ONCOLYTICS TODAY

EMPOWERING THE MEDICALLY INTEGRATED ONCOLOGY PHARMACY PRACTICE | SPRING 2022

HARNESSING TECHNOLOGY

INFORMATICS INITIATIVE PROVIDES MEMBER PRACTICES WITH A POWERFUL DATA TOOL

PAGE 48

ARTIFICIAL INTELLIGENCE IS HELPING RETOOL WORLD OF ONCOLOGY

PAGE 53

NCODA OPTIMIZES TSK OPERATIONS WITH A ROBUST NEW SYSTEM

PAGE 60

NCODA

NCODA.ORG

NCODA | TSK

Why Choose NCODA Treatment Support Kits?

- Provide patients and caregivers with resources that make sense for adverse event managment during treatment with oral anti-cancer medications
- Equip patients with unique education and supportive care products
- Increase utilization of support kits (avoid manufacturer branding hurdles)
- Generic kit options are available

TSKs Currently Available:

- Abiraterone Acetate
- Capecitabine
- Decitabine and Cedazuridine
- Mobocertinib
- Neratinib
- Regorafenib
- Selinexor
- Temozolomide
- Tivozanib

To Order Kits, Scan QR Code Or Visit:
www.ncoda.org/Treatment-Support-Kits

VisualStrata®
Powered by XIFIN®

Raise Your **Data IQ**

Integrate. Curate. Visualize.

Attract more clinical trial opportunities for your oncology practice. It just got easier with the NCODA Informatics Initiative powered by VisualStrata.®

Free for NCODA members. Learn more at
www.ncoda.org/informatics

Health Informatics Platform Purpose-built for Oncology

- Centralize "locked-up" patient data so that it is integrated, organized, and accessible
- Facilitate identification of clinical trial patients
- Visualize patient journey patterns
- Conduct retrospective analyses of data
- Reduce labor costs associated with manual chart reviews

Contact us
www.visualstrata.com/demo
866.934.6364

NCODA Cost Avoidance and Waste Tracker

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

How it works:

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

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

How to use the data:

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

HELP US CREATE CHANGE AND ACCOUNTABILITY FOR HEALTHCARE SPENDING NATIONWIDE!

Cost Avoidance & Waste Reported *To Date* by NCODA Members

Cost Avoidance

$7,899,763

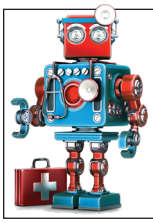
Waste

$12,521,434

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.

CONTENTS

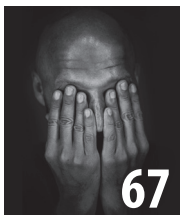


HARNESSING TECHNOLOGY

NCODA Informatics Initiative, Artificial Intelligence and Precision Medicine Provide Powerful New Tools in the World of Oncology | Coverage Starts on Page 48

REGULAR SECTIONS

FEATURED ARTICLES



Oncolytics Today

PUBLISHED BY THE
NATIONAL COMMUNITY ONCOLOGY
DISPENSING ASSOCIATION, INC.

SPRING 2022 | VOLUME 4, NO. 1

Oncolytics Today™ (ISSN 2643-2544) is published by the National Community Oncology Dispensing Association, Inc., and is issued semiannually in print and online.

THE COMING OF SPRING BRINGS MANY NEW AND EXCITING DEVELOPMENTS FOR NCODA

It's spring, and time to move away from the winter weather and think about the return of baseball and the upcoming NCODA Spring Forum.

With the current great decrease in the number of COVID cases, we still plan to have our meeting on-site in Atlanta on April 27-29. As always, it will feature an agenda filled with relevant, impactful presentations (based on your recommendations) and great keynote speakers.

Jim Schwartz

I hope everyone who is a member of NCODA has a chance to participate in at least one live meeting. I'm admittedly biased, but all the NCODA meetings I've attended (and I've participated in all of them) have been among the best professional meetings in my experience.

There has been a lot happening on the legal front throughout the country, and the NCODA **Legislative & Policy Advisory Committee** (LPAC) has been working hard to assimilate information on state legislative actions throughout the country.

The committee has created the **State Legislation Tracking Tool**, a first-of-its-kind resource within the oncology space, that allows healthcare professionals and other users to stay up-to-date on the latest state legislation pertaining to relevant issues, such as Pharmacy Benefit Managers (PBMs), Copay Accumulators and other healthcare issues.

Active parlimentary participation by NCODA members is encouraged to advance legislation at the state level, which will drive Congress to take action that will benefit all oncology/urology practices.

For more information on LPAC and the new State Legislation Tracking Tool, check out the story on Page 38 in this issue of **Oncolytics Today**.

Ginger Blackmon is busy with NCODA's **PQI Podcast,** with 25 recordings currently available covering several important issues. For more information on the podcast, see Page 20.

NCODA's **Oral Chemotherapy Education** (OCE) initiative has been expanded to include intravenous chemotherapy.

The recently launched **Intravenous Cancer Treatment Education** (IVE) program, was created in cooperation with the Association of Community Cancer Centers (ACCC), the Hematology/Oncology Pharmacy Association (HOPA) and the Oncology Nursing Association (ONS). For more information on the collaboration between the four organizations, see Page 74.

The IVE initiative has produced numerous well-written documents, currently sharing important information on 28 clinic-infused regimens for patient education.

Both OCE and IVE documents are complimentary to all NCODA members.

In other news, NCODA has joined Texas Oncology as an active participant with **Pharmacy Quality Alliance** (PQA) to develop quality metrics specific to the treatment of cancer patients.

The alliance was founded in 2005 in response to the Medicare Modernization Act (MMA), which called upon healthcare providers to improve the quality of the services delivered.

Aware of the glaring absence of quality measures around cancer care, PQA has been very receptive to input provided by the oncology community.

What this means for cancer care pharmacies and dispensaries is that these new oncology-specific criteria would be used in place of the current criteria (statins, hypoglycemics, anti-hypertensives) used by Pharmacy Benefit Managers (PBMs) to evaluate practices for the imposition of Direct and Indirect Remuneration (DIR) fees.

We are cautiously optimistic that this effort will succeed, resulting in a great reduction (if not elimination) of the current high DIR fees imposed on our practices.

NCODA also has partnered with the health information technology company XIFIN, Inc., to offer the healthcare informatics platform **VisualStrata®** as a complimentary service to all NCODA members.

VisualStrata collates structured and unstructured clinical, diagnostic, molecular, genomic and financial data from disparate systems into a single source, enabling healthcare professionals to gain insight, make decisions and improve care and outcomes. For more information, see Page 48.

The growth in the number of highly skilled healthcare professionals continues to drive the efforts of NCODA. We hope that each of you are taking advantage of all the resources provided by this great organization.

We ask you to consider taking part in the development of all the information provided by NCODA, as well as serving as leaders/participants in one of our important committees.

If each of us spends a little time supporting the services and information provided by NCODA, it will benefit the care given to every cancer patient worldwide.

James R. Schwartz, RPh
NCODA President

PROFESSIONAL STUDENT ORGANIZATION

Empowering The Future Generation of Oncology Leaders

> "Being a part of the NCODA Professional Student Organization (PSO) community is such a remarkable experience. Together, we keep each other updated and informed on current clinical oncology practices, while also providing opportunities that aid in developing leadership skills."

- Jonathan Rivera
PharmD Candidate | Class of 2023
University of North Texas Health Science Center

ABOUT PSO

Our focus is to offer an international community for healthcare students with a passion in oncology and pharmaceutical industry. The NCODA Professional Student Organization (PSO) was established for students interested in oncology, association management, healthcare advocacy and policy, and industry leadership.

PSO BENEFITS

- First professional student organization for students interested in oncology/association management/industry leadership
- Opportunities to attend NCODA international meetings
- International public presentation opportunities
- Create educational materials to help impact cancer care
- International publishing opportunities ***(ForumRewind, SummitRewind & Oncolytics Today publications)***
- Increased networking opportunities with oncology clinical and industry professionals, and key opinion leaders
- Access to over 50+ hours of oncology video education (Student Educational Talks)
- Oncology clinical practice experience and mentorship
- Healthcare advocacy and policy experience
- Additional student opportunities:
  - 1-year post-graduate oncology fellowships
  - International elective APPE rotation in oncology
  - Participate in NCODA's international clinical oncology competition

Locations of Established PSO Chapters

FOR MORE INFORMATION OR TO SUGGEST NEW CHAPTERS
Email **Cooper Bailey** at **cooper.bailey@ncoda.org**
Scan to visit, or check out **www.ncoda.org/professional-student-organizations**

NCODA is a grassroots, not-for-profit organization, founded to strengthen oncology organizations with medically integrated pharmacy (MIP) services.

ENTHUSIASM SOARS FOLLOWING THE LAUNCH OF NCODA CoE MIP ACCREDITATION PROGRAM

Interest and participation in the **NCODA Center of Excellence (CoE) Medically Integrated Pharmacy (MIP) Accreditation Program** has soared since its launch at the beginning of 2022.

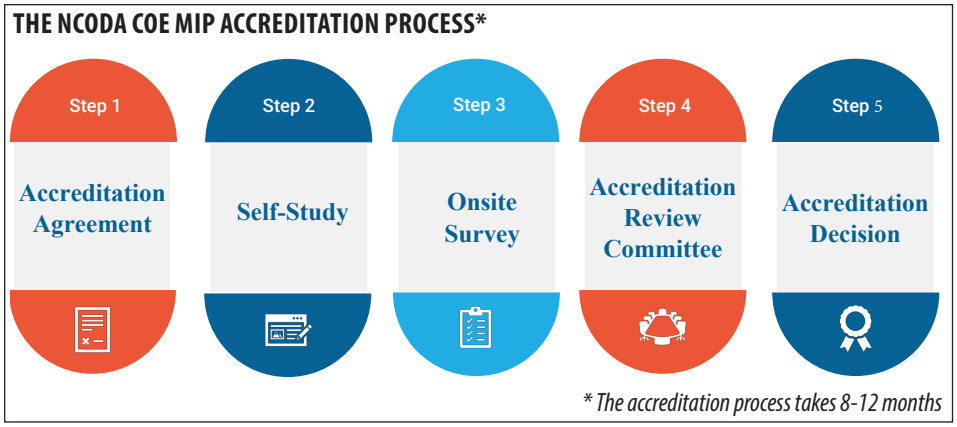
Several practices have since contracted with NCODA and started the formal accreditation process, include: Mission Cancer + Blood in Des Moines, Iowa, Urology Cancer Center in Omaha, Nebraska, New York Oncology Hematology in Albany, New York, and New Jersey Hematology Oncology Associates in Brick, New Jersey.

Practices committed to starting the program in 2022 include Texas Oncology in Dallas; Utah Cancer Specialists in Salt Lake City; Intermountain Specialty Pharmacy in Taylorsville, Utah; Cancer Treatment Centers of America in Newnan, Georgia; and Florida Cancer Specialists in Fort Myers, Florida.

The program, based on compliance with the **Patient-Centered Standards for Medically Integrated Dispensing: ASCO/NCODA Standards** established in December 2019, focuses on enhanced integrated patient care and quality of services.

It supports *Going Beyond the First Fill* and its value has been recognized by the healthcare industry. NCODA CoE MIP Accreditation is now the preferred accreditation for Prime Therapeutics' IntegratedRx®, a new clinically integrated program available to millions of Blue Cross and Blue Shield members across the United States.

That's because the program was designed specifically for MIP practices, said Michael Reff, RPh, MBA, NCODA Founder & Executive Director



"We're giving medically integrated pharmacies a program tailored to their needs, a program designed to help them reach and maintain the highest level of patient care," Reff said.

What sets the program apart is its commitment to the **CoE MIP Tenets**: Patient-Centered, Always Collaborative, Quality & Value, Robust, Independent, Innovative and Budget-Neutral.

It's designed to hit the **Quadruple Aim** of better outcomes, improved patient experience, improved clinician experience and lower (healthcare) costs.

"This accreditation really focuses on real-world medically integrated pharmacy processes and documentation. There weren't any unnecessary or burdensome requirements that would not apply to our practice."

Paul Forsberg, PharmD, MHA
Director of Pharmacy | Minnesota Oncology

While other pharmacy accreditations are available, NCODA CoE MIP Accreditation is radically different than anything else on the market, according to Elizabeth Bell, Director of Medically Integrated Pharmacy Accreditation for NCODA.

First, it's the only oncology accreditation designed specifically for the medically integrated pharmacy. Existing pharmacy accreditation programs, such as URAC and ACHC, focus primarily on the needs of mail-order pharmacies. For MIP practices, such standards are not always relevant or applicable to medically integrated patient care.

The NCODA CoE MIP Standards focus on elimination of clinical fragmentation through seamless coordination with the patient's healthcare team, clinical pathway and care plan protocol.

Second, the cost of the program is substantially less than other pharmacy accreditations, which can cost tens of thousands of dollars, especially for larger practices.

"NCODA CoE MIP Accreditation is designed to be a budget-neutral initiative for NCODA," Bell said. "It's not meant to generate a profit, so it is much less expensive than the existing pharmacy accreditations out there today."

CONTINUED ON NEXT PAGE

ACCREDITATION

CONTINUED FROM PREVIOUS PAGE

Finally, the program is designed to not only confirm that practices have met the ASCO/NCODA Standards, but to assist in that achievement. To that end, NCODA's full toolbox of initiatives, including Oral Chemotherapy Education (OCE) sheets, Positive Quality Interventions (PQI), Cost Avoidance and Waste Tracker (CAWT) and other tools, are available to help participants attain accreditation.

The program was launched Jan. 3, 2022, following pilot programs last year at Minnesota Oncology in Minneapolis, and Ocala Oncology in Ocala, Florida.

"The NCODA Accreditation does a really great job at balancing the rigorous quality measurement requirements with real common sense, patient-focused guidance," said Paul Forsberg, PharmD, MHA, Director of Pharmacy, Minnesota Oncology.

"This accreditation really focuses on real-world medically integrated pharmacy processes and documentation. There weren't any unnecessary or burdensome requirements that would not apply to our practice."

And while NCODA CoE MIP Accreditation currently focuses on oncology, NCODA plans to expand it into a multispecialty accreditation by year's end.

