Medications

In patients with previously untreated Stage III/IV cHL who are treated with ADCETRIS +AVD, administer G-CSF beginning with Cycle 1.

2.3 Dose Modification

Peripheral Neuropathy: For Grade 2 peripheral neuropathy, reduce dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks. For Grade 3 peripheral neuropathy, hold dosing until improvement to Grade 2 or lower. Restart at 0.9 mg/kg, up to a maximum of 90 mg, every 2 weeks. Consider modifying the dose of other neurotoxic chemotherapy agents. For Grade 4 peripheral neuropathy, discontinue dosing. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

Neutropenia: For Grade 3 or 4 neutropenia, administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis.

4 CONTRAINDICATIONS

ADCETRIS is contraindicated with concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Neuropathy

ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative.

In ECHELON-1 (Study 5), 67% of patients treated with ADCETRIS+AVD experienced any grade of neuropathy. The median time to onset of any grade was 2 months (range, 0-7), of Grade 2 was 3 months (range, 0-6), and of Grade 3 was 4 months (range, <1-7). The median time from onset to resolution or improvement of any grade was 2 months (range, 0-32), of Grade 2 was 3 months (range, 0-28), and of Grade 3 was 4 months (range, 0-32). Of these patients, 43% had complete resolution, 24% had partial improvement (a decrease in severity by one or more grades from worst grade) and 33% had no improvement at the time of their last evaluation. Of the patients with residual neuropathy at the time of their last evaluation (57%), patients had Grade 1 (36%), Grade 2 (16%), Grade 3 (4%), or Grade 4 (<1%) neuropathy.

Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADCETRIS.

5.2 Anaphylaxis and Infusion Reactions

Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCETRIS and administer appropriate medical therapy. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

5.3 Hematologic Toxicities

Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCETRIS.

Start primary prophylaxis with G-CSF beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV cHL.

Monitor complete blood counts prior to each dose of ADCETRIS. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCETRIS doses.

5.4 Serious Infections and Opportunistic Infections

Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Monitor patients closely during treatment for the emergence of possible bacterial, fungal, or viral infections.

5.5 Tumor Lysis Syndrome

Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

5.6 Increased Toxicity in the Presence of Severe Renal Impairment

The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment (CrCL <30 mL/min).

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment

The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

5.8 Hepatotoxicity

Fatal and serious cases of hepatotoxicity have occurred in patients receiving ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin. Cases have occurred after the first dose of ADCETRIS or after ADCETRIS rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

5.9 Progressive Multifocal Leukoencephalopathy

Fatal cases of JC virus infection resulting in PML have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

5.10 Pulmonary Toxicity

Fatal and serious events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), have been reported. Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

5.11 Serious Dermatologic Reactions

Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

5.12 Gastrointestinal Complications

Fatal and serious events of acute pancreatitis have been reported. Other fatal and serious gastrointestinal (GI) complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

5.13 Hyperglycemia

Serious events of hyperglycemia, such as new-onset hyperglycemia, exacerbation of preexisting diabetes mellitus, and ketoacidosis (including fatal outcomes) have been reported in ADCETRIS-treated patients. In studies of ADCETRIS monotherapy, 8% of patients experienced any grade hyperglycemia, with 6% experiencing Grade 3 or 4 hyperglycemia. The median time to onset for any grade or Grade 3 or 4 was 1 month (range 0-10). Hyperglycemia occurred more frequently in patients with high body mass index or diabetes. Monitor serum glucose and if hyperglycemia develops, administer anti-hyperglycemic medications as clinically indicated.

5.14 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADCETRIS in pregnant women. In animal reproduction studies, brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability, and fetal malformations at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every three weeks.

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise a pregnant woman of the potential risk to the fetus.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 most common adverse reactions (≥20%) in combination with AVD were peripheral neuropathy, neutropenia, nausea, constipation, vomiting, fatigue, diarrhea, pyrexia, alopecia, decreased weight, abdominal pain, anemia, and stomatitis.

Previously Untreated Stage III/IV cHL (Study 5: ECHELON-1)

ADCETRIS in combination with AVD was evaluated for the treatment of previously untreated patients with Stage III/IV cHL in a randomized, open-label, multicenter clinical trial of 1334 patients. Patients were randomized to receive up to 6 cycles of ADCETRIS+AVD or ABVD on Days 1 and 15 of each 28-day cycle. The recommended starting dose of ADCETRIS was 1.2 mg/kg intravenously over 30 minutes, administered approximately 1 hour after completion of AVD therapy. A total of 1321 patients received at least one dose of study treatment (662 ADCETRIS+AVD, 659 ABVD). The median number of treatment cycles in each study arm was 6 (range, 1-6); 76% of patients on the ADCETRIS+AVD arm received 12 doses of ADCETRIS.

After 75% of patients had started study treatment, the use of prophylactic G-CSF was recommended with the initiation of treatment for all ADCETRIS+AVD-treated patients, based on the observed rates of neutropenia and febrile neutropenia. Among 579 patients on the ADCETRIS+AVD arm who did not receive G-CSF primary prophylaxis beginning with Cycle 1, 96% experienced neutropenia (21% with Grade 3; 67% with Grade 4), and 21% had febrile neutropenia (14% with Grade 3; 6% with Grade 4). Among 83 patients on the ADCETRIS+AVD arm who received G-CSF primary prophylaxis beginning with Cycle 1, 61% experienced neutropenia (13% with Grade 3; 27% with Grade 4), and 11% experienced febrile neutropenia (8% with Grade 3; 2% with Grade 4).

Serious adverse reactions, regardless of causality, were reported in 43% of ADCETRIS+AVD-treated patients and 27% of ABVD-treated patients. The most common serious adverse reactions in ADCETRIS+AVD-treated patients were febrile neutropenia (17%), pyrexia (7%), neutropenia and pneumonia (3% each).

Adverse reactions that led to dose delays of one or more drugs in more than 5% of ADCETRIS+AVD-treated patients were neutropenia (21%) and febrile neutropenia (8%). Adverse reactions led to treatment discontinuation of one or more drugs in 13% of ADCETRIS+AVD-treated patients. Seven percent of patients treated with ADCETRIS+AVD discontinued due to peripheral neuropathy.

There were 9 on-study deaths among ADCETRIS+AVD-treated patients; 7 were associated with neutropenia, and none of these patients had received G-CSF prior to developing neutropenia.

Table 4: Adverse Reactions Reported in ≥10% of ADCETRIS+AVD-treated Patients in Previously Untreated Stage III/IV cHL (Study 5: ECHELON-1)

	ADCETRIS+AVD Total N = 662 % of patients			ABVD Total N = 659 % of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Anemia*	98	11	<1	92	6	<1
Neutropenia*	91	20	62	89	31	42
Febrile neutropenia	19	13	6	8	6	2
Gastrointestinal disorders						
Constipation	42	2	-	37	<1	<1
Vomiting	33	3	-	28	1	-
Diarrhea	27	3	<1	18	<1	-
Stomatitis	21	2	-	16	<1	-
Abdominal pain	21	3	-	10	<1	-
Nervous system disorders						
Peripheral sensory neuropathy	65	10	<1	41	2	-
Peripheral motor neuropathy	11	2	-	4	<1	-
General disorders and administration site conditions						
Pyrexia	27	3	<1	22	2	-
Musculoskeletal and connective tissue disorders						
Bone pain	19	<1	-	10	<1	-
Back pain	13	<1	-	7	-	-
Skin and subcutaneous tissue disorders						
Rashes, eruptions and exanthems†	13	<1	<1	8	<1	-
Respiratory, thoracic and mediastinal disorders						
Dyspnea	12	1	-	19	2	-
Investigations						
Decreased weight	22	<1	-	6	<1	-
Increased alanine aminotransferase	10	3	-	4	<1	-
Metabolism and nutrition disorders						
Decreased appetite	18	<1	-	12	<1	-
Psychiatric disorders						
Insomnia	19	<1	-	12	<1	-

*Derived from laboratory values and adverse reaction data; data are included for clinical relevance irrespective of rate between arms.

†Grouped term includes rash maculo-papular, rash macular, rash, rash papular, rash generalized, and rash vesicular.

AVD = doxorubicin, vinblastine, and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine.

Events were graded using the NCI CTCAE Version 4.03. Events listed are those having a ≥5% difference in rate between treatment arms.

Additional Important Adverse Reactions

Infusion reactions

In a study of ADCETRIS in combination with AVD (Study 5, ECHELON-1), infusion-related reactions were reported in 57 patients (9%) in the ADCETRIS+AVD-treated arm. Grade 3 events were reported in 3 of the 57 patients treated with ADCETRIS+AVD who experienced infusion-related reactions. The most common adverse reaction (≥2%) associated with infusion-related reactions was nausea (2%).

Pulmonary toxicity

In a trial in patients with cHL that studied ADCETRIS with bleomycin as part of a combination regimen, the rate of non-infectious pulmonary toxicity was higher than the historical incidence reported with ABVD. Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids. The concomitant use of ADCETRIS with bleomycin is contraindicated.

In a study of ADCETRIS in combination with AVD (Study 5, ECHELON-1), non-infectious pulmonary toxicity events were reported in 12 patients (2%) in the ADCETRIS+AVD arm. These events included lung infiltration (6 patients) and pneumonitis (6 patients), or interstitial lung disease (1 patient).

Cases of pulmonary toxicity have also been reported in patients receiving ADCETRIS monotherapy. In Study 3 (AETHERA), pulmonary toxicity was reported in 8 patients (5%) in the ADCETRIS-treated arm and 5 patients (3%) in the placebo arm.

6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of ADCETRIS. 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.

Blood and lymphatic system disorders: febrile neutropenia.

Gastrointestinal disorders: acute pancreatitis and gastrointestinal complications (including fatal outcomes).

Hepatobiliary disorders: hepatotoxicity.

Infections: PML, serious infections and opportunistic infections.

Metabolism and nutrition disorders: hyperglycemia.

Respiratory, thoracic and mediastinal disorders: noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes).

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, including fatal outcomes.

6.3 Immunogenicity

As with all therapeutic proteins, there is 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 ADCETRIS in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Patients with cHL and systemic anaplastic large cell lymphoma (sALCL) in Studies 1 and 2 were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescence immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 time points) and 30% developed transiently positive antibodies (positive at 1 or 2 post-baseline time points). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or

persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patient samples that were either transiently or persistently positive for anti-brentuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent (62%) of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ADCETRIS

CYP3A4 Inhibitors: Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE, which may increase the risk of adverse reaction. Closely monitor adverse reactions when ADCETRIS is given concomitantly with strong CYP3A4 inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action. In animal reproduction studies, administration of brentuximab vedotin to pregnant rats during organogenesis at doses similar to the clinical dose of 1.8 mg/kg every three weeks caused embryo-fetal toxicities, including congenital malformations *[see Data]*. The available data from case reports on ADCETRIS use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Advise a pregnant woman of the potential risk to a 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 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption (≥99%), post-implantation loss (≥99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with cHL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation

Risk Summary

There is no information regarding the presence of brentuximab vedotin 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 from ADCETRIS, including cytopenias and neurologic or gastrointestinal toxicities, advise patients that breastfeeding is not recommended during ADCETRIS treatment.