AN OVERVIEW OF THE NCODA CoE MIP ACCREDITATION STANDARDS

Accreditation Standards:

1.1 Patient Relationships
- Written and verbal communication with patients, caregivers, prescribers, and other stakeholders
- Patient access to MIP team
- Contingency planning to ensure continuity of services during an emergency

1.2 Patient Evaluation and Education
- Patient Evaluation prior to initiation of therapy
- Formalized patient education

1.3 Adherence and Persistence
- Measuring & monitoring patient adherence
- Addressing non-adherence

1.4 Safety
- Identity verification
- Drug utilization review
- Medication stability during shipping
- Labeling

1.5 Refilling of Prescriptions
- Refill requirements
- Discontinuation of treatment
- Interventions

1.6 Documentation
- Patient record requirements

1.7 Benefits Investigation
- Benefits investigation process
- Financial assistance/support

1.8 Medication Disposal
- Patient and MIP disposal of medications

1.9 Patient Satisfaction
- Patient satisfaction
- Complaint process

Foundational Elements (FE):

FE 1.1 Mission Statement
- Mission statement requirements

FE 1.2 Organization Management
- Organizational chart
- Employee management

FE 1.3 Business Plan
- Practice scope and limitations

FE 1.4 Operational Elements
- Practice workflow
- Billing and claims
- Audit preparation & readiness regulatory compliance
- Reporting of violations
- Addressing third-party audits

FE 1.5 Communication Plan
- Marketing and communication materials
- Coordination of care

FE 1.6 Continuous Quality Improvement
- Continuous Quality Improvement (CQI) Program
- CQI Committee

FE 1.7 Electronic Systems Infrastructure
- Integration of systems
- Protection of PHI

FE 1.8 Handling of Medications
- Inventory
- Medication storage
- Handling of hazardous drugs and materials
- Handling of controlled substances
- Medication handling for patients

FE 1.9 Adverse Drug Reactions
- Documenting, addressing & reporting ADRs

EXECUTIVE ACCREDITATION COUNCIL & ACCREDITATION WORKING GROUP OVERSEE PROGRAM

NCODA has established two groups to oversee the NCODA CoE MIP Accreditation Program.

The **Executive Accreditation Council** will serve to provide guidance on the CoE MIP accreditation program, insight on the current/future oncology ecosystem and network and program support. Members include:

Jonas Congelli, RPh | Chief of Pharmacy, Laboratory, & Clinical Services | HOACNY; **Gury Doshi,** MD | Oncologist / Hematologist | Texas Oncology; **Michele Galioto, DNP**, RN, CNS | Executive Director – Center For Innovation | ONS; **Lucio Gordan**, MD | Chief Medical Officer Therapeutics and Analytics | Florida Cancer Specialists; **Stacey McCullough**, PharmD | Senior VP Pharmacy | Tennessee Oncology; **Brian Morrissey**, MBA | VP – Oncology National Customer Group | Pfizer; and **Luis Raez**, MD | Medical Director & Chief Scientific Officer | Memorial Healthcare System.

The **Accreditation Working Group** will serve to provide guidance and assistance in the development and revision of accreditation tools and resources. Members include:

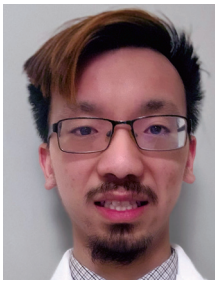
Meg Butler, PharmD | Clearview Cancer Center; **Brittney Carden**, PharmD | Mitchell Cancer Institute; **Austin Cox**, PharmD | Alabama Oncology; **Jenelle Griffiths**, PharmD, CPh, CSP | Baptist Health South Florida Specialty Pharmacy; **Hind Hamid**, PharmD, BCOP | DCH Health System; **Colby Hancock**, PharmD | Utah Cancer Specialists; **Jason Harlow** | AmerisourceBergen/ION; **Kristina Hazard**, PharmD, BCOP | Kaiser Permanente; **Jonathan Heller**, MBA | Virginia Cancer Institute; **Kyle Kitchen**, PharmD, BCACP | Utah Cancer Specialists; **Kristin LaFollette**, RPH | Cancer Care Specialists of Illinois; **Tiffany Mitchem**, PharmD | Southern Cancer Center & Coastal Pharmacy; **Stephanie Parker**, PharmD | Illinois Cancer Care; **Kara Sammons**, MSPharmReg, CPhT (Co-Chair), RPhT | Rx To Go/Florida Cancer Specialists; **Chris Sellers**, RPh | Texas Oncology; **Ryan Scott**, PharmD, MBA, MHA (Co-Chair) | Intermountain Specialty Pharmacy; **Christie Smith**, PharmD, MBA | AmerisourceBergen; **Ernestine Wigelsworth**, PharmD | Cancer Specialists of North Florida; and **Jaelynn Wynn**, PharmD, CSP | Intermountain Specialty Pharmacy.

PROTACs PROTEOLYSIS-TARGETING CHIMERAS OFFER NEW THERAPEUTIC PROSPECT

By Huy Pham

Proteolysis-targeting chimeras (PROTACs) are small molecules that target and degrade specific proteins of interest by directing the proteins toward the ubiquitin-proteasome system.

Originally conceived of by Crew et al. in 2001, they are heterobifunctional molecules composed of two distinct ligands connected by a linker chain. One of the ligands binds to the protein of interest and the other ligand interacts with an E3 ubiquitin ligase, thereby forming a ternary complex that promotes ubiquitination and subsequent protein degradation.



Huy Pham

Once the protein is ubiquitinated sufficiently for degradation, the molecule is released and free to bind to and ubiquitinate another protein **(see Figure 1)**.

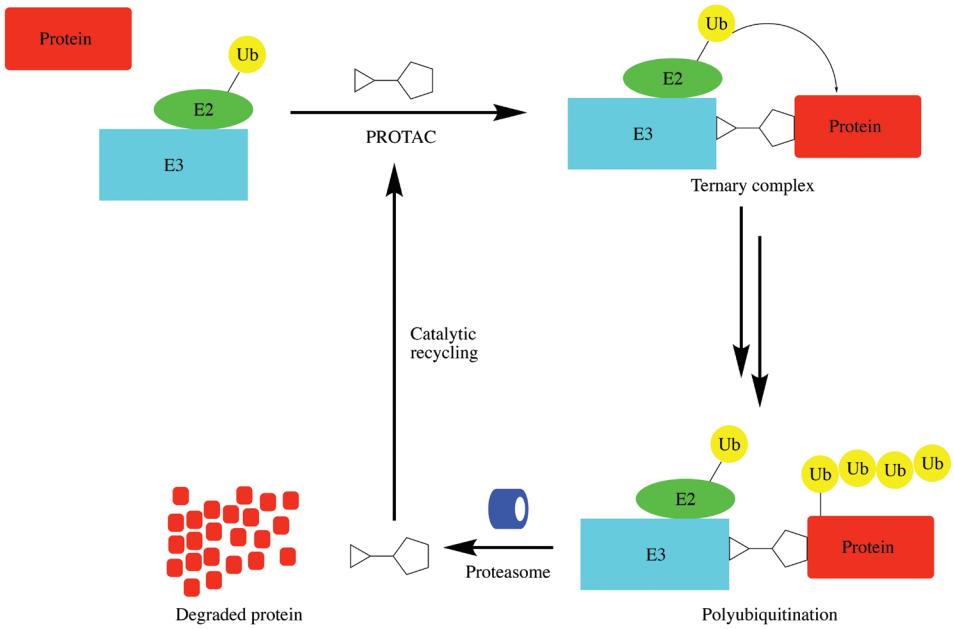
As a result, PROTACs act catalytically, thereby a sub-stoichiometric dose with micromolar or even sub-nanomolar concentrations being needed for a response and potentially allowing for a longer duration of action.[1-6]

Unlike traditional small-molecule drugs, which follow occupancy-driven pharmacology to affect protein function, PROTACs follow event-driven pharmacology to affect protein abundance.

BENEFITS OF PROTACs

Since the affinity to the target protein itself is a factor in activity and not the direct effect on protein function, PROTACs present a way to target the broad array of "undruggable" proteins.

FIGURE 1: MECHANISM OF ACTION OF PROTACs



These include transcription factors,[7-8] scaffolding proteins,[2,9,10] components of protein complexes,[11,12] and solute carrier transporters.[13]

A 2021 study by Schneider identified 1,336 targets that can be considered "PROTACtable," 1,067 of them being potential targets that have not been reported in the literature.

In addition, through an analysis using ChEMBL and Open Targets Platform, the study found that of the 269 targets that are reported in the literature, 199 of them lacked an approved drug and 145 of them lacked an approved drug or compound undergoing clinical development.[14]

As for the 1,067 potential "PROTACtable" targets that were not reported in the literature, 856 of them lacked an approved drug or compound undergoing clinical trials.

Table 1 on the following page provides a quick comparison between PROTACs and other therapeutic modalities.

Given that PROTACs act by degrading the entire protein, they may be used to interfere with the non-enzymatic functions of known drug targets of traditional small-molecule inhibitors.

For instance, Cromm et al. developed a PROTAC called PROTAC-3 that targets and degrades focal adhesion kinase, a protein involved in tumor growth through enzyme-dependent and enzyme-independent mechanisms. When compared to defactinib, a small-molecule inhibitor of focal adhesion kinase, they observed that the PROTAC had a greater efficacy in inhibiting downstream signaling of and a greater selectivity to the kinase than defactinib.[2]

In addition, Chen et al. developed a PROTAC targeted against interleukin-1 receptor-associated kinase 4 (IRAK4) that inhibited the enzymatic and scaffolding activity of the protein, as well as had a greater efficacy in inhibiting the activation of downstream signaling.[10]

CONTINUED ON NEXT PAGE

PROTACs

CONTINUED FROM PREVIOUS PAGE

A major issue in chemotherapy is the development of resistance, where mutations interfere with the activity of small-molecule inhibitors. PROTACs can overcome this obstacle since their activity relies on the binding to the protein without necessarily inhibiting the protein and instigating its degradation.

One example of such a PROTAC was MT-802, which was based on the structure of ibrutinib and produced a response against C481S-mutated chronic lymphocytic leukemia cancer cells that displayed resistance to ibrutinib. The PROTAC also had greater selectivity to Burton's tyrosine kinases.[15]

Other instances include the enzalutamide-derived ARCC-4 that can degrade mutant androgen receptors,[16] the SIAIS117 that used brigatinib as the warhead, which inhibited the growth of G1202R-mutant ALK (anaplastic lymphoma kinase) cell lines at a greater degree than brigatinib,[17] and GMB-475, which degraded BCR-ABL1, c-ABL1 and imatinib-resistant T315I BCR-ABL1.[18]

PROTACs may also aid in imparting improved target selectivity. For instance, Khan et al. developed DT2216 from a B-cell lymphoma extra-large (BCL-XL) inhibitor called ABT263 or navitoclax.

The issue with ABT263 was that it causes thrombocytopenia and thus is dose limited. Khan et al. observed that the PROTAC had a greater potency against MOLT-4 cells than ABT263 and less platelet toxicity.

The PROTAC also had a synergistic effect in combination with docetaxel against tumor growth and in combination with von Hippel-Lindau (VHL) chemotherapy in increasing survival in mice with CUL76 T-cell acute lymphoblastic leukemias patient-derived xenografts (PDX).[19]

In another case, Bondeson et al. developed PROTACs from foretinib, a promiscuous inhibitor of c-Met tyrosine kinase that they observed to have bonded to 133 different kinases at a concentration of 10 nM.

One VHL-recruiting PROTAC bonded to 52 of the tested kinases while a Cereblon-recruiting PROTAC bonded to 62 kinases.

For 54 kinases that are targets of foretinib and of which there is quantitative proteomics data, the VHL PROTAC degraded nine kinases while the Cereblon PROTAC degraded 14 kinases.[20]

TABLE 1: COMPARISON AMONG PROTACS, SMALL-MOLECULE INHIBITORS, MONOCLONAL ANTIBODIES, siRNA AND CRISPR

	PROTAC	Small-molecule inhibitors	Monoclonal antibodies	siRNA	CRISPR
Targets	Proteins on cell surfaces and inside the cell	Proteins on cell surfaces and inside the cell	Proteins on cell surfaces	RNA	DNA
Degree of Selectivity	Sufficient	Poor	Sufficient	Sufficient	Sufficient
Oral Bioavailability	Yes	Yes	No	No	No
Tissue Penetration	Yes	Yes	Poor	Poor	Yes
Targets Proteins with Scaffolding Function	Yes	No	Yes	Yes	Yes
Elimination of Pathogenic Proteins	Yes	No	No	Yes	Yes
Catalytic Mechanism of Action	Yes	No	No	Yes	Yes

CHALLENGES OF PROTACs

There are some issues in PROTAC development. One of these issues is the hook effect that occurs at high concentrations. This is due to binding saturation that results in the formation of unintended binary PROTAC-E3 and PROTAC-protein complexes, as opposed to the intended ternary E3-PROTAC-protein complex. These binary complexes have the potential for off-target protein degradation in the case of the E3-PROTAC complexes and for an alternative pharmacological response in the case of the PROTAC-protein complex.[21]

Off-target protein degradation is also a concerning challenge and has been observed in multiple studies.[7,12,20]

In addition, drug resistance can develop as a result of PROTACs themselves. Zheng et al. observed acquired resistance to BET-PROTACs due to genomic alterations that affect components of the E3 ligand complex, primarily chromosomal deletion of the CRBN gene and alterations to the CUL2 locus resulting in loss of function.[22]

Only a few of the more than 600 known E3 ligases in the human genome were recruited for the development of PROTAC, providing opportunities in expanding the repertoire.[23]

Finally, toxicity secondary to prolonged protein degradation may be present as an obstacle for determining the optimal dose and schedule for these drugs.

PROTACs IN CLINICAL DEVELOPMENT

PROTACs and other forms of targeted protein degradation like molecule glues are of great interest to the pharmaceutical industry.

Some companies, though relatively small, have targeted protein degraders in their research and pipelines and include Arvinas, BioTheryx, and Monte Rosa Therapeutics. There are currently several PROTACs undergoing clinical trials **(see Table 2)**, a portion of which with published structures **(see Figure 2)**.

ARV-110, which is undergoing Phase I and II trials (NCT05177042 and NCT03888612), targets androgen receptors and promotes their degradation.

The molecule degraded the AR in all the tested lines with an observed 50% degradation concentration under 1 nM, as well as degraded mutant AR proteins.

CONTINUED ON NEXT PAGE

PROTACs

CONTINUED FROM PREVIOUS PAGE

In addition, the PROTAC inhibited tumor growth in castrated and intact VCap models and AR-expressing prostate PDX models. The molecule has sufficient oral bioavailability.[24]

Investigators in a first-in-human Phase I study (NCT03888612) of 18 patients with metastatic castrate-resistant prostate cancer (mCRPC) with at least two prior therapies (one of which being enzalutamide, abiraterone or both) observed that two patients, who had concurrent rosuvastatin, had increased rosuvastatin plasma concentrations and Grade 3 or higher elevated alanine transaminase or aspartate transaminase. Out of the 15 patients evaluated for prostate specific antigen response, two had a reduction over 50% and were both in the 140 mg dose group.[25]

The other study (NCT05177042) is a Phase Ib clinical trial which is evaluating the safety, tolerability and pharmacokinetics of ARV-110 oral tablets in combination with abiraterone in mCRPC patients.[26]

Arvinas's October 2019 press release on the initial data stated that 35, 70 and 140 mg doses of ARV-110 were well tolerated and lacked any observed grade 2 or higher related adverse events.[27]

In its third quarter 2021 financial report, Arvinas stated that it intends to present the complete data from a Phase I dose escalation study and the interim data from a Phase II dose expansion study in February 2022.[28]

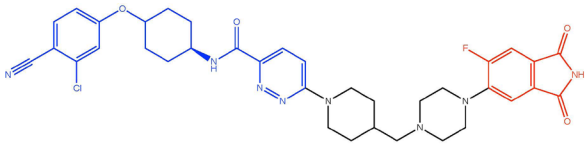
ARV-471 is a PROTAC that targets estrogen receptors (ER) and is intended for the treatment of breast cancer. The molecule degraded ER in ER-positive breast cancer cell lines at a 50% degradation concentration of approximately 2 nM, resulting in the inhibition of cell proliferation.

Preclinical oral administration of ARV-471 at 3, 10, and 30 mg/kg doses daily resulted in an inhibition of tumor growth in estradiol-dependent MCF7 xenograft models and a reduction of tumor ER proteins by over 90%. ARV-471, at 10 mg/kg doses, also inhibited the growth and decreased levels of mutant ER in a hormone-independent PDX model. ARV-471 also produces a 130% tumor growth inhibition and significant knockdown of ER when used in combination with the CDK4/6 inhibitor palbociclib.[29]

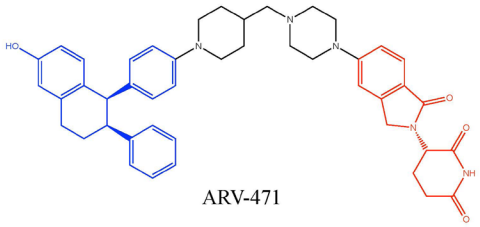
An October 2019 press release about an ongoing Phase 1/2 trial of ARV-471 (NCT04072952) stated that 30 mg ARV-471 was well-tolerated.[27]

FIGURE 2: CHEMICAL STRUCTURE OF SELECTED PROTACS UNDERGOING CLINICAL TRIALS

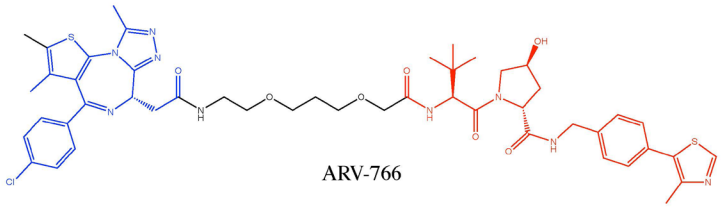
- **WARHEADS, OR PROTEIN-BINDING LIGANDS ARE LABELED IN RED**
- **LINKERS ARE LABELED IN BLACK**
- **E3 LIGANDS ARE LABELED IN BLUE**



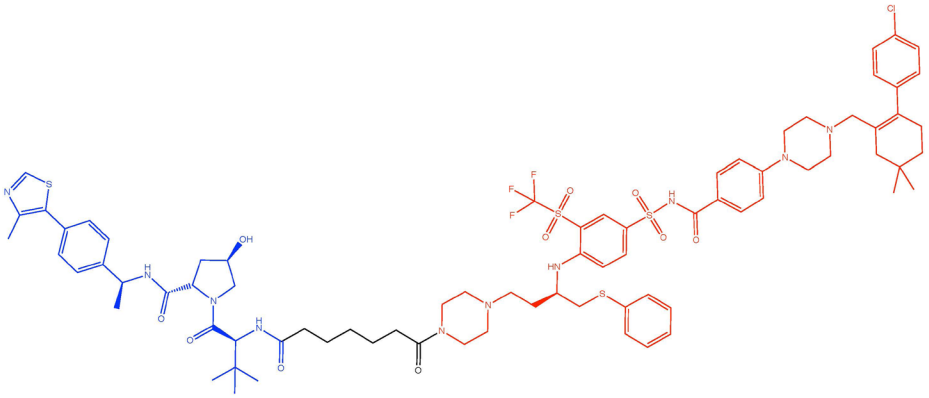
ARV-110



ARV-471



ARV-766



DT22216

In a December 2021 press release by Arvinas and its collaborator Pfizer, the companies announced that in 2022, they anticipated beginning Phase III trials for ARV-471 in metastatic breast cancer, beginning additional Phase I and II trials and presenting the data collected from the ongoing trials.[30]

The sponsor of the previously mentioned DT2216 is Dialectic

CONTINUED ON NEXT PAGE

PROTACs

CONTINUED FROM PREVIOUS PAGE

Therapeutics. A recent preclinical study found that the combination of DT2216 and gemcitabine caused a synergistic killing of pancreatic cancer cell lines.

In addition, the combination induced a greater inhibition of G-68 xenografts and PDX tumors in mice and further increased the survival of mice than either agent alone.[31]

Dialectic Therapeutics is currently performing a first-in-human, dose escalation Phase I study in patients with advanced or metastatic malignancies to determine DT2216's safety, efficacy, tolerability and pharmacokinetics.[32]

CONCLUSION

Overall, PROTACs are a continually developing therapeutic modality that could greatly benefit the field of oncology. These protein degraders can target the "undruggable" genome, impart more target selectivity, and be effective against cancer cells resistant to small molecule inhibitors.

However, there are still challenges and opportunities for PROTACs, whether it's the challenge of preventing the hook effect or expanding the E3 toolbox.

With several PROTACs undergoing clinical trials and many more in preclinical development, there soon may be an entirely new class of drugs for the treatment of cancers and other disorders.

▲ **Huy Pham** is a PharmD Candidate (2024) at the University of Toronto – Leslie Dan Faculty of Pharmacy in Toronto, Ontario (Canada).

TABLE 2: PROTACs CURRENTLY UNDERGOING AND APPROACHING CLINICAL DEVELOPMENT

DRUG	SPONSOR	TARGET	INDICATION	STATUS	CLINICAL TRIALS
ARV-110	Arvinas	Androgen receptor	Metastatic castration-resistant prostate cancer	Phase II	NCT03888612 NCT05177042
ARV-471	Arvinas	Estrogen receptor	ER-positive/HER2-negative breast cancer	Phase II	NCT04072952
ARV-766	Arvinas	Androgen receptor	Metastatic castration-resistant prostate cancer	Phase I	NCT05067140
CC-94676	Bristol Myers Squibb	Androgen receptor	Metastatic castration-resistant prostate cancer	Phase I	NCT04428788
DT2216	Dialectic	B-cell lymphoma extra large	Liquid and solid cancer	Phase I	NCT04886622
FHD-609	Foghorn	Bromodomain Containing 9	Synovial sarcoma	Phase I	NCT04965753
KT-474	Kymera/ Sanofi	Interleukin 1 receptor associated kinase 4	Immuno-inflammatory diseases such as atopic dermatitis	Phase I	NCT04772885
NX-2127	Nurix	Bruton's tyrosine kinase w/ immunomodulatory imide drug activity	B-cell malignancies	Phase I	NCT04830137
NX-5948	Nurix	Bruton's tyrosine kinase	B-cell malignancies	Phase I	NCT05131022
CFT8634	C4 Therapeutics	Bromodomain Containing 9	Synovial sarcoma and SMARCB1-deleted solid tumors	Filing an IND	N/A
CG001419	Cullgen	Tropomyosin receptor kinase	Cancer	Filing an IND	N/A
KT-413	Kymera	Interleukin 1 receptor associated kinase 4 with immunomodulatory imide drug activity	Relapsed/refractory B cell lymphomas	Yet to enter Phase I	N/A
KT-333	Kymera	Signal transducer and activator of transcription 3	Liquid and solid tumors	Yet to enter clinical trials	N/A
KT-253	Kymera	Mouse double minute 2 homolog	Liquid and solid tumors	Filing an IND	N/A

REFERENCES

1. Bondeson DP, Mares A, Smith IE, et al. Catalytic in vivo protein knockdown by small-molecule PROTACs. Nature Chemical Biology. 2015;11(8):611-617. doi:10.1038/nchembio.1858.

2. Cromm PM, Samarasinghe KT, Hines J, Crews CM. Addressing kinase-independent functions of FAK via PROTAC-mediated degradation. Journal of the American Chemical Society. 2018;140(49):17019-17026. doi:10.1021/jacs.8b08008.

3. Lu J, Qian Y, Altieri M, et al. Hijacking the E3 ubiquitin ligase Cereblon to efficiently target BRD4. Chemistry & Biology. 2015;22(6):755-763. doi:10.1016/j.chembiol.2015.05.009.

4. Olson CM, Jiang B, Erb MA, et al. Pharmacological perturbation of CDK9 using selective CDK9 inhibition or degradation. Nature Chemical Biology. 2017;14(2):163-170. doi:10.1038/nchembio.2538.

5. Raina K, Lu J, Qian Y, et al. PROTAC-induced BET protein degradation as a therapy for castration-resistant prostate cancer. Proceedings of the National Academy of Sciences. 2016;113(26):7124-7129. doi:10.1073/pnas.1521738113.

6. Zhou B, Hu J, Xu F, et al. Discovery of a small-molecule degrader of Bromodomain and extra-terminal (BET) proteins with picomolar cellular potencies and capable of achieving tumor regression. Journal of Medicinal Chemistry. 2017;61(2):462-481. doi:10.1021/acs.jmedchem.6b01816.

7. Bai L, Zhou H, Xu R, et al. A potent and selective small-molecule degrader of STAT3 achieves complete tumor regression in vivo. Cancer Cell. 2019;36(5):304-314. doi:10.1016/j.ccell.2019.10.002.

8. Zhou H, Bai L, Xu R, et al. Structure-based discovery of SD-36 as a potent, selective, and efficacious PROTAC degrader of STAT3 protein. Journal of Medicinal Chemistry. 2019;62(24):11280-11300. doi:10.1021/acs.jmedchem.9b01530.

9. Nunes J, McGonagle GA, Eden J, et al. Targeting IRAK4 for degradation with protacs. ACS Medicinal Chemistry Letters. 2019;10(7):1081-1085. doi:10.1021/acsmedchemlett.9b00219.

10. Chen Y, Ning Y, Bai G, et al. Design, synthesis, and biological evaluation of IRAK4-targeting protacs. ACS Medicinal Chemistry Letters. 2020;12(1):82-87. doi:10.1021/acsmedchemlett.0c00474.

11. Dölle A, Adhikari B, Krämer A, et al. Design, synthesis, and evaluation of WD-repeat-containing protein 5 (WDR5) degraders. Journal of Medicinal Chemistry. 2021;64(15):10682-10710. doi:10.1021/acs.jmedchem.1c00146.

CONTINUED ON NEXT PAGE

PROTACs

CONTINUED FROM PREVIOUS PAGE

12. Hsu JH-R, Rasmusson T, Robinson J, et al. EED-targeted protacs degrade EED, EZH2, and SUZ12 in the PRC2 complex. Cell Chemical Biology. 2020;27(1):41-46. doi:10.1016/j.chembiol.2019.11.004.

13. Bensimon A, Pizzagalli MD, Kartnig F, et al. Targeted degradation of SLC transporters reveals amenability of multi-pass transmembrane proteins to ligand-induced proteolysis. Cell Chemical Biology. 2020;27(6):728-739. doi:10.1016/j.chembiol.2020.04.003.

14. Schneider M, Radoux CJ, Hercules A, et al. The PROTACtable genome. Nature Reviews Drug Discovery. 2021;20(10):789-797. doi:10.1038/s41573-021-00245-x.

15. Buhimschi AD, Armstrong HA, Toure M, et al. Targeting the C481s ibrutinib-resistance mutation in Bruton's tyrosine kinase using PROTAC-mediated degradation. Biochemistry. 2018;57(26):3564-3575. doi:10.1021/acs.biochem.8b00391.

16. Salami J, Alabi S, Willard RR, et al. Androgen receptor degradation by the proteolysis-targeting Chimera ARCC-4 outperforms enzalutamide in cellular models of Prostate Cancer Drug Resistance. Communications Biology. 2018;1(1):100. doi:10.1038/s42003-018-0105-8.

17. Sun N, Ren C, Kong Y, et al. Development of a brigatinib degrader (SIAIS117) as a potential treatment for ALK positive cancer resistance. European Journal of Medicinal Chemistry. 2020;193:112190. doi:10.1016/j.ejmech.2020.112190.

18. Burslem GM, Schultz AR, Bondeson DP, et al. Targeting BCR-ABL1 in chronic myeloid leukemia by PROTAC-mediated targeted protein degradation. Cancer Research. 2019;79(18):4744-4753. doi:10.1158/0008-5472.can-19-1236.

19. Khan S, Zhang X, Lv D, et al. A selective Bcl-XL PROTAC degrader achieves safe and potent anti-tumor activity. Nature Medicine. 2019;25(12):1938-1947. doi:10.1038/s41591-019-0668-z.

20. Bondeson DP, Smith BE, Burslem GM, et al. Lessons in PROTAC design from selective degradation with a promiscuous warhead. Cell Chemical Biology. 2018;25(1):78-87. doi:10.1016/j.chembiol.2017.09.010.

21. Moreau K, Coen M, Zhang AX, et al. Proteolysis-targeting chimeras in drug development: A safety perspective. British Journal of Pharmacology. 2020;177(8):1709-1718. doi:10.1111/bph.15014.

22. Zhang L, Riley-Gillis B, Vijay P, Shen Y. Acquired resistance to BET-PROTACs (proteolysis-targeting chimeras) caused by genomic alterations in core components of E3 ligase complexes. Molecular Cancer Therapeutics. 2019;18(7):1302-1311. doi:10.1158/1535-7163.mct-18-1129.

23. Ishida T, Ciulli A. E3 ligase ligands for PROTACs: How they were found and how to discover new ones. SLAS DISCOVERY: Advancing the Science of Drug Discovery. 2020;26(4):484-502. doi:10.1177/2472555220965528.

24. Neklesa T, Snyder LB, Willard RR, et al. ARV-110: An oral androgen receptor PROTAC degrader for prostate cancer. Journal of Clinical Oncology. 2019;37(7 Supplement):259-259. doi:10.1200/jco.2019.37.7_suppl.259.

25. Petrylak DP, Gao X, Vogelzang NJ, et al. First-in-human phase I study of ARV-110, an androgen receptor (AR) PROTAC degrader in patients (PTS) with metastatic castrate-resistant prostate cancer (mCRPC) following enzalutamide (ENZ) and/or abiraterone (ABI). Journal of Clinical Oncology. 2020;38(15 Supplement):3500-3500. doi:10.1200/jco.2020.38.15_suppl.3500.