8.3 Females and Males of Reproductive Potential

ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action.

Pregnancy Testing

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

Contraception

Females

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise females to immediately report pregnancy.

Males

ADCETRIS may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Infertility

Males

Based on findings in rats, male fertility may be compromised by treatment with ADCETRIS.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical trial of ADCETRIS in combination with AVD for patients with previously untreated Stage III/IV cHL (Study 5: ECHELON-1), 9% of ADCETRIS+AVD-treated patients were aged 65 or older. Older age was a risk factor for febrile neutropenia, occurring in 39% of patients aged 65 or older vs 17% of patients less than age 65, who received ADCETRIS+AVD. The ECHELON-1 trial did not contain sufficient information on patients aged 65 and over to determine whether they respond differently from younger patients.

Other clinical trials of ADCETRIS in cHL (Studies 1 and 3: AETHERA) and sALCL (Study 2) did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (CrCL <30 mL/min). No dosage adjustment is required for mild (CrCL >50-80 mL/min) or moderate (CrCL 30-50 mL/min) renal impairment.

8.7 Hepatic Impairment

Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Dosage reduction is required in patients with mild (Child-Pugh A) hepatic impairment.

10 OVERDOSAGE

There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

17 PATIENT COUNSELING INFORMATION

Peripheral Neuropathy: Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbness or tingling of the hands or feet or any muscle weakness.

Fever/Neutropenia: Advise patients to contact their health care provider if a fever of 100.5°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops.

Infusion Reactions: Advise patients to contact their health care provider if they experience signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion.

Hepatotoxicity: Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

Progressive Multifocal Leukoencephalopathy: Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms:

- changes in mood or usual behavior
- confusion, thinking problems, loss of memory
- changes in vision, speech, or walking
- decreased strength or weakness on one side of the body

Pulmonary Toxicity: Instruct patients to report symptoms that may indicate pulmonary toxicity, including cough or shortness of breath.

Acute Pancreatitis: Advise patients to contact their health care provider if they develop severe abdominal pain.

Gastrointestinal Complications: Advise patients to contact their health care provider if they develop severe abdominal pain, chills, fever, nausea, vomiting, or diarrhea.

Hyperglycemia: Educate patients about the risk of hyperglycemia and how to recognize associated symptoms.

Females and Males of Reproductive Potential: ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately.

Lactation: Advise patients to avoid breastfeeding while receiving ADCETRIS.

Please see full Prescribing Information, including BOXED WARNING, at adcetrispro.com

Seagen®

REF-4613 12/20

LIKE MOTHER, LIKE SON: QUEST FOR AFFORDABLE ORAL ONCOLYTICS IS SHARED BY BOTH LISA AND DEREK GYORI

This acorn falls close to the tree. The acorn is NCODA member Derek Gyori, PharmD, BCOP, at the University of Toledo. Derek, an assistant lecturer in the College of Pharmacy and Pharmaceutical Sciences, is passionate about educating students and the public about the affordability of oral cancer drugs.

The tree? His mother, Lisa, 56, a 16-year cancer survivor and self-taught expert at managing out-of-pocket expenses for medications. Lisa and her husband, Jim, have weathered fiscal challenges for more than a decade that would have bankrupted other families.

When his mother was diagnosed with Chronic Myeloid Leukemia (CML), Derek was in junior high and "had no idea what my mom went through in regards to getting her medication."

Lisa Gyori is an exceptional self-advocate. She, along with husband Jim, have preserved their health and family's financial stability by foresight, strategic thinking and persistence.

Their story starts in December 2005. Lisa, then 41, felt tired. It was understandable. The wife and mother of four was juggling a full-time job as an administrative assistant at a hospital. Jim, her husband and an Army Reserve sergeant, was returning from a year-long deployment to Iraq. Now Christmas was coming, and the couple added gift-shopping for their children to their list.

Her fatigue "is just from stress," Lisa thought, shrugging off bruises and high blood pressure as well. She soldiered on, until the day her heart hammered so hard at work that she stopped by the emergency department.

THE DIAGNOSIS

The team performed an EKG and bloodwork and Lisa was admitted to the hospital. The diagnosis: CML. Her white blood count was 328,000, compared to the normal range of 4,000 to 11,000.

Derek Gyori (left), with his parents, Jim and Lisa Gyori, at a recent family gathering.

The good news: "You don't have *leukemia* leukemia," the medical director said. While this slow-growing CML is hard to cure, it is highly treatable and can be managed by medications.

Lisa's relief over her prognosis was eclipsed by sticker shock. Her doctor prescribed Gleevec®, the groundbreaking tyrosine kinase inhibitor priced launched in 2001.

When it debuted, a typical daily dose of the "miracle drug" amounted to $26,000 annually. By the time Lisa was diagnosed, the annual price had soared to more than $40,000, an economic calamity for a middle-class family.

Living with CML was acceptable. Paying for her medication was the challenge.

"That's the tricky part, going forward with the medication," Lisa said. "They told me, 'You are going to be on this forever.'"

TAKING CHARGE

If diagnosed today, Lisa and Jim could conduct a worldwide Google search in seconds for drug assistance programs. Or consult a pharmacist about copay savings options. But this was not the case in 2005.

Fortunately the Gyoris had been proactive. Before being deployed, Jim had signed up for Tricare, considered the gold standard in military family insurance. The policy covered Lisa's hospital bill and a three-month supply of Gleevec. Their copay: About $10 a month.

Jim's Tricare policy lapsed when he resumed his job as a U.S. letter carrier. Fortunately, the postal service offered an option with generous drug coverage, with a copay of $50 or $100 for a three-month supply of Gleevec®.

A few years later, her pharmacy recommended a copay assistance program. "Then I didn't have to pay anything," Lisa said.

Lisa's out-of-pockets have inched up again over the past few years. She now pays $150 out-of-pocket for her medication, an expense she takes in stride.

ASKING TOUGH QUESTIONS

Her advice to anyone reeling from a cancer diagnosis and expensive drugs: Don't panic. Ask the hard questions about treatments and costs. Ask about options for financial assistance and MIDs.

"People need to ask those questions. Not just ones about health, but about costs, too," she said.

"Looking back, my mother was a great example of being a self-advocate," Derek said. "She was able to manage the uncharted medical and financial needs thrown at our family. My family was lucky."

"Unfortunately, this is rarely the case for many cancer patients these days, especially for older patients on Medicare and those in under-served populations. The role of medically integrated dispensing (MID) pharmacy has become more important with the ever-evolving landscape of oncology."

"Without the assistance of healthcare professional, patients often are left on their own to deal such issues as side effects, adherence and financial toxicity. Be an advocate for yourself. Ask the tough questions about your disease, medication and financials."

DAN KLEIN

PATIENT ACCESS NETWORK (PAN) FOUNDATION

Dan Klein is President and Chief Executive Officer of the Patient Access Network (PAN) Foundation in Washington, D.C. Since joining the PAN Foundation in 2014, Klein has expanded PAN's capacity to help the growing number of patients who need financial assistance, strengthened PAN's compliance program to ensure that PAN continues to fulfill its mission in strict compliance with regulations and implemented new technology to enhance the patient experience and better support the needs of healthcare providers.

How did you become involved with NCODA and what prompted you to join its Executive Advisory Board?

The PAN Foundation has been collaborating with oncology providers and pharmacists for more than 16 years, helping patients pay for the out-of-pocket costs of specialty cancer medications. So, when Michael Reff asked me to join the NCODA Executive Advisory Board, it was an easy decision to make both professionally and personally.

Professionally, it is important for PAN to stay in close touch with the oncology dispensing community to make sure that we are doing all we can to facilitate access and affordability to critical medications for cancer patients. Personally, as a cancer survivor who benefited from access to the best care and treatment, I want to make sure that all cancer patients have the same opportunity to thrive and survive as long as possible.

Tell us a little about your business and clinical expertise.

I have been working in the healthcare field for more than 40 years, since completing a graduate degree in public health. My first job, at the Pan American Health Organization, involved bringing public health administrators from around the world together to share strategies and methods of health planning. This led me to various health planning positions in the public and not-for-profit sectors, including serving as a consultant on health promotion for the U.S. Department of Health and Human Services. Eventually, I found my way into senior-level positions in several managed care companies, providing utilization management services to Blue Cross Blue Shield plans and large corporations.

After a five-year stint serving as the Chairman and CEO of an IT company, I returned to the healthcare field as the Senior Vice President of Cystic Fibrosis Services, the captive specialty pharmacy at the Cystic Fibrosis Foundation, where I also managed the Cystic Fibrosis Patient Assistance Foundation. In 2014, I was offered the opportunity to join the PAN Foundation as President & CEO. Since joining PAN, I have focused my efforts on expanding our assistance programs, advocating for lower out-of-pocket costs, and building a more robust and capable organization.

What do you see as the most critical challenge ahead for oral oncology from the perspective of your organization?

As a charitable patient assistance organization, PAN is primarily focused on ensuring that all cancer patients can afford their prescribed oncology medications, regardless of whether they are administered orally or infused. In accordance with the OIG Advisory Opinion under which PAN operates, we must remain agnostic with regard to the particular medications or methods of administration prescribed for the patients we serve.

That said, our greatest concern with regard to cancer treatment is the high out-of-pocket costs that many patients, particularly Medicare beneficiaries, are required to pay for their critical medications. Moreover, the need for financial assistance often far exceeds the availability of funding that PAN receives, which ultimately means that some cancer patients may be unable to get all the care they need when they need it most. So, from PAN's perspective, access and affordability are the most critical challenges facing oral oncology.

At the end of the day, NCODA is primarily focused on improving patient care. What are some of the key concerns that oral oncolytic patients face, and what can be done to relieve their burden?

High out-of-pocket costs are one of the key concerns facing cancer patients. In particular, many low-to-moderate income Medicare beneficiaries struggle to afford their critical oncology medications. As part of its role as a patient advocate, PAN has identified several fundamental changes in the Medicare benefit that would go a long way to addressing this concern. These include:

▲ Placing an annual or monthly cap on Medicare Part D out-of-pocket costs;

▲ Smoothing or spreading out-of-pocket costs more evenly throughout the benefit year;

▲ Raising the income limit for the Low Income Subsidy program.

For commercially insured patients, PAN supports the elimination of accumulator adjustors by insurance companies. These programs greatly increase the out-of-pocket costs for specialty medications, including those used to treat cancer.

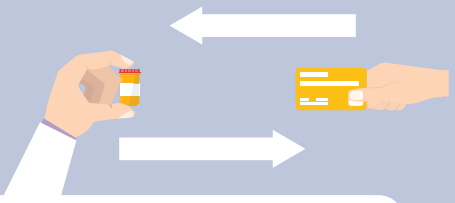
How do you see NCODA and your organization collaborating to improve patient care in the future?

PAN is committed to working with NCODA, as well as other organizations concerned about access and affordability, to advocate for lower out-of-pocket costs. In addition, PAN values its collaboration with NCODA as an effective means to communicate with cancer patients, providers, and pharmacists about the availability of financial assistance to help pay for the out-of-pocket costs for many oncology medications.