26. Trial of ARV-110 and abiraterone in patients with metastatic castration resistant prostate cancer (mCRPC). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05177042. Published January 6, 2022. Accessed January 16, 2022.

27. Arvinas. Arvinas presents a platform update, including initial data from the first two clinical trials of PROTAC® targeted protein Degraders. Arvinas. https://ir.arvinas.com/news-releases/news-release-details/arvinas-presents-platform-update-including-initial-data-first. Published October 23, 2019. Accessed January 16, 2022.

28. Arvinas. Arvinas reports third quarter 2021 financial results and provides Corporate Update. Arvinas. https://ir.arvinas.com/news-releases/news-release-details/arvinas-reports-third-quarter-2021-financial-results-and. Published November 3, 2021. Accessed January 16, 2022.

29. Flanagan JJ, Qian Y, Gough SM, et al. Abstract P5-04-18: ARV-471, an oral estrogen receptor PROTAC degrader for breast cancer. Cancer Research. 2019;79(4 Supplement). doi:10.1158/1538-7445.sabcs18-p5-04-18.

30. Arvinas. Arvinas and Pfizer announce PROTAC® protein Degrader ARV-471 continues to demonstrate encouraging clinical benefit rate in patients with locally advanced or metastatic ER+/HER2- breast cancer. Arvinas. https://ir.arvinas.com/news-releases/news-release-details/arvinas-and-pfizer-announce-protacr-protein-degrader-arv-471. Published December 10, 2021. Accessed January 16, 2022.

31. Thummuri D, Khan S, Underwood PW, et al. Overcoming gemcitabine resistance in pancreatic cancer using the bcl-XL–specific degrader DT2216. Molecular Cancer Therapeutics. 2021;21(1):184-192. doi:10.1158/1535-7163.mct-21-0474.

32. A study of DT2216 in relapsed/refractory malignancies - full text view. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04886622. Published October 12, 2021. Accessed January 16, 2022.

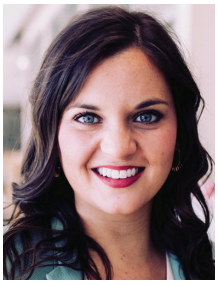
NCODA UNIVERSITY TO PROVIDE EDUCATIONAL RESOURCES TO PATIENTS, MEMBERS, INDUSTRY PARTNERS AND STUDENTS

NCODA is launching **NCODA University** to meet the growing needs of patients, members, industry partners and students.

NCODA University will utilize a four-columned structure encompassing educational initiatives specifically designed for each of the different facets.

Julianne Darling, PharmD, BCOP, Manager of Education at NCODA, will oversee the program.

"NCODA University includes education for all of our stakeholders," Darling said. "Continuing Education (CE) for our membership is the backbone of the program. However, we also recognize that increased educational opportunities for our students and industry stakeholders are crucial to improving oncology care."



Julianne Darling

NCODA University will continue to offer existing NCODA resources for patients, including Oral Chemotherapy Education (OCE) and Intravenous Cancer Treatment Education (IVE) sheets. Additional patient educational material, including adherence resources and adverse event graphics, also are in development.

Already accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education for pharmacists and pharmacy technicians, NCODA now plans to seek additional accreditation to offer CE to nursing and physician members.

NCODA University also will expand educational services for member practices through new options, including a program that will allow experts from oncology practices to share their expertise with faculty from pharmacy schools. This program will continue meeting the needs of our clinical members that work in the community, academic and hospital/health system setting, whether in the infusion or oral dispensing pharmacy.

NCODA University will provide industry stakeholders with a virtual expert speaker library, Medically Integrated Pharmacy (MIP) Significance Training and a learning module designed specifically to empower them to have more meaningful conversations with practice leaders in the clinic setting. Each facet of an industry stakeholder's organization, whether it be commercial or medical for example, will have access to relevant and timely training and education.

For trainees — including students, residents and fellows — NCODA University will host several new offerings:

- An "introduction to oncology" program that will compliment the collegiate oncology pharmacy course;
- Disease-state modules that will build on basic oncology pharmacy learning and allow trainees to focus on specific hematology/oncology topics;
- A NAPLEX prep program to assist pharmacy students preparing to take the North American Pharmacist Licensure Examination®; and
- Simulated interview prep to help students prepare for job interviews.

"As part of our Mission to empower the medically integrated oncology team, we are excited to announce NCODA University," said Michael Reff, Executive Director and Founder of NCODA.

"This new educational platform will help us continue providing quality education to a variety of different stakeholders in oncology — from our students and industry partners to our clinical members and the patients they serve."

For more information or questions about NCODA University, email **Julianne.Darling@NCODA.org**.

MEN LIVED 2X LONGER WITHOUT CANCER SPREADING[1,2]

40.4 months vs 18.4 months for ADT alone

HR: 0.41; 95% CI: 0.34-0.50; *P*<0.0001 (intent-to-treat).

REDUCED RISK OF DEATH BY NEARLY A THIRD[1,3]

31% reduction in the risk of death vs ADT alone

Secondary endpoint: HR: 0.69; 95% CI: 0.53-0.88; *P*=0.003. Medians not estimable.

INDICATION

NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

IMPORTANT SAFETY INFORMATION

Embryo-Fetal Toxicity: Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥1 % of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs 11%), pain in extremity (6% vs 3%) and rash (3% vs 1%).

Clinically significant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs 3.4% on placebo) and heart failure (2.1% vs 0.9% on placebo).

Drug Interactions

Effect of Other Drugs on NUBEQA – Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

For your patient with non-metastatic castration-resistant prostate cancer (nmCRPC)

HELP HIM LIVE FOR WHAT HE LOVES

PROVIDED THE RELIEF OF AN EXTRA 15 MONTHS WITHOUT PAIN PROGRESSION[1,3]*

40.3 months vs 25.4 months for ADT alone

Secondary endpoint: HR: 0.65; 95% CI: 0.53-0.79; *P*<0.0001.

POSTPONED CYTOTOXIC CHEMOTHERAPY—MORE TIME WITHOUT CHEMO[1,3]

42% risk reduction in time to chemo vs ADT alone

Secondary endpoint: HR: 0.58; 95% CI: 0.44-0.76; *P*<0.0001. Medians not estimable.

CHOOSE NUBEQA® 1st FOR EXTENDED SURVIVAL.[1-3] NUBEQAHCP.COM

Drug Interactions (cont'd)

Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible. If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Review the prescribing information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.[1]

*Time to pain progression was defined as at least a 2-point worsening from baseline of pain score on BPI-SF (a validated health-related quality-of-life instrument) or initiation of opioids and reported in 28% of all patients on study.

Study design

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled phase III study (ARAMIS) in nmCRPC patients on ADT with a PSA doubling time ≤10 months. 1509 patients were randomized 2:1 to 600 mg NUBEQA twice daily (n=955) or placebo (n=554). MFS was defined as time from randomization to time of first evidence of BICR-confirmed distant metastasis or death from any cause ≤33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, ^{99m}Tc bone scan by BICR, unacceptable toxicity, or withdrawal.[1,2]

ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; BPI-SF=Brief Pain Inventory Short Form; PSA=prostate-specific antigen; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging.

Please see the following page for the brief summary of Prescribing Information.

NUBEQA® (darolutamide) 300 mg tablets

NUBEQA® (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NUBEQA is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female *[see Clinical Pharmacology (12.1)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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.

ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC). In this study, patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.

Overall, serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1 % of patients who received NUBEQA included urinary retention, pneumonia and hematuria. Overall 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

Table 1 shows adverse reactions in ARAMIS reported in the NUBEQA arm with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.

Table 1: Adverse Reactions in ARAMIS

Adverse Reaction[2]	NUBEQA (n=954)		Placebo (n=554)	
	All Grades %	Grades ≥ 3 %	All Grades %	Grade ≥ 3 %
Fatigue[1]	16	0.6	11	1.1
Pain in extremity	6	0	3	0.2
Rash	3	0.1	1	0

[1] Includes fatigue and asthenia
[2] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Additionally, clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure (2.1% versus 0.9% on placebo).

Table 2: Laboratory Test Abnormalities in ARAMIS

Laboratory Abnormality	NUBEQA (N=954)[1]		Placebo (N=554)[1]	
	All Grades[2] %	Grade 3-4[2] %	All Grades[2] %	Grade 3-4[2] %
Neutrophil count decreased	20	4	9	0.6
AST increased	23	0.5	14	0.2
Bilirubin increased	16	0.1	7	0

[1] The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.
[2] Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NUBEQA

Combined P-gp and Strong or Moderate CYP3A4 Inducer

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity *[see Clinical Pharmacology (12.3)]*. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Combined P-gp and Strong CYP3A4 Inhibitors

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure *[see Clinical Pharmacology (12.3)]* which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed *[see Dosage and Administration (2.2)]*.

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and C_{max} of BCRP substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of BCRP substrate-related toxicities.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug.

References: 1. NUBEQA (darolutamide) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; January 2021. **2.** Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2019;380(13):1235-1246. **3.** Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med.* 2020;383(11):1040-1049.

NUBEQA is an inhibitor of OATP1B1 and OATP1B3 transporters. Concomitant use of NUBEQA may increase the plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA *[see Clinical Pharmacology (12.3)]*.

Review the prescribing information of the BCRP, OATP1B1 and OATP1B3 substrates when used concomitantly with NUBEQA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy *[see Clinical Pharmacology (12.1)]*. Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Use in Specific Populations (8.1)]*.

Infertility

Males

Based on animal studies, NUBEQA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m^2) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30-89 mL/min/1.73 m^2). The effect of end stage renal disease (eGFR ≤15 mL/min/1.73 m^2) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function *[see Clinical Pharmacology (12.3)]*.

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was clastogenic in an *in vitro* chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the *in vivo* combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, hypospermia, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

17 PATIENT COUNSELING INFORMATION

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

Dosage and Administration

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose *[see Dosage and Administration (2.1)]*.

Embryo-Fetal Toxicity

Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy *[see Use in Specific Populations (8.1)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)]*.

Infertility

Advise male patients that NUBEQA may impair fertility *[see Use in Specific Populations (8.3)]*.

Manufactured by: Orion Corporation, Orion Pharma, FI-02101 Espoo, Finland

Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA

For more information, call Bayer HealthCare Pharmaceuticals Inc. at Bayer at 1-888-842-2937 or go to www.NUBEQA-us.com

6711101BS1

DIGITAL MONITORING STRATEGY BOOSTS SYMPTOM RESPONSE IN PATIENT-REPORTED OUTCOMES STUDY

NCODA's PQI Podcast recently featured an interview with Ethan Basch, MD, MSc, an oncologist and outcomes researcher at the University of North Carolina, where he is Chief of Oncology and Physician-in-Chief of the North Carolina Cancer Hospital. Basch is also a member of the Board of Directors of American Society of Clinical Oncology, an editor for *The Journal of the American Medical Association* (JAMA), and has served on the Board of Scientific Advisors of the National Cancer Institute.

Basch has led a research program for many years focused on bringing the patient voice into cancer drug development and into daily oncology practice. He became interested in the topic at the beginning of his career.

"It started to become clear to me that patients were experiencing a lot of symptoms that we were not necessarily capturing," Basch explained. "This became most clear to me in clinical trials that we were conducting where many patients had to discontinue drugs or come off trial because of symptomatic side effects like severe fatigue or nausea."

"But when we looked at the results of the trials, the symptoms were invisible to us. We didn't see it there. We had a sense that this was going on, but we weren't capturing that information. This led me to do some research in this area, looking at whether or not in fact we're missing what the patients are experiencing."

Basch's group began a number of studies, where they simply asked patients to self-report what their symptoms were during care. They then asked the patients' clinical teams to record the same thing.

The group's findings were startling.

"We found that we, as providers, miss about half of the symptoms that our patients are experiencing," Basch said.

On **The PQI Podcast**, Dr. Basch explains his study, the monitoring system and the care team response in greater detail. **Scan the QR code to listen to the interview.**

"Patients with cancer are a highly symptomatic group, particularly those who have advanced or metastatic disease, or who are receiving active therapy either with chemotherapy or radiation, or some of our new targeted immunotherapy agents."

As a result of this data, Basch began focusing on an issue known as Patient Reported Outcomes (PROs), utilizing digital monitoring technology.

"The basic idea is the use of connected health technologies to capture how patients are feeling and functioning in order to convey that information back to the clinical team," Basch said.

Basch now heads an ongoing national cluster randomized trial on the issue. An abstract on the trial, "Digital symptom monitoring with patient-reported outcomes in community oncology practices," was recently published in the *Journal of Clinical Oncology*.

The trial randomized patients 1:1 to digital symptom monitoring with PRO surveys or to usual care control. The PRO surveys could occur via handheld devices, or web-based or automated telephone-based systems. Whenever a patient reported a severe worsening symptom, it triggered a real-time alert to the clinical team.

An initial analysis "found significant and clinically meaningful improvement in quality of life, symptom control and physical function for patients using the electronic monitoring strategy compared to routine care," Basch said. "This is a strategy that can benefit our patients."

The PQI Podcast provides an overview of new Positive Quality Intervention (PQI) documents as well as PQI in Action articles and other oncology topics. The podcast features clinical and administrative experts who are utilizing these documents at their care centers nationwide. Listen to the podcast on Apple and Spotify by searching "The PQI Podcast." Links also can be found at NCODA.org, or follow us on Instagram @thepqipodcast. Have a topic or a speaker recommendation for The PQI Podcast? Email **Ginger.Blackmon@NCODA.org**.

AN ENTERPRISE APPROACH TO INTEGRATE PHARMACY OPERATIONS & CLINICAL PHARMACY SERVICES IN THE COMMUNITY ONCOLOGY SETTING

By Melody Chang, RPh, MBA, BCOP, Camilo Rodriguez, CPhT-Adv, CSPT, PRS, Jenny Li, PharmD, BCPS, BCOP, Darell Connor, MHA, FWSPA, CSPT, CPhT, & April Arredondo, CPhT, CAPM

Melody Chang

Camilo Rodriguez

Jenny Li

Darell Connor

April Arredondo

The role of pharmacists and pharmacy technicians in community oncology has evolved and increased over the last few decades.

While many medically integrated pharmacy (MIP) models hold a strong focus on oral oncolytics, an area of continued development remains in the management of infusion pharmacy services. Thriving in today's cancer care environment can be challenging with the continuous changes in healthcare regulation and increasing complexities of new infusion therapies.

At the American Oncology Network, LLC (AON) the Pharmacy Operations team delivers operational, clinical and financial efficiencies based on the most sustainable infusion practices. By integrating best principles and determining optimal methods to support pharmaceutical services' inpatient care delivery, AON's Pharmacy Operations team empowers its practice partners to succeed.