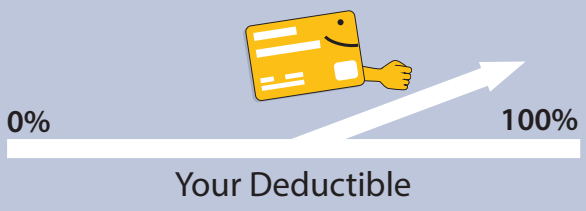
COPAY ACCUMULATORS: WHAT TO KNOW

WHAT'S THE DIFFERENCE?

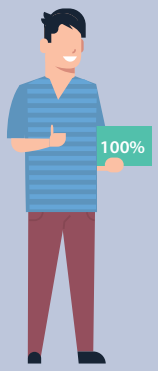
WITHOUT ACCUMULATOR PROGRAMS



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



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



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

RECEIPT

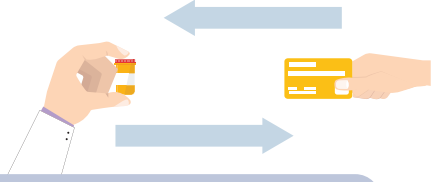
Prescription Drug Cost	$2,000.00
Manufacturer Coupon Value	-$1,995.00
Your Total at the Counter	$5.00

$2,000.00
Annual Deductible

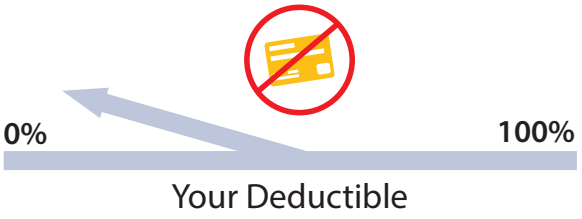
$0.00
Remaining Deductible After Coupon*

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

WITH ACCUMULATOR PROGRAMS



Patients can still use their coupon cards but ...



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

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

RECEIPT

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

$2,000.00
Annual Deductible

$1,995.00
Remaining Deductible After Coupon*

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

VS.

An example of what happens at the pharmacy counter

NCODA

Scan QR Code To View NCODA's Copay Accumulator Info Video

COMMUNITY PHARMACIES IN GERMANY SEE GREATER ROLE IN ORAL ONCOLOGY

By Ilka Lorenz, MBA

Pharmacies in Germany can be classified as community pharmacies (19,075 in 2019) and hospital pharmacies (372 in 2019).

German pharmacists are healthcare professionals, merchants and part of the freelance professions such as architects who "assume an obligation for the common good of society."[1]

According to German law, no third-party ownership of pharmacies is allowed. The owner of a community pharmacy or leading operator of a hospital pharmacy must be a registered pharmacist.

Ilka Lorenz

Pharmacists are allowed to own one main pharmacy, with a maximum of three subsidiaries in the "nearby local vicinity."[1] These subsidiaries are run by pharmacists as designated store/branch/subsidiary managers. Because of this rule, chain pharmacies are prohibited in Germany.

THE GERMAN HEALTHCARE SYSTEM[2]

More than 80% of the German population is covered by the statutory health insurance — Gesetzliche Krankenversicherung (GKV) — which is mandatory for everyone with an income lower than 5,062€ per month.

People with a higher income are allowed to choose between the statutory or various private schemes, but having health insurance is compulsory for everyone in Germany.

It's remarkable that the statutory system ensures free healthcare for all via health insurance funds.

A pharmaceutical technical assistant prepares a prescription at a community pharmacy in Germany.

Insurance payments are income-related (14.6% of monthly income before taxes in 2021) and shared equally between employees and employers or paid by the social security system in special cases, for example when people are unemployed.

Copayments must be made for special services — e.g. between 5€ and 10€ — based on the wholesale prices of the medications have to be paid for every prescribed product. These copayments are collected by the community pharmacies and transmitted to the insurance companies.

Patients who are covered by private insurances are required pay the wholesale price of the medications. They are then refunded by their insurance companies according to individual contract terms and conditions.

A huge amount of approved and available pharmaceuticals are eligible for refund by the various insurance companies – both private and statutory.

Drugs that are not subject to the health insurance funds are listed in the so-called "Negative List." The list names all drugs that cause unnecessary costs for the statutory health insurance and have no recognizable health benefits.

PHARMACEUTICALS

All pharmaceuticals need to be governmentally approved, either on the federal level in accordance with the Medicinal Products Act —Arzneimittelgesetz (AMG) — or on the European level before they are allowed to be distributed.

Pharmaceuticals are divided into:

- **Prescription-only (Rx)** with the subcategories: prescription-only narcotics, pharmaceuticals requiring a special prescription (e.g., T-prescription for thalidomide containing products) and other prescription-only pharmaceuticals;
- **Pharmacy-only** e.g., Panadol, Strepsils, aspirin and various herbal remedies; and
- **Unrestricted OTC Pharmaceuticals.**

In contrast to other countries, all Rx and pharmacy-only pharmaceuticals are exclusively sold in (community) pharmacies in each one of the 16 federal states of Germany, and not in drugstores or supermarkets.

Even hospital pharmacies are prohibited from selling drugs to walk-in clients. Hospital pharmacies can only provide medications to admitted in-house patients or patients who receive treatments, such as dialysis or chemotherapy, in the clinic.

The prices for all pre-packed Rx-pharmaceuticals are fixed and identical in all federal states, and the sales

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INTERNATIONAL

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pricing for individually produced standard formulations such as ointments but also parenteral solutions, cytostatics, etc., are regulated nationwide in the Drug Price Ordinance — Arzneimittelpreisverordnung (AMPreisV) — and based on the pharmacy purchase prices of the ingredients.