The network is an alliance of physicians and seasoned healthcare leaders partnering to ensure the long-term success of community oncology. Established in 2018, the rapidly-growing AON enterprise represents 107 physicians and 85 nurse practitioners and physician assistants practicing across 17 states.

As part of AON's Central Services, the Pharmacy Operations department is structured to support infusion pharmacy services using its board-certified pharmacist and technician administrators. The department is serviced by three teams:

- Operations & Administration
- Clinical Pharmacists
- Pharmacy Services

While this structure may seem unique compared to other pharmacy models in health systems, academic settings, and other community oncology settings, these three teams within the department help provide a wide range of services and support to ensure optimal patient outcomes.

OPERATIONS & ADMINISTRATION

The Pharmacy Operations team works with practice administrators to deliver various services, including inventory management, pharmacy staff training, regulatory affairs and compliance. The team is comprised of pharmacy technician administrators with vast experience in operational and administrative support.

As a growing network, AON understands the value that pharmacy technician advancement brings to an organization and routinely encourages growth across all areas. Allowing pharmacy technicians to practice at the top of their field has enabled the Pharmacy Operations team to grow its skillsets to best support our network. We are incredibly proud of our team. Our diverse group has technicians that are certified and experienced in:

- Sterile compounding (CSPT);
- Advanced Pharmacy Technicians (CPhT-Adv), including Hazardous Drug Management, Technician Product Verifications and Controlled Substance Diversion Prevention;
- Project Management;
- Pharmacy Regulatory Compliance; and
- Data Analytics.

CONTINUED ON NEXT PAGE

AON

CONTINUED FROM PREVIOUS PAGE

Many of the core services provided by this team help ensure the long-term success of community oncology, especially with the strong focus on inventory management and drug loss.

Mitigating drug losses is pivotal to an organization and knowing how to leverage spoilage reimbursement programs is equally important. Through our size and scale, we have been able to work with many manufacturers to recover losses incurred from the mishandling of injectable products.

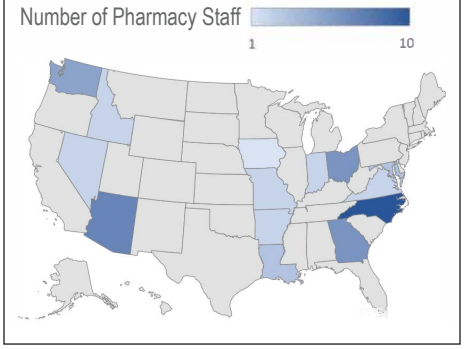
With changes in the regulatory landscape and oversight increasing, we work with each state board of pharmacy and medicine to stay updated on any regulatory changes that may impact our practice, ranging from USP 797 & 800 matters to other regulatory matters.

Ensuring that our network has established best pharmacy practices is a duty of our Pharmacy Transition Associates, who have trained more than 75 pharmacy staff members since AON's inception in 2018 **(see map)**.

Our Pharmacy Transition Associates play an essential role in our network, ranging from training support, post-training support, auditing, monitoring of inventory and more.

The creation of this team has allowed AON to provide a standard framework giving practices the tools and resources they need to best manage their infusion pharmacies and staff.

PHARMACY STAFF TRAINING



CLINICAL ONCOLOGY PHARMACISTS

Our Clinical Oncology Pharmacist team is comprised of pharmacists board certified in clinical oncology and pharmacotherapy. Through education, support and guidance on the safe and effective use of parenteral pharmaceuticals, our Clinical Oncology Pharmacists help to improve patient outcomes.

With more oncology treatment options with similar safety and efficacy profiles receiving FDA approval, drug formulary selection and adherence are becoming more important than ever before. Specifically, in the community oncology practice setting, frequent payor formulary exclusions also contribute to additional layers of complexity.

Our Clinical Oncology Pharmacist team plays an important role in maintaining the AON drug formulary and helps provide guidance to healthcare providers across our network to optimize formulary adherence.

Additional core clinical services provided by the Clinical Oncology Pharmacist team include:

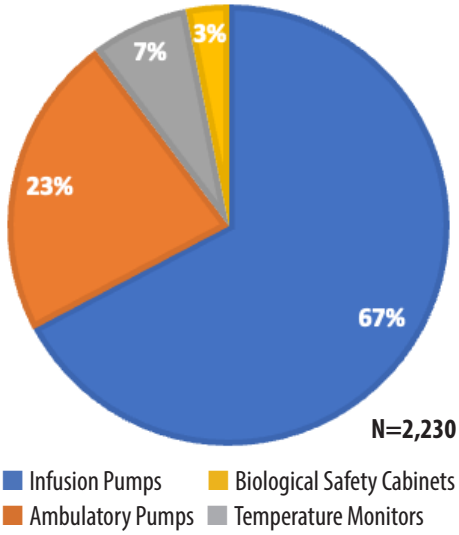
- Evidence-based therapeutic recommendations and clinical consultations;
- Drug shortage strategies and monitoring;
- Adverse event management, and surveillance;
- Medication error and near-miss reporting program, and root cause analyses;
- Drug & medication use evaluations; and
- Drug information & clinical in-services.

PHARMACY SERVICES

Our Pharmacy Services team is led by experts with extensive knowledge in pharmacy facilities, including cleanrooms and segregated compounding areas, waste management programs and asset management of everything ranging from infusion pumps, biological safety cabinets and temperature monitoring **(see pie chart)**.

The Pharmacy Services team continuously collaborates with subject matter experts within the healthcare space, especially with technological advancements and best practices within the infusion pharmacy environment.

PHARMACY SERVICES MANAGED ASSETS



This team provides an additional level of support that most community oncology practices would typically outsource to USP 800 consultants.

The optimal performance delivered by our pharmacy assets significantly contributes to the overall efficiency in workflows and enhancements in safety for both patients and the clinical team.

SUMMARY

Administration and Operations, Services and Asset Management, and Clinical Support are the three pillars that identify the core functions that Pharmacy Operations offers to all clinics within the American Oncology Network enterprise.

Through these pillars, Pharmacy Operations can fulfill the strategic initiatives outlined in its mission and vision statement to reshape the future of community oncology practice.

▲ **Melody Chang**, RPh, MBA, BCOP, is Vice President of Pharmacy Operations; **Camilo Rodriguez**, CPhT-Adv, CSPT, PRS, is Director of Pharmacy Operations; **Jenny Li**, PharmD, BCPS, BCOP, is Clinical Pharmacy Services Manager; **Darell Connor**, MHA, FWSPA, CSPT, CPhT, is a Pharmacy Intern and a Project Manager within Pharmacy Operations; and **April Arredondo**, CPhT, CAPM, is a Project Manager within Pharmacy Operations. All are members of the Pharmacy Operations team at American Oncology Network (AON).

OPTA OFFERS PHARMACY TECHNICIANS VALUE IN TRAINING AND COLLABORATION

The Oncology Pharmacy Technician Association (OTPA) has made significant strides in its mission to provide education, training, networking, and career opportunities for these valuable members of the medically integrated team.

Taryn Newsome

Over the past year, OPTA membership has doubled to nearly 700 members as more and more pharmacy technicians learn about its unique and valuable resources, which include regular networking opportunities, monthly webinars on oncology pharmacy technician specific topics, and OPTAReview, the group's monthly digital newsletter.

The group also has seen expansion in both the value and scope of its existing resources, namely OPTAReview and its monthly webinars.

OPTAReview has expanded to approximately five pages per issue, featuring articles written by OPTA leaders and special guest authors.

Special guest authors have included pharmacists from the University of Chicago Medicine, Baptist Health of Miami and NCODA's APPE Students.

Regular features include a **Technician in Focus** article profiling members and an **OPTA Leader in Focus** section introducing leaders to the membership.

OPTA's monthly webinars, which are held at 2 p.m. Eastern on the second Wednesday of each month, have proven to be well-attended by members.

OPTA members have the opportunity to network, engage and problem-solve with one another during a segment called the **Hot Topic** discussion.

During this discussion, OPTA members are welcome to unmute their microphones and contribute to the conversation.

Topics for roundtable discussions have included healthcare professional burn-out, the availability of new generic oncolytics, inventory essentials, dose adjustment and inventory management.

In addition to presentations by OPTA members, the webinars now provide opportunities for technicians to learn new drug indications and new drug updates from NCODA APPE students, as well as from corporate partners providing education on medications, side-effect management and drug interactions.

"The content we provide is a huge value," said Taryn Newsome, CPhT, OPTA Coordinator for NCODA. "Technicians tell us they enjoy our newsletter, networking opportunities and webinars, and our membership is continuing to increase."

In related news, OPTA has received its first corporate sponsorship to provide educational presentations at its monthly meetings. OPTA is now sponsored by Janssen Biotech, Inc./Pharmacyclics LLC, an AbbVie company.

Also, OPTA will participate in the 2022 NCODA Spring Forum, with three breakout tracks specifically for oncology pharmacy technicians.

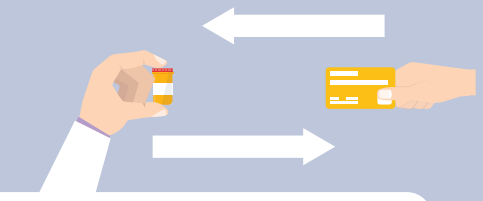
There is tremendous value in providing oncology pharmacy technician specific tracks, Newsome noted.

"OPTA's goal is to maximize the development of our members through training, collaboration, and sharing of resources so that we can continue providing exceptional care to cancer patients," Newsome said.

COPAY ACCUMULATORS: WHAT TO KNOW

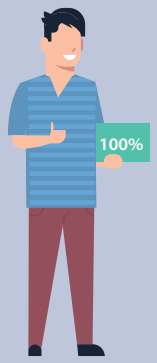
WHAT'S THE DIFFERENCE?

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

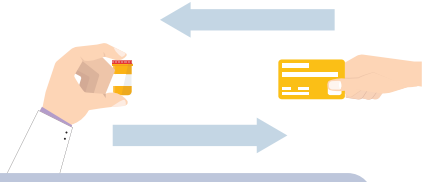
Prescription Drug Cost	$2,000.00
Manufacturer Coupon Value	-$1,995.00
Your Total at the Counter	$5.00

$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 What States Have Enacted Laws Or Active Legislation Regarding Copay Accumulators

By Tiba Al Sagheer, PharmD, BCOP, BCACP, & Cesar Ochoa, MD

SMALL-MOLECULE INHIBITORS AND THE ROLE OF THE PHARMACIST IN MANAGING

CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in Western countries. The incidence increases with age and is considered a disease of the elderly as the median age of diagnosis is approximately 68 years.[1]

In the U.S., it accounts for approximately one-third of all leukemias and in 2020, the estimated number of new cases was 21,040 with 4,060 reported deaths.[2,3]

Tiba Al Sagheer

Cesar Ochoa

The disease is characterized by a progressive accumulation of monoclonal, morphologically mature but functionally incompetent lymphocytes in the peripheral blood, bone marrow, and lymphoid tissue.[4-5]

The clinical presentation is highly variable. Most patients present with an indolent, asymptomatic disease and are diagnosed incidentally after a routine blood count reveals absolute lymphocytosis or after developing painless lymphadenopathy, which can be localized or generalized, while others can present with constitutional symptoms such as fatigue, unexplained fever, unintentional weight loss and drenching night sweats.

Splenomegaly and hepatomegaly are common, while skin involvement is an unusual manifestation.[6]

In a small subset of patients, CLL presents with autoimmune complications such as autoimmune hemolytic anemia, immune thrombocytopenia, pure red cell aplasia and rarely, agranulocytosis.[7]

Richter's transformation is the conversion of CLL into an aggressive lymphoma, typically diffuse large B-cell lymphoma with an incidence of 0.5 – 1% per year in newly diagnosed CLL patients. Richter's transformation manifests with rapidly enlarging lymphadenopathy, constitutional symptoms and extranodal involvement. The prognosis is poor.[8]

The diagnosis of CLL requires the presence of at least 5 X 109 /L monoclonal B-lymphocytes in the peripheral blood over a period of three months or longer, these cells might be admixed with larger atypical cells and the clonality of these B cells must be confirmed by peripheral blood flow cytometry.[9]

Immunophenotyping is key to establish a diagnosis, as CLL cells express CD5, CD19, CD20 and CD23 antigens, in addition to being negative for CD10 and cyclin D1.[9] On review of the peripheral blood smear, mechanically disrupted cells known as "smudge cells" are seen in virtually all patients. This phenomenon has been associated to a reduced expression of vimentin.[10]

Bone marrow aspiration and biopsy are generally not required for diagnosis or follow-up.

CLINICAL STAGING

The Rai and Binet classifications are widely accepted, simple and inexpensive systems for the clinical staging of CLL. Both rely on physical examination and blood parameters to assess the degree of tumor burden and describe three major prognostic groups with discrete clinical outcomes.[9-11]

In the modified Rai classification, patients stratified to low-risk disease (Rai Stage 0), intermediate-risk disease (Rai Stage I-II) and high-risk disease (Rai Stage III-IV) have median survival times of 150 months, 71-101 months and 19 months, respectively. In the Binet system, patients with Stage A disease have a median survival comparable to age-matched controls, while patients with Stage B and C have a median survival of 84 and 24 months, respectively.[9-11]

Specific cytogenetic abnormalities identified by fluorescence in situ hybridization (FISH) analysis, immunoglobulin heavy chain variable (IGHV) gene mutations and certain genes identified by molecular genetic testing confer prognostic significance in CLL. Patients with del(13)q, trisomy 12 and normal beta-2 microglobulin levels are considered to have a favorable prognosis, while patients with del(17p) or del(11q) are less likely to respond to initial therapy and more likely to develop disease relapse.[11]

Higher IGHV levels are incrementally associated with a favorable progression-free survival (PFS) and overall survival (OS). CD38, CD49d and ZAP-70 expression correlated with an unmutated IGHV and are used as surrogate markers of IGHV mutation status.[4]

The CLL International Prognostic Index (CLL-IPI) utilizes TP53 dysfunction,

CONTINUED ON NEXT PAGE

LEUKEMIA

CONTINUED FROM PREVIOUS PAGE

IGHV mutational status, serum beta-2 microglobulin, clinical stage and age to separate patients into four different groups with different overall survivals and allows for a more individualized management of CLL patients in clinical practice.[14]

The median time to initial therapy for patients in the CLL-IPI low- or intermediate-risk categories is seven years, while for patients in the high- or very high-risk categories it is only two years.[5]

Initial observation is considered standard of care for patients with early asymptomatic CLL, since the disease is considered incurable without an allogeneic hematopoietic stem cell transplant (HSCT). Many patients in this group will have survival rates comparable to those of the general population and there is evidence that immediate treatment does not improve long-term survival.[15]

INITIATING THERAPY

Therapy is generally indicated for patients with active disease. The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) defines active disease by the presence of one or more of the following criteria:

- Evidence of progressive bone marrow failure manifested by the development or worsening of anemia and/or thrombocytopenia;
- Massive, progressive or symptomatic splenomegaly;
- Massive, progressive or symptomatic lymphadenopathy;
- Progressive lymphocytosis with an increase of >50% over a two-month period or a lymphocyte doubling time of <6 months;
- Autoimmune hemolytic anemia and/or thrombocytopenia that is poorly responsive to corticosteroid therapy;
- Symptomatic or functional extranodal involvement; or
- The presence of constitutional symptoms such as unintentional weight loss, significant fatigue, fevers or drenching night without other evidence of infection.[9]

TREATMENT APPROACHES AND PHARMACOLOGIC CONSIDERATIONS

Historically, CLL therapy was based on alkylating agents such as chlorambucil, cyclophosphamide and bendamustine, nucleoside analogues such as fludarabine, pentostatin and cladribine as well as glucocorticoids.[5]

Elderly patients and those with comorbidities would receive lower intensity regimens with the most intensive therapy reserved for younger, fit patients.[5]

The addition of the anti-CD20 monoclonal antibodies rituximab, obinutuzumab and ofatumumab to these regimens resulted in an improved survival, becoming the standard of care before the advent of the current agents.[16,17]

As treatment approaches have evolved, the introduction of small molecule inhibitors has been favored due to the preferable route of administration, outcomes, and side effect profile.

There is currently no single agreed front-line treatment for CLL, and the most appropriate regimen is selected based on patient and disease characteristics, comorbidities, concomitant medications as well as the patient's goals and preferences.

In the following sections, we discuss the use of the small molecule inhibitors and the role of the pharmacist in management of therapy.

BTK INHIBITORS

Ibrutinib (IMBRUVICA®) is the first-in-class small molecule inhibitor of Bruton's tyrosine kinase (BTK), which targets the B cell receptor (BCR) signaling pathway, by blocking the nuclear factor KB (NF-KB). Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site leading to inhibition of BTK enzymatic activity.[18]

Ibrutinib is currently approved by the U.S. Food and Drug Administration (FDA) for patients with CLL. Ibrutinib was first studied in patients with relapsed or refractory (R/R) CLL and small group of previously untreated patients in which it showed high response rates and durable responses.[19]

Following that, five randomized controlled clinical trials RESONATE, RESONATE-2, HELIOS, iLLUMINATE, and E1912 also investigated ibrutinib use in frontline therapy and R/R CLL, which ultimately led to FDA approval for this patient population.[20-24]

The most commonly reported adverse reactions with ibrutinib in patients with CLL are thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, bruising and nausea.[18,20-24]

Other adverse events include bleeding, cardiac arrhythmias (ventricular arrhythmias, atrial fibrillation and atrial flutter), hypertension and increased risk of infections.[18,34]

Diarrhea with ibrutinib frequently occurs early on in the treatment course; it is self-limiting and can be managed with supportive care therapy.[25]

Minor bleeding has been reported in up to 66% and serious bleeding events in up to 6% of patients, the highest risk of bleeding is during the first three to six months of therapy initiation and decreases with continued therapy.[25, 26]

Acalabrutinib (CALQUENCE®) is a second-generation BTK inhibitor. It forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity.[27]

Acalabrutinib has higher BTK selectivity compared to ibrutinib, as it does not inhibit epidermal growth factor receptor (EGFR), interleukin-2–inducible T-cell kinase (ITK), or TEC, which are partially inhibited by ibrutinib.[5]

The efficacy of acalabrutinib in patients with previously untreated and R/R CLL was demonstrated in two randomized, controlled trials, ELEVATE-TN and ASCEND, which led to the FDA approval of acalabrutinib in both frontline and R/R treatment of CLL.[28,29]

The most common adverse reactions of acalabrutinib are similar to ibrutinib, with a few notable differences.

The ELEVATE-RR trial reported

CONTINUED ON NEXT PAGE

LEUKEMIA

CONTINUED FROM PREVIOUS PAGE

analysis of head-to-head comparison between acalabrutinib and ibrutinib in patients with previously treated CLL with del(17) or del(11). Acalabrutinib demonstrated noninferior PFS with less frequency of diarrhea, arthralgia, contusion, back pain, muscle spasms and dyspepsia, and higher frequency of headache and cough compared to ibrutinib.

Atrial fibrillation/atrial flutter incidence was significantly lower with acalabrutinib versus ibrutinib (9.4% vs 16.0%; P=0 .02) and hypertension was also less frequent with acalabrutinib versus ibrutinib (9.4% vs 23.2%).[30]

Acalabrutinib-associated headaches were reported at 40% and are generally observed early in therapy, they subside over time typically within the first two months of treatment. Headaches pose concerns with patient compliance. Thus, it is important to consider analgesics such as acetaminophen and caffeine supplements.[4,27]

Coadministration of acalabrutinib with gastric acid-reducing agents must be avoided as the solubility decreases with increasing pH. If treatment with gastric acid suppressant is deemed necessary, considering histamine 2 receptor antagonists (H2-RA) or antacids such as calcium carbonate is preferred over the use of proton pump inhibitors (PPIs), due to the long lasting effects of PPIs.

Acalabrutinib doses should be staggered and separated by at least two hours before taking H2-RA or antacids to allow for maximum absorption.[4,27]

Zanubrutinib (BRUKINSA®) is a second-generation BTK inhibitor. Compared with ibrutinib, zanubrutinib has shown greater selectivity for BTK and fewer off-target effects in multiple in vitro enzymatic and cell-based assays.[31,32] However, zanubrutinib is not currently approved by the FDA for CLL.

Nonetheless, it is a category 2A preferred regimen as a first-, second- or subsequent-line therapy per the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).

More recently, the ALPINE study presented at the European Hematology Association 2021 Virtual Congress reported data of head-to-head comparison between zanubrutinib and ibrutinib in patients with previously treated CLL. The interim analysis data shows overall response rate (ORR) higher with zanubrutinib vs ibrutinib (78.3% vs 62.5%, P=0.0006) and OS rates (97.0% vs 92.7%).[33]

The rate of atrial fibrillation/flutter was lower with zanubrutinib vs ibrutinib (2.5% vs 10.1%, P=0.0014), and rates of major bleeding, grade ≥3 infections, and adverse events leading to discontinuation or death were also lower with zanubrutinib vs ibrutinib, while rate of neutropenia was higher with zanubrutinib (28.4% vs 21.7%).[33]

Additionally, zanubrutinib is currently being investigated in combination with obinutuzumab and venetoclax (NCT03824483).[34]

Pirtobrutinib (LOXO-305), is an investigational highly selective, non-covalent BTK inhibitor. In the phase 1/2 BRUIN study presented at ASH 2021, pirtobrutinib demonstrated promising efficacy in CLL patients previously treated with other BTK inhibitors. Its efficacy was independent of BTK C481 mutation status, reason for prior BTK inhibitor discontinuation, and prior therapies received. [35]

CLASS EFFECT OF BTK INHIBITORS:

• **Lymphocytosis:** Lymphocytosis can occur upon initiation of therapy with BTK inhibitors; this is due to the inhibition of the kinases involved in the B-cell migration and homing process such as spleen tyrosine kinase (SYK), BTK, and phosphatidylinositol 3-kinase (PI3K).[36-87]

The lymphocytosis is asymptomatic and in the majority of patients it resolves within the initial months of therapy. However, it may persist for more than 12 months in a subgroup of patients. Nonetheless, this lymphocytosis is not a sign of drug resistance or a suboptimal response.[36]

• **Increased risk of bleeding, atrial fibrillation and hypertension:** The increased risk of bleeding is in part due to the BTK inhibition of platelet adhesion and activation.[39] It is important to monitor patients closely for bleeding events and consider risk versus benefits of BTK inhibitor therapy in patients on concurrent anticoagulation therapy.

Of note, clinical trials excluded patients on concurrent warfarin therapy. Therefore, considering a non-warfarin anticoagulation therapy is noteworthy.

In practice, if an oral anticoagulant is warranted, it is preferred to use apixaban or rivaroxaban due to minimal drug interactions with ibrutinib, acalabrutinib and zanubrutinib.[27,40,60]

Furthermore, these agents should be held at least three to seven days pre- and post-procedures depending upon type of surgery and bleeding risk.[5,18,27,41,60]

While on therapy with BTK inhibitors, patients are advised to discontinue vitamins and herbal supplements that increase risk of bleeding or have an effect on platelet aggregation, such as vitamin E, non-steroidal anti-inflammatory agents and fish oils.

Given that CLL is a disease of the elderly, atrial fibrillation is by nature higher in this patient population. Conditions that have been associated with increased risk of atrial fibrillation while on ibrutinib therapy include older age, male sex, history of hypertension, history of coronary artery disease, diabetes and history of valvular heart disease.[42]

If atrial fibrillation occurs during ibrutinib therapy, it is not recommended to hold or reduce the dose of ibrutinib while treatment is initiated. Withholding ibrutinib does not result in higher resolution rates of atrial fibrillation, but may compromise PFS and OS,[41] similarly preexisting atrial fibrillation is not an absolute contraindication to therapy.

The development of new onset hypertension while on a BTK inhibitor may occur at any time during treatment and does not warrant therapy discontinuation, unless medically necessary. It is important to consider the delayed onset of hypertension, as

CONTINUED ON NEXT PAGE

LEUKEMIA

CONTINUED FROM PREVIOUS PAGE

reported by Lee et al. [61] When considering an antihypertensive medication, drug-drug interactions should be examined as ibrutinib, acalabrutinib and zanubrutinib are metabolized primarily by cytochrome P 3A4 (CYP3A4).[5]

RESISTANCE PATTERN TO BTK INHIBITORS

Disease progression during treatment with ibrutinib typically occurs in high risk patients later on in the treatment.[19,43] Acquired resistance to ibrutinib is predominantly mediated by BTK and phospholipase C gamma 2 (PLCG2) mutations.[44,45] Similar mutations have been described in patients treated with acalabrutinib.[46]

Testing for mutations in patients with suspected resistance who are having progression may provide further guidance. However, mutation status alone is not an indication to change treatment. It is important to note that acalabrutinib and zanubrutinib have not been shown to be effective for ibrutinib refractory CLL with BTK C481S mutations.[4,45]

BCL-2 ANTAGONIST

Venetoclax (Venclexta®) is a selective and orally bioavailable small-molecule inhibitor of B-cell lymphoma 2 (BCL-2), an antiapoptotic protein located on the outer mitochondrial membrane.[47]

Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumor cell survival and resistance to chemotherapeutic agents. Venetoclax binds directly to BCL-2 protein and displaces proapoptotic proteins, hence restoring the process of apoptosis.[47]

Venetoclax is FDA-approved for the treatment of CLL in the frontline setting in combination with obinutuzumab based on the CLL14 trial and in R/R disease in combination with rituximab on a fixed duration schedule based on the MURANO trial, as well as monotherapy based on the single-arm studies M13-982, M14-032 and M12-175.[48-52]

The recommended dose of venetoclax is 400mg PO daily. However, in order to achieve this dose, a stepwise five-week course of dose escalation is needed to minimize the risk of tumor lysis syndrome (TLS).

Venetoclax is initiated at 20mg for one week, and then escalated weekly as follows: 50mg, 100mg, 200mg, then 400mg. If treatment is interrupted during the ramp-up phase for longer than one week, or greater than two weeks after completing the ramp-up, consider reinitiating therapy at a lower dose and continuing dose escalation as appropriate.[47]

Alternative ramp-up dosing schedules have also been studied.[62]

Recommendations for TLS prophylaxis are based on tumor burden. It is crucial to follow the prescribing information for management.[47]

Venetoclax therapy is associated with neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue and edema.[48-52]

Venetoclax is primarily metabolized by CYP3A4 and concomitant use of strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated. After completion of ramp-up, venetoclax must be reduced accordingly when coadministered with a strong or moderate CYP3A4 inhibitor and or a P-glycoprotein inhibitor.[5,47]

PI3K INHIBITORS

Idelalisib (ZYDELIG®) is an inhibitor of PI3Kδ kinase, which is expressed in normal and malignant B cells. Idelalisib induces apoptosis and inhibits proliferation in cell lines derived from malignant B-cells and in primary tumor cells. Idelalisib is approved by the FDA for the treatment of R/R CLL in combination with rituximab.[52]

Idelalisib is associated with immune mediated adverse events including hepatotoxicity, diarrhea, colitis, pneumonitis and cutaneous reactions, as well as infectious complications such cytomegalovirus (CMV) reactivation, hepatitis B reactivation and other infectious complications.[54]

Duvelisib (COPIKTRA®) an inhibitor of PI3K with dual inhibitory activity against PI3K-δ and PI3K-γ isoforms expressed in normal and malignant B-cells. Duvelisib is approved by the FDA for the treatment of R/R CLL based on the DUO trial.[53] Duvelisib is associated with similar toxicities as Idelalisib.[55,56]

Both PI3K inhibitors pose a great risk for infectious reactivations. Therefore, appropriate prophylactic therapy is recommended. Additionally, they are metabolized by CYP3A4 and are inhibitors of CYP3A4 themselves, thus, caution and dose adjustments are warranted when coadministered with other medications.[54,56]

Lastly, the consideration of allogeneic HSCT is important for eligible patients with high risk disease such as those with del(17p), and or TP53 mutation, or complex karyotype. This group of patients should be offered treatment with a BTK inhibitor or venetoclax-based therapy or both to induce disease control initially. [56,58]

Once maximum response is achieved, treatment options include proceeding with consolidating HSCT or continuing on BTK inhibitor or venetoclax based therapy until progression, thereby postponing the HSCT option to the next treatment line.[57,58]

CONCLUSIONS

Over the last decade, the introduction of small-molecule inhibitors has changed the treatment course of CLL and replaced traditional chemotherapy based regimens.

While oral anticancer medications offer a convenient route of administration for the patient compared with injectable therapy, the use of oral agents is accompanied by challenges such as adherence, drug interactions, tolerability, medication acquisition, affordability and complexity of regimens.

For instance, coadministration of acalabrutinib with gastric acid-reducing agents can have an effect on drug solubility and absorption. Thus, a closer follow-up and

CONTINUED ON NEXT PAGE

LEUKEMIA

CONTINUED FROM PREVIOUS PAGE

monitoring of patients on such therapy is crucial, especially when as these antacid medications are available over the counter and are easily accessible.[27]

Moreover, oral agents that are metabolized by CYP3A4 can have clinically relevant drug-drug interactions. For example, dose reductions of venetoclax when coadministered with an azole antifungal are needed to minimize drug toxicity.[47]

Additionally, given the nature of the disease, the majority of patients are elderly and may have challenges with adherence and remembering to take their medications. Utilizing patient-specific medication calendars and alarms, or incorporation of medication into the daily routine, can optimize adherence.