While all community pharmacies produce individually prescribed standard formulations such as ointments, solutions for internal or external use, capsules or suppositories on a regular basis, only about 500 community and hospital pharmacies produce specialized parenteral solutions and cytostatics.[3]

ONCOLYTICS — AN EVOLVING MARKET

Between the aforementioned 500 local speciality pharmacies and about a dozen bigger manufacturers, the market for these individually produced IV oncolytics and other parenteral products is fiercely competitive.[4]

Large companies in Germany must follow EU-wide established quality manufacturing standards - called GMP guidelines.

The smaller, locally operating specialty pharmacies also face strict regulations, but have the advantage of maintaining much smaller production facilities and shorter delivery distances.

Pharmacists who work in companies that produce cytostatics usually are trained as specialized pharmacists for oncology.

The Oncological Pharmacy program was developed to ensure the appropriate handling and proper manufacturing of cytostatics. It includes 100 hours of seminars, a certain practical experience and an oral exam.[5]

Due to the rapid development and registration of more and more oral oncolytics, community pharmacies are now dealing with an increasing number of cancer patients.

Because of this trend, it has become important to train community pharmacists and pharmaceutical technical assistants in the administration of oral oncolytics, including awareness and treatment of potential side effects, limitations in the use of special OTC drugs and other related issues.

▲ **Ilka Lorenz**, MBA, is a Community Pharmacist at Aquarius Apotheke in Hamburg, Germany.

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SOUTHERN CANCER CENTER

MISSION STATEMENT:

Established in 2007, Southern Cancer Center (SCC) is South Alabama's only community-based multidisciplinary oncology practice, comprised of 18 providers and six clinic locations. Through an integrated, team-based approach, SCC is dedicated to finding and providing the most advanced therapies and innovative treatment options for patients fighting cancer and diseases of the blood.

SCC is committed to treating the whole patient, not just their disease. Patients need more than medicine; they need collaborative support in every aspect of their care. SCC offers drug, disease and dietary education, social services and support groups for patients and caregivers. SCC has a certified genetic counseling and high-risk cancer assessment program, an in-house specialty pharmacy, advanced laboratory services and access to cutting-edge clinical trials through its partnership with The US Oncology Network. SCC's providers work closely with its patients and their families to create personalized treatment plans that address both physical and emotional health.

Simply put, at SCC, patients come first. It's their mission and their culture.

LOCATIONS:

SCC has clinics at three Mobile, Alabama, hospitals and two sites in nearby cities:

- Springhill Medical Center, Mobile
- Providence Hospital, Mobile
- Mobile Infirmary, Mobile
- Daphne
- Foley

PRACTICE DETAILS:

SCC has 180 employees, including:

- Nine physicians
- Eight medical oncologists
- One radiation oncologist
- Nine nurse practitioners

PHARMACY SERVICES STAFF:

SCC's pharmacy has three dedicated medically integrated dispensing (MID) pharmacists, two pharmacy technicians and one pharmacy coordinator. Tiffany Mitchem, PharmD, CSP, serves as Director of Pharmacy & Admix Services.

QUALIFICATIONS/CREDENTIALS: SCC's Coastal Pharmacy is ACHC- and URAC-accredited.

DISPENSING TYPE: Retail

SCAN QR CODE TO VIEW PRACTICE IN FOCUS FEATURE DURING NATIONAL MONTHLY WEBINAR

Tiffany Mitchem, PharmD, CSP, Director of Pharmacy & Admix Services for Southern Cancer Center, was awarded the "Best Pharmacist in a Medically Integrated Dispensary" award in 2020 from The US Oncology Network.

SERVICES PROVIDED:

Chemotherapy, hematology, MID pharmacy, radiation, research/clinical trials.

WHY DID YOU JOIN NCODA?

Oncology pharmacy was a new practice setting for Mitchem. "NCODA was able to provide that information in an easy-to-understand format," she said. "The organization provided all the information and resources I needed to become clinically competent."

HOW CAN NCODA HELP YOU?

"I would like to see NCODA create a message board," Mitchem said. "I get a lot of value from the Listserv but my Outlook will delete messages after so long. I really would like to be able to reference something that may have been brought up a year ago if it becomes relevant to my practice now. I understand that community oncology is a rapidly changing landscape, but being able to do a quick search of a message board for something saves a lot of time.

WHAT ONCOLOGY CHALLENGES ARE YOU FACING NOW OR ENVISION IN THE FUTURE?

"I think a lot of our challenges center around what amounts to PBM bullying," MItchem said. These include such practices as increased DIR fees, network limitations, step therapy requirements, general healthcare waste forced on practices from payer/PBM relationships and over-charging of patient copays.

Mitchem also identified pharmacist competency as a "very real issue," especially in the oral oncology space. "Trying to keep up with all the changes in guidelines, drug literature and insurance requirements is pretty overwhelming," Mitchem said. "Pharmacists have always been the gatekeepers of medicine and it is up to us to make sure our patients are treated appropriately and safely as best we can. So having a specially trained, oncology-centered pharmacist is vital."

BE NCODA'S NEXT PRACTICE IN FOCUS

NCODA is committed to creating a collaborative community environment, providing a platform for practice members to share common experiences and help one another succeed. Practice in Focus connects practices to one another as we all strive to provide better care to patients.

The Practice in Focus application process is simple and takes approximately 20 minutes to complete. Once an application is submitted, NCODA will help develop an online profile for the respective practice.