Lastly, medication affordability and acquisition continue to be challenges in the era of oral chemotherapy.

Typically charity grants, free drug applications and coupons are utilized to assist with cost coverage, and the proactive approach to allocate the appropriate contracted pharmacy facilitates medication acquisition, especially when some are only available via a limited distribution network pharmacy, such as duvelisib.[59]

The active contribution of pharmacists trained in hematology/oncology to the aforementioned items is essential.

In our current practice, pharmacist specialists are heavily involved with therapy determination and dosing, literature evaluation, patient education, monitoring for adherence, managing side effects and drug-drug interactions, in addition to facilitating drug acquisition and affordability impediments. Therefore, it is imperative that providers collaborate with the clinical pharmacist to optimize patient care and outcomes.

▲ **Tiba Al Sagheer,** PharmD, BCOP, BCACP, is an HSCT/Bone Marrow Transplant Clinical Pharmacist Specialist. **Cesar Ochoa**, MD, is a Hematologist/ Oncologist. Both practice at Baptist Health South Florida - Miami Cancer Institute in Miami.

REFERENCES

1. Smith, A., et al. "Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network." British journal of cancer 105.11 (2011): 1684-1692.

2. Siegel RL, Miller KD, Jemal A. "Cancer statistics, 2020." CA: A Cancer Journal for Clinicians: CLIN 2020;70:7–30 available at: https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.3322/caac.21590.

3. SEER database Chronic Lymphocytic Leukemia — Cancer Stat Facts.

4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Guideline Chronic lymphocytic leukemia / small cell lymphoma V.2.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed [February 7, 2022]. 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.

5. Burger, Jan A. "Treatment of chronic lymphocytic leukemia." New England Journal of Medicine 383.5 (2020): 460-473.

6. Szukalski, Łukasz, et al. "Cutaneous manifestation of chronic lymphocytic leukemia: a case report and a literature review." Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii 36.6 (2019): 778.

7. Tsang, Mazie, and Sameer A. Parikh. "A concise review of autoimmune cytopenias in chronic lymphocytic leukemia." Current hematologic malignancy reports 12.1 (2017): 29-38.

8. Ding, Wei. "Richter transformation in the era of novel agents." Hematology 2018.1 (2018): 256-263.

9. Hallek, Michael, et al. "iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL." Blood 131.25 (2018): 2745-2760.

10. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46:219-234.

11. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.

12. Nowakowski, Grzegorz S., et al. "Percentage of smudge cells on routine blood smear predicts survival in chronic lymphocytic leukemia." Journal of Clinical Oncology 27.11 (2009): 1844.

13. Montserrat, Emili. "New prognostic markers in CLL." ASH Education Program Book 2006.1 (2006): 279-284.

14. International CLL-IPI Working Group. "An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data." The Lancet Oncology 17.6 (2016): 779-790.

15. CLL Trialists' CollaborativeGroup. "Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials." Journal of the National Cancer Institute91.10 (1999): 861-868.

16. Goede, Valentin, et al. "Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions." New England Journal of Medicine 370.12 (2014): 1101-1110.

17. Hallek, Michael, et al. "Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial." The Lancet 376.9747 (2010): 1164-1174.

18. Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics LLC: 2020.

19. Byrd, John C., et al. "Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia." New England Journal of Medicine 369.1 (2013): 32-42.

20. RESONATE: Byrd, John C., et al. "Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia." New England Journal of Medicine 371.3 (2014): 213-223.

21. RESONATE-2: Burger, Jan A., et al. "Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study." Leukemia 34.3 (2020): 787-798.

22. iLLUMINATE: Moreno, Carol, et al. "Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial." The Lancet Oncology 20.1 (2019): 43-56.

23. E1912: Shanafelt, Tait D., et al. "Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia." New England Journal of Medicine 381.5 (2019): 432-443.

24. HELIOS: Chanan-Khan, Asher, et al. "Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study." The Lancet Oncology 17.2 (2016): 200-211.

CONTINUED ON NEXT PAGE

LEUKEMIA

CONTINUED FROM PREVIOUS PAGE

25. Stephens, Deborah M., and John C. Byrd. "How I manage ibrutinib intolerance and complications in patients with chronic lymphocytic leukemia." Blood 133.12 (2019): 1298-1307.

26. Boriani, Giuseppe, et al. "Practical management of ibrutinib in the real life: focus on atrial fibrillation and bleeding." Hematological oncology 36.4 (2018): 624-632.

27. Calquence [package insert]. Wilmington, de: Astrazeneca pharmaceuticals lp: 2019.

28. ELEVATE-TN: Sharman, Jeff P., et al. "Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial." The Lancet 395.10232 (2020): 1278-1291.

29. ASCEND: Ghia, Paolo, et al. "ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia." Journal of Clinical Oncology 38.25 (2020): 2849-2861.

30. Byrd, John C., et al. "Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial." Journal of Clinical Oncology (2021): JCO-21.

31. Tam, Constantine, et al. "The BTK inhibitor, Bgb-3111, is safe, tolerable, and highly active in patients with relapsed/refractory B-cell malignancies: initial report of a phase 1 first-in-human trial." (2015): 832-832.

32. Tam, Constantine S., et al. "Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL." Blood 134.11 (2019): 851-859.

33. Hillmen, P., B. Eichhorst, and J. R. Brown. "First interim analysis of ALPINE study: Results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma." European Hematology Association Annual Meeting (Virtual). 2021.

34. Zanubrutinib : Study of Zanubrutinib, Obinutuzumab, and Venetoclax in Patients With Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Leukemia (SLL) - Full Text View - ClinicalTrials.gov Accessed February 10, 2021.

35. Mato, Anthony R., et al. "Pirtobrutinib, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Updated Results from the Phase 1/2 BRUIN Study." Blood 138 (2021): 391.

36. Woyach, Jennifer A., et al. "Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy." Blood, The Journal of the American Society of Hematology 123.12 (2014): 1810-1817.

37. de Rooij, Martin FM, et al. "The clinically active BTK inhibitor PCI-32765 targets B-cell receptor–and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia." Blood, The Journal of the American Society of Hematology 119.11 (2012): 2590-2594.

38. Ponader, Sabine, et al. "The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo." Blood 119.5 (2012): 1182-1189.

39. Nicolson, Phillip LR, et al. "Low-dose Btk inhibitors selectively block platelet activation by CLEC-2." Haematologica 106.1 (2021).

40. Chai, Khai Li, et al. "Practical recommendations for the choice of anticoagulants in the management of patients with atrial fibrillation on ibrutinib." Leukemia & lymphoma 58.12 (2017): 2811-2814.

41. de Weerdt, Iris, et al. "Incidence and management of toxicity associated with ibrutinib and idelalisib: a practical approach." Haematologica 102.10 (2017): 1629.

42. Shanafelt, Tait D., et al. "Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL)." Leukemia & lymphoma 58.7 (2017): 1630-1639.

43. Thompson, Philip A., et al. "Complex karyotype is a stronger predictor than del (17p) for an inferior outcome in relapsed or refractory chronic lymphocytic leukemia patients treated with ibrutinib-based regimens." Cancer 121.20 (2015): 3612-3621.

44. Woyach, Jennifer A., et al. "Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib." New England Journal of Medicine 370.24 (2014): 2286-2294.

45. Woyach, Jennifer A., et al. "BTKC481S-mediated resistance to ibrutinib in chronic lymphocytic leukemia." Journal of Clinical Oncology 35.13 (2017): 1437.

46. Woyach, Jennifer, et al. "Resistance to acalabrutinib in CLL is mediated primarily by BTK mutations." (2019): 504-504.

47. Venclexta [package insert]. North chicago, il; abbvie inc.: 2020.

48. MURANO: Seymour, John F., et al. "Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia." New England Journal of Medicine 378.12 (2018): 1107-1120.

49. Fischer, Kirsten, et al. "Venetoclax and obinutuzumab in patients with CLL and coexisting conditions." New England Journal of Medicine 380.23 (2019): 2225-2236.

50. Stilgenbauer, Stephan, et al. "Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a phase II pivotal trial." Journal of Clinical Oncology 36.19 (2018): 1973-1980.

51. Coutre, Steven, et al. "Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy." Blood, The Journal of the American Society of Hematology 131.15 (2018): 1704-1711.

52. Jones, Jeffrey A., et al. "Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial." The lancet oncology 19.1 (2018): 65-75.

53. Furman, Richard R., et al. "Idelalisib and rituximab in relapsed chronic lymphocytic leukemia." New England Journal of Medicine 370.11 (2014): 997-1007.

54. ZYDELIG [package insert]. Foster City, CA; Gilead Sciences, Inc: 2014.

55. Flinn, Ian W., et al. "The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL." Blood 132.23 (2018): 2446-2455.

56. Copiktra [package insert]. Needham, ma: Verastem, Inc., 2018.

57. Dreger, Peter, et al. "Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents?." Blood, The Journal of the American Society of Hematology 124.26 (2014): 3841-3849.

58. Krämer, Isabelle, et al. "Allogeneic hematopoietic cell transplantation for high-risk CLL: 10-year follow-up of the GCLLSG CLL3X trial." Blood, The Journal of the American Society of Hematology 130.12 (2017): 1477-1480.

59. "COPIKTRA (Duvelisib) Available for Order at Biologics, Inc." McKesson, Claire Crye, 26 Sept. 2018, www.mckesson.com/about-mckesson/newsroom/press-releases/2018/copiktra-available-for-order-at-biologics/.

60. BRUKINSA [package insert]. San Mateo, CA; BeiGene, Ltd: 2021.

61. Lee, Dae Hyun, et al. "Association between ibrutinib treatment and hypertension." Heart 108.6 (2022): 445-450.

62. Davids, Matthew, et al. "Modified venetoclax dose ramp-up in select high-risk patients with chronic lymphocytic leukemia (CLL) with progression after B-cell receptor pathway inhibitors (BCRi)." Clinical Lymphoma, Myeloma and Leukemia 17 (2017): S302.

Margenza®
(margetuximab-cmkb)
250 mg/10 mL injection for intravenous use

Fc region engineered to improve immune engagement[1]

J-code is **J9353**

MARGENZA is an Fc-engineered monoclonal antibody that targets HER2+ cells[1-3]

- The Fc region of MARGENZA is purposely distinct from trastuzumab in that it has 5 specific mutations engineered to improve immune engagement via increased binding to activating Fc receptors (CD16A) and decreased binding to inhibitory Fc receptors (CD32B) *in vitro*

  The clinical relevance of *in vitro* data is unknown.

SEE THE MARGENZA MECHANISM OF ACTION (MOA) AT WWW.MARGENZAHCP.COM

MARGENZA is a HER2/neu receptor antagonist indicated, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

CD = cluster of differentiation; Fc = fragment crystallizable; HER2+ = human epidermal growth factor receptor 2 positive.

SCAN TO SEE MARGENZA MOA

IMPORTANT SAFETY INFORMATION

WARNING: LEFT VENTRICULAR DYSFUNCTION AND EMBRYO-FETAL TOXICITY

- **Left Ventricular Dysfunction:** MARGENZA may lead to reductions in left ventricular ejection fraction (LVEF). Evaluate cardiac function prior to and during treatment. Discontinue MARGENZA treatment for a confirmed clinically significant decrease in left ventricular function.
- **Embryo-Fetal Toxicity:** Exposure to MARGENZA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.

WARNINGS & PRECAUTIONS:

Left Ventricular Dysfunction

- Left ventricular cardiac dysfunction can occur with MARGENZA.
- In SOPHIA, left ventricular dysfunction occurred in 1.9% of patients treated with MARGENZA.
- MARGENZA has not been studied in patients with a pretreatment LVEF value of <50%, a prior history of myocardial infarction or unstable angina within 6 months, or congestive heart failure NYHA class II-IV.
- Withhold MARGENZA for ≥16% absolute decrease in LVEF from pretreatment values or LVEF below institutional limits of normal (or 50% if no limits available) and ≥10% absolute decrease in LVEF from pretreatment values.
- Permanently discontinue MARGENZA if LVEF decline persists greater than 8 weeks, or dosing is interrupted more than 3 times due to LVEF decline.
- Evaluate cardiac function within 4 weeks prior to and every 3 months during and upon completion of treatment. Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan.
- Monitor cardiac function every 4 weeks if MARGENZA is withheld for significant left ventricular cardiac dysfunction.

Embryo-Fetal Toxicity

- Based on findings in animals and mechanism of action, MARGENZA can cause fetal harm when administered to a pregnant woman. Post-marketing studies of other HER2 directed antibodies during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.
- Verify pregnancy status of women of reproductive potential prior to initiation of MARGENZA.

Embryo-Fetal Toxicity (cont'd)

- Advise pregnant women and women of reproductive potential that exposure to MARGENZA during pregnancy or within 4 months prior to conception can result in fetal harm.
- Advise women of reproductive potential to use effective contraception during treatment and for 4 months following the last dose of MARGENZA.

Infusion-Related Reactions (IRRs)

- MARGENZA can cause IRRs. Symptoms may include fever, chills, arthralgia, cough, dizziness, fatigue, nausea, vomiting, headache, diaphoresis, tachycardia, hypotension, pruritus, rash, urticaria, and dyspnea.
- In SOPHIA, IRRs were reported by 13% of patients on MARGENZA plus chemotherapy. Most of the IRRs occur during Cycle 1. Grade 3 IRRs were reported in 1.5% of MARGENZA-treated patients.
- Monitor patients during and after MARGENZA infusion. Have medications and emergency equipment to treat IRRs available for immediate use.
- In patients experiencing mild or moderate IRRs, decrease rate of infusion and consider premedications, including antihistamines, corticosteroids, and antipyretics. Monitor patients until symptoms completely resolve.
- Interrupt MARGENZA infusion in patients experiencing dyspnea or clinically significant hypotension and intervene with supportive medical therapy as needed. Permanently discontinue MARGENZA in all patients with severe or life-threatening IRRs.

MOST COMMON ADVERSE REACTIONS:

The most common adverse drug reactions (>10%) with MARGENZA in combination with chemotherapy are fatigue/asthenia (57%), nausea (33%), diarrhea (25%), vomiting (21%), constipation (19%), headache (19%), pyrexia (19%), alopecia (18%), abdominal pain (17%), peripheral neuropathy (16%), arthralgia/myalgia (14%), cough (14%), decreased appetite (14%), dyspnea (13%), infusion-related reactions (13%), palmar-plantar erythrodysesthesia (13%), and extremity pain (11%).

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch or to MacroGenics at (844)-MED-MGNX (844-633-6469).

Please see brief summary of full Prescribing Information, including Boxed Warning on following pages.