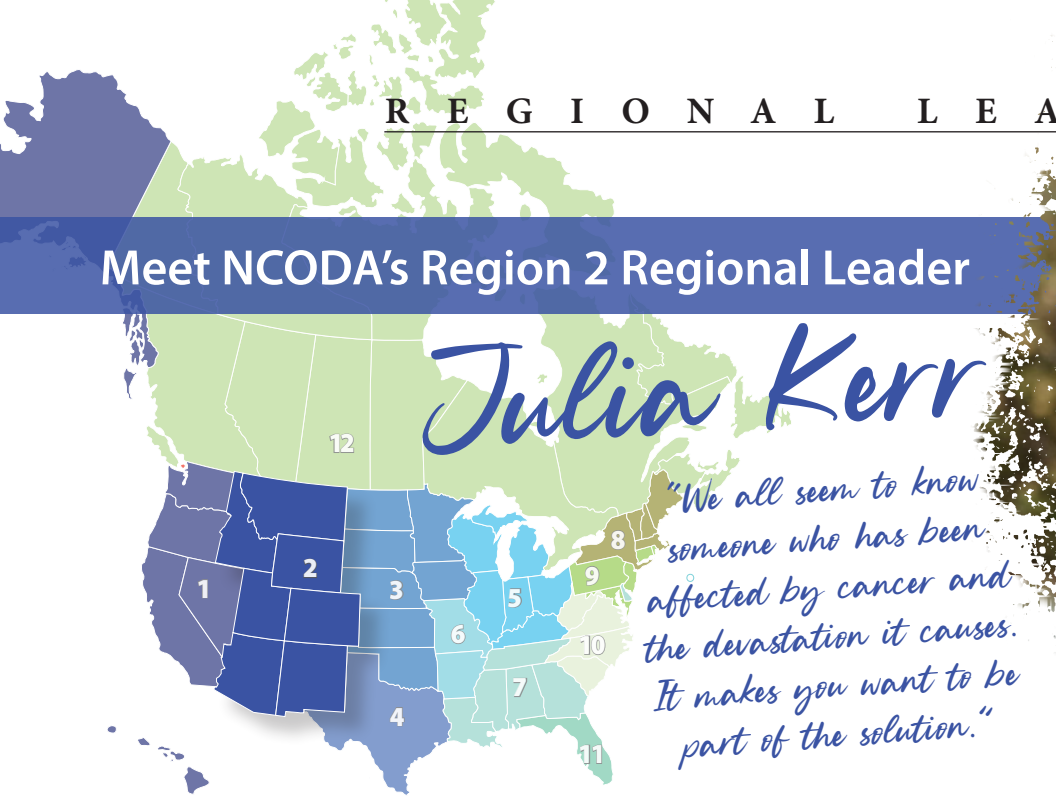
Practice in Focus participants have the opportunity to talk about their practice each month during the NCODA National Monthly Webinar, an ideal way to highlight the work being done within their facility.

In order to be considered for selection:

- An NCODA member must submit a completed application.
- Applications are considered when one person from each facet of the practice/organization's medically integrated team (i.e., doctor, nurse, pharmacist, pharmacy technician, financial counselor, etc.) is an NCODA member.
- One or more members of your medically integrated team will present during the National Monthly Webinar as the featured practice.

For an application, visit:
www.ncoda.org/practice-in-focus

Meet NCODA's Region 2 Regional Leader



Julia Kerr

"We all seem to know someone who has been affected by cancer and the devastation it causes. It makes you want to be part of the solution."

Julia Kerr, PharmD
St. Luke's Cancer Institute

Julia R. Kerr, PharmD, is NCODA's Regional Leader for Region 2, which includes Montana, Idaho, Wyoming, Colorado, Utah, Arizona and New Mexico.

Kerr, a graduate of the University of Wyoming | Laramie, underwent an epiphany while studying for her pharmacy degree, an intense personal experience that inspired her to specialize in oncology.

"At the time, I had a grandma going through treatment for leukemia, so I was able to see firsthand some of the challenges she was experiencing," Kerr said. "We all seem to know someone who has been affected by cancer and see the devastation it causes. It makes you want to be part of the solution."

After graduating from pharmacy school, Kerr was accepted into the oncology residency program at St. Luke's Cancer Institute in Boise, Idaho (known then as Mountain States Tumor Institute).

After completing her residency program, she opted to stay on as an oncology pharmacist, working primarily in chemo infusion. But as oral oncolytics came to the forefront, Kerr shifted gears and served as the program coordinator for St. Luke's Oral Oncology Department for several years.

"I think our program was one that really got started early on," Kerr said. "We've been kind of a leader in the field."

Kerr became involved with NCODA in 2016, after receiving a call from Executive Director and Founder Michael Reff, who invited her to attend the 2016 Fall Summit in Atlanta.

"I was really excited to be a part of an organization that focused on oral chemotherapy agents because it is such an important piece of our patients' treatment and it's so different from anything we'd ever done before," she said. "I became an NCODA member and attended the first meeting, where I met Michael. It's been such a great experience."

Kerr said she especially appreciates that NCODA has given her the opportunity to network with her peers.

"I've personally had the opportunity to meet several people within my region and have enjoyed seeing our group expand over the years," she said. "I particularly enjoy it when I get an email from somebody within my region who's just reaching out with a question. You know (one of your peers) has encountered this situation and can provide some help. So, it's really an opportunity for us to help one another."

Kerr also has a found a great deal of value in NCODA's Oral Chemotherapy Patient Education sheets. "They've been a tremendous help," she said. "Patients love them. They're well-written, easy to follow and a huge asset for our patients and our oncology department."

SCAN QR CODE BELOW TO JOIN THE REGION 2 FACEBOOK GROUP

As it has with other healthcare professionals, the COVID-19 pandemic has drastically affected Kerr's work environment.

"It's definitely affected our interactions with patients," said Kerr, who recently stepped down from her coordinator position to focus on patient care in oncology pharmacy. Mailed prescriptions have taken precedence over face-to-face opportunities to meet with patients, she said, noting, "This has been the biggest adjustment."

"It's hard to assess the patient over the telephone. But we're trying to do our best to keep them from coming to the clinic and risking exposure."

Kerr's husband of nearly 20 years, Todd, also is a pharmacist. The couple has two children, Ava, 14, and Gavin, 12. The family enjoys backpacking and hiking. Kerr, who has trekked to Machu Picchu, is looking forward to a trip to the Grand Tetons this summer.

Kerr would like Region 2 members to tell other oncology professionals they meet about NCODA and encourage them to become part of the community.

ACHIEVEMENT THROUGH ADVERSITY: CHALLENGE OF ONCOLOGY IS NOT UNLIKE THAT OF COVID-19

The world underwent a dramatic metamorphosis in 2020, a grim transformation brought on by the deaths of millions of people worldwide who succumbed to COVID-19.

The healthcare community has been battling the virus nonstop for more than a year now. During that time, we've had to rethink the way we interact with our patients, our peers and even our own loved ones.


Michael Reff

It's been a difficult process, as many of our members attested to during NCODA's "Supporting Patients and Practices Through the COVID-19 Pandemic" webinar series last spring.

Oncology practices suddenly were faced with juggling multiple unforeseen issues, including everything from shortages of personal protective equipment (PPE) and new requirements for social distancing to remote staffing and massive drops in new patient volumes.

But now, in 2021, there finally appears to be light at the end of the tunnel.

Innovation from our pharmaceutical and biotech partners has achieved nothing less than a scientific miracle. Vaccines that once took a decade or more to develop were produced in a matter of months.

Multiple vaccines have been approved now in the U.S. and abroad, and the vaccination process, despite initial logistical challenges, finally has begun picking up steam.

It's great story: achievement in the face of unremitting adversity.

Yet it's also a theme that we in oncology healthcare already know all too well. Each day we strive to help our patients fight the good fight against a relentless and often incurable enemy.

We commend our NCODA members and partners for continuing to put patients first in the midst of the pandemic.

Our pharmaceutical partners, in particular, analyzed the environment during the pandemic and made changes to their support programs, improving access to needed oncology medications and making them more affordable.

NCODA's Mission is to support oncology healthcare in this fight by empowering the medically integrated team to deliver positive, patient-centered outcomes by providing leadership, expertise, quality standards and best practices.

Like you, we've also had to cope with changes brought on by the pandemic to help keep our members safe.

That's because our top priority is the health and safety of our patients, members, corporate partners, meeting faculty and families.

It's for that reason that we've decided to host our 2021 International Spring Forum in a virtual format, as we did for the 2020 Fall Summit.

SCAN QR CODE BELOW TO VIEW 2021 SPRING FORUM AGENDA

The Forum will be held April 28-30, and will feature clinical updates, medically integrated dispensing (MID) presentations, best practice sessions and more, including an up-to-date report on what you should know about the COVID-19 vaccines.

Outside of the COVID-19 arena, NCODA has seen several other changes:

▲ NCODA's membership has increased by more than 60% in the past year; we now have approximately 3,200 members worldwide. Talk about impressive growth in a tumultuous time!

▲ NCODA has grown internally with the hiring of three new team members in the past few months to assist this growth. These team members will help support our growing international meetings, as well as strengthen the clinical initiatives that we are working on.

▲ We've begun developing IV Education (IVE) sheets in addition to NCODA's Oral Chemotherapy Education (OCE) sheets. It is clear to us that our members need comprehensive education on both oral and IV products due to increasingly complex combination treatment regimens.

As always, we're dedicated to embracing new ideas and new concepts as healthcare moves forward. Because as the world of oncology continues to evolve, so too must NCODA.

Michael J. Reff, RPh, MBA
Executive Director and Founder | NCODA

BE THE MATCH®

NCODA

ENDING BLOOD CANCER *STARTS WITH US*

TOGETHER WE CAN MAKE A LIFE-SAVING IMPACT

As As the global leader in bone marrow transplantation, Be The Match® helps blood cancer patients find their donor match—and delivers their cure from across the world. But thousands each year are still searching for their match. They depend on Be The Match and supporters like NCODA to overcome the odds.

We are proud to partner with Be The Match in recruiting new donors to the Be The Match Registry® and raising funds to help more patients get a second chance at life.

Since 2017, NCODA has recruited over 210 new registry members and raised over $19,700.

LaShonda, marrow transplant recipient (left), with Akeem, her donor.

PATIENTS ARE COUNTING ON US

You can help more patients find their life-saving donor. Scan with your phone or visit

ncoda.org/community/non-profit-partners

to learn how to get involved.

You Help Cancer Patients.

Let NCODA Help You!

Join NCODA's growing membership of
more than 3,500 oncology healthcare professionals

Who Is NCODA?

- NCODA is a grassroots, not-for-profit organization founded to strengthen oncology organizations with medically integrated dispensing (MID) services

Why Should I Join NCODA?

- Membership is complimentary
- Access to cutting-edge clinical and educational resources for your staff and patients
- Opportunities to network with a diverse group of community and academic thought leaders
- Complimentary registration to both NCODA international meetings (Spring Forum & Fall Summit)

Am I Eligible To Join?

- NCODA offers membership to all medically integrated team members
- This includes nurses, pharmacists, technicians, providers, educators, researchers, administrators, etc.
- Membership is also extended to students in professional healthcare programs (pharmacy, medical, nursing)

How Do I Register For Complimentary Membership?

- Register via **www.ncoda.org/register**
- Or scan the QR code

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

NCODA

PASSION FOR PATIENTS

NCODA.ORG