References: 1. MARGENZA Prescribing Information. MacroGenics, Inc.; 2020. **2.** Nordstrom JL, Gorlatov S, Zhang W, et al. Anti-tumor activity and toxicokinetics analysis of MGAH22, an anti-HER2 monoclonal antibody with enhanced Fcγ receptor binding properties. *Breast Cancer Res*. 2011;13(6):R123. doi:10.1186/bcr3069. **3.** Rugo HS, Im S, Cardoso F, et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. Published online January 22, 2021. doi:10.1001/jamaoncol.2020.7932.

MACROGENICS®

Brief Summary of Full Prescribing Information

MARGENZA® (margetuximab-cmkb) 250 mg/10 mL injection, for intravenous use
Initial U.S. approval: 2020

WARNING: LEFT VENTRICULAR DYSFUNCTION AND EMBRYO-FETAL TOXICITY

Left Ventricular Dysfunction: MARGENZA may lead to reductions in left ventricular ejection fraction (LVEF). Evaluate cardiac function prior to and during treatment. Discontinue MARGENZA treatment for a confirmed clinically significant decrease in left ventricular function.

Embryo-Fetal Toxicity: Exposure to MARGENZA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.

INDICATIONS AND USAGE

MARGENZA is indicated, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

DOSAGE AND ADMINISTRATION

Recommended Doses and Schedules - The recommended dose of MARGENZA is 15 mg/kg, administered as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Administer MARGENZA as an intravenous infusion at 15 mg/kg over 120 minutes for the initial dose, then over a minimum of 30 minutes every 3 weeks for all subsequent doses. On days when both MARGENZA and chemotherapy are to be administered, MARGENZA may be administered immediately after chemotherapy completion. Refer to the respective Prescribing Information for each therapeutic agent administered in combination with MARGENZA for the recommended dosage information, as appropriate. **Dose Modification or Important Dosing Considerations -** If a patient misses a dose of MARGENZA, administer the scheduled dose as soon as possible. Adjust the administration schedule to maintain a 3-week interval between doses. *Left Ventricular Dysfunction* - Assess left ventricular ejection fraction (LVEF) before starting MARGENZA and regularly during treatment. Withhold MARGENZA dosing for at least 4 weeks for any of the following: ≥ 16% absolute decrease in LVEF from pretreatment values; LVEF below institutional limits of normal (or 50% if no limits are available) and ≥ 10% absolute decrease in LVEF from pretreatment values. MARGENZA dosing may be resumed if, within 8 weeks, LVEF returns to normal limits and absolute decrease from baseline is ≤ 15%. Permanently discontinue MARGENZA if LVEF decline persists for greater than 8 weeks, or if dosing is interrupted on greater than 3 occasions for LVEF decline. *Infusion-Related Reactions* - Decrease the rate of infusion for mild or moderate infusion-related reactions (IRRs). Interrupt the infusion for dyspnea or clinically significant hypotension. Permanently discontinue MARGENZA dosing in patients with severe or life-threatening IRRs. **Preparation for Administration** - Administer as an intravenous infusion after dilution. Preparation for Intravenous Infusion - Prepare solution for infusion, using aseptic technique, as follows: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution is clear to slightly opalescent, colorless to pale yellow or pale brown. Some visible, translucent, inherent proteinaceous particles may be present; **Swirl the vial(s) gently.** Do not shake the vial(s); Calculate the required volume of MARGENZA needed to obtain the appropriate dose according to patient's body weight. The calculated total dose volume should be rounded to the nearest 0.1 mL; Withdraw appropriate volume of MARGENZA solution from the vial(s) using a syringe; Transfer MARGENZA into an intravenous bag containing 100 mL or 250 mL 0.9% Sodium Chloride Injection, USP. Polyvinyl chloride (PVC) intravenous bags or intravenous bags made with polyolefins (polyethylene and polypropylene) and polyamide or polyolefins only or copolymer of olefins may be used. Do not use 5% Dextrose Injection, USP solution; The final concentration of the diluted solution should be between 0.5 mg/mL to 7.2 mg/mL; **Gently invert the intravenous bag to mix the diluted solution.** Do not shake the intravenous bag; Discard any unused portion left in the vial(s). Do not administer as an intravenous push or bolus. Do not mix MARGENZA with other drugs. Storage of Diluted Solution - The product does not contain a preservative. If diluted infusion solution is not used immediately, it can be stored at room temperature up to 4 hours or stored refrigerated at 2°C to 8°C (36°F to 46°F) up to 24 hours. If refrigerated, allow the diluted solution to come to room temperature prior to administration. **Do not freeze.** Administration - Administer diluted infusion solution intravenously over 120 minutes for the initial dose, then over a minimum of 30 minutes every 3 weeks for all subsequent doses. Administer through an intravenous line containing a sterile, non-pyrogenic, low-protein binding polyethersulfone (PES) 0.2 micron in-line or add-on filter; Do not co-administer other drugs through the same infusion line.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Left Ventricular Dysfunction - Left ventricular cardiac dysfunction can occur with MARGENZA. In SOPHIA, left ventricular dysfunction occurred in 1.9% of patients treated with MARGENZA. MARGENZA has not been studied in patients with a pretreatment LVEF value of < 50%, a prior history of myocardial infarction or unstable angina within 6 months, or congestive heart failure NYHA class II-IV. Withhold MARGENZA for ≥ 16% absolute decrease in LVEF from pretreatment values or LVEF value below institutional limits of normal (or 50% if no limits are available) and ≥ 10% absolute decrease in LVEF from pretreatment values. Permanently discontinue MARGENZA if LVEF decline persists for greater than 8 weeks, or if dosing is interrupted on greater than 3 occasions due to LVEF decline. *Cardiac Monitoring* - Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended: Baseline LVEF measurement within 4 weeks prior to initiation of MARGENZA; LVEF measurements (MUGA/echocardiogram) every 3 months during and upon completion of MARGENZA; Repeat LVEF measurement at 4-week intervals if MARGENZA is withheld for significant left ventricular cardiac dysfunction. **Embryo-Fetal Toxicity** - Based on findings in animals and mechanism of action, MARGENZA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of MARGENZA in pregnant women to inform the drug-associated risk. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death. In an animal reproduction study, intravenous administration of margetuximab-cmkb to pregnant cynomolgus monkeys once every 3 weeks starting at gestational day (GD) 20 until delivery resulted in oligohydramnios and delayed infant kidney development. Animal exposures were ≥ 3 times the human exposures at the recommended dose, based on C_{max}. Verify pregnancy status of females of reproductive potential prior to initiation of MARGENZA. Advise pregnant women and females of reproductive potential that exposure to MARGENZA during pregnancy or within 4 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 4 months following the last dose of MARGENZA. **Infusion-Related Reactions** - MARGENZA can cause infusion-related reactions (IRRs). Symptoms may include fever, chills, arthralgia, cough, dizziness, fatigue, nausea, vomiting, headache, diaphoresis, tachycardia, hypotension, pruritus, rash, urticaria, and dyspnea. In SOPHIA, IRRs were reported by 13% of patients on MARGENZA plus chemotherapy. Most of the IRRs occur during Cycle 1. Grade 3 IRRs were reported in 1.5% of MARGENZA-treated patients. All IRRs resolved within 24 hours, irrespective of severity. In SOPHIA, IRRs leading to interruption of treatment occurred in 9% in patients treated with MARGENZA and chemotherapy. One patient (0.4%) on MARGENZA discontinued treatment due to IRR. An infusion substudy in 88 patients in SOPHIA evaluated MARGENZA administered over 120 minutes for the initial dose, then 30 minutes from Cycle 2 forward. IRRs were ≤ Grade 2 and most occurred during the first (120 minutes) administration of MARGENZA. From Cycle 2 onward, one patient (1.1%) had an IRR (Grade 1). Monitor patients for IRRs during MARGENZA administration and as clinically indicated after completion of infusion. Have medications and emergency equipment to treat IRRs available for immediate use. Monitor patients carefully until resolution of signs and symptoms. In patients who experience mild or moderate IRRs, consider premedications, including antihistamines, corticosteroids, and antipyretics. Decrease the rate of infusion for mild or moderate IRRs. Interrupt MARGENZA infusion in patients experiencing dyspnea or clinically significant hypotension and intervene with medical therapy which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanently discontinue MARGENZA in all patients with severe or life-threatening IRRs.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label: Left Ventricular Dysfunction; Embryo-Fetal Toxicity; Infusion-Related Reactions. **Clinical Trials Experience -** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice. The safety of MARGENZA was evaluated in HER2-positive breast cancer patients who received two or more prior anti-HER2 regimens in SOPHIA. Patients were randomized (1:1) to receive either MARGENZA 15 mg/kg every 3 weeks plus chemotherapy or trastuzumab plus chemotherapy. Among patients who received MARGENZA, 40% were exposed for 6 months or longer and 11% were exposed for greater than one year. Serious adverse reactions occurred in 16% of patients who received MARGENZA. Serious adverse reactions in > 1% of patients included febrile neutropenia (1.5%), neutropenia/neutrophil count decrease (1.5%) and infusion-related reactions (1.1%). Fatal adverse reactions occurred in 1.1% of patients who received MARGENZA, including viral pneumonia (0.8%) and aspiration pneumonia (0.4%). Permanent discontinuation due to an adverse reaction occurred in 3% of patients who received MARGENZA. Adverse reactions which resulted in permanent discontinuation in > 1% of patients who received MARGENZA included left ventricular dysfunction and infusion-related reactions. Dosage interruptions due to an adverse reaction occurred in 11% of patients who received MARGENZA. Adverse reactions which required dosage interruption in > 5% of patients who received MARGENZA included infusion-related reactions. **Table 1 in the full Prescribing Information summarizes Adverse Reactions (> 10%) in Patients with Metastatic HER2-Positive Breast Cancer Who Received MARGENZA in SOPHIA.** Percentage values displayed in parentheses reflect: (MARGENZA + Chemotherapy (n = 264) All Grades, Grade 3 or 4, Trastuzumab + Chemotherapy (n = 266) All Grades, Grade 3 or 4). Adverse Reactions are as follows: **General disorders and administration site conditions:** Fatigue/Asthenia (57, 7, 47, 4.5); Pyrexia (19, 0.4, 14, 0.4). **Gastrointestinal disorders:** Nausea (33, 1.1, 32, 0.4); Diarrhea (25, 2.3, 25, 2.3); Vomiting (21, 0.8, 14, 1.5); Constipation (19, 0.8, 17, 0.8); Abdominal pain[a] (17, 1.5, 21, 1.5). **Skin and Subcutaneous tissue:** Alopecia (18, 0, 15, 0); Palmar-plantar erythrodysesthesia (13, 0, 15, 3). **Nervous System Disorders:** Headache[b] (19, 0, 16, 0);Peripheral neuropathy[c] (16, 1.1, 15, 2.3). **Respiratory, thoracic and mediastinal disorders:** Cough (14, 0.4, 12, 0); Dyspnea (13, 1.1, 11, 2.3). **Metabolism and nutrition disorders:** Decreased appetite (14, 0.4, 14, 0.4). **Musculoskeletal and connective tissue disorders:** Arthralgia/Myalgia (14, 0.4, 12, 0.8); Extremity pain (11, 0.8, 9, 0). **Injury, poisoning and procedural complications:** Infusion-related reaction (13, 1.5, 3, 0). [a]Includes abdominal pain, abdominal discomfort, lower abdominal pain and upper abdominal pain; [b]Includes headache and migraine; [c]Includes peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, and neuropathy. Clinically relevant adverse reactions in ≤ 10% of patients who received MARGENZA in combination with chemotherapy included: dizziness and stomatitis (10%) each, decreased weight, dysgeusia, rash, and insomnia (6%) each, hypertension (5%), and syncope (1.5%). **Table 2 in the full Prescribing Information summarizes Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with Metastatic HER2-Positive Breast Cancer Who Received MARGENZA in SOPHIA.** Percentage values displayed in parentheses reflect: (MARGENZA + chemotherapy[1] All grades, Grade 3 or 4, Trastuzumab + chemotherapy[1] All Grades, Grade 3 or 4). Laboratory abnormalities are as follows: **Hematology:** Decreased hemoglobin (52, 3.2, 43, 2.4); Decreased leukocytes (40, 5, 36, 3.2); Decreased neutrophils (34, 9, 28, 9); Increased aPTT (32, 3.4, 34, 4.3); Decreased lymphocytes (31, 4.4, 38, 4.4); Increased INR (24, 1.2, 25, 0.4). **Chemistry:** Increased creatinine (68, 0.4, 60, 0); Increased ALT (32, 2, 30, 0.8); Increased lipase (30, 6, 24, 3.2); Increased AST (23, 2, 22, 0.8); Increased alkaline phosphatase (21, 0, 23, 0.8). [1]The denominator used to calculate the rate varied from 229 to 253 based on the number of patients with a baseline value and at least one post-treatment value. aPTT: activated partial thromboplastin time; INR: prothrombin international normalized ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase. **Immunogenicity** - As with all therapeutic proteins, there is potential for immunogenicity with MARGENZA. The detection of antibody formation is highly dependent on assay sensitivity and specificity. 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 MARGENZA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. In SOPHIA, samples were obtained from patients on MARGENZA for immunogenicity testing at baseline, every 2 cycles, and at end of study therapy. All patients enrolled in SOPHIA received trastuzumab previously, and treatment-emergent anti-margetuximab antibodies were observed in 4 patients (1.7%). Of these 4 patients, anti-margetuximab antibodies were detected prior to Cycle 7 of MARGENZA dosing in 1 patient, and more than 2 months after the last MARGENZA dose in 3 patients. In the infusion substudy, treatment-emergent anti-margetuximab antibodies were observed in 2 patients (3.8%). Of these 2 patients, anti-margetuximab antibodies were detected prior to Cycle 3 of MARGENZA

dosing in 1 patient, and more than 6 months after the last MARGENZA dose in 1 patient. Due to the limited number of patients who developed anti-margetuximab antibodies during treatment with MARGENZA, the impact of anti-margetuximab antibodies on the PK, safety and efficacy of MARGENZA is unknown.

DRUG INTERACTIONS

Anthracyclines - Patients who receive anthracyclines less than 4 months after stopping MARGENZA may be at increased risk of cardiac dysfunction. While this interaction has not been studied with MARGENZA, clinical data from other HER2-directed antibodies warrants consideration. Avoid anthracycline-based therapy for up to 4 months after stopping MARGENZA. If concomitant use is unavoidable, closely monitor patient's cardiac function.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary - Based on findings in animals and mechanism of action, MARGENZA can cause fetal harm when administered to a pregnant woman. There are no available data on use of MARGENZA in pregnant women to inform the drug-associated risk. In postmarketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. In an animal reproduction study, intravenous administration of margetuximab-cmkb to pregnant cynomolgus monkeys once every 3 weeks, starting at gestational day (GD) 20 until delivery, resulted in oligohydramnios and delayed infant kidney development. Animal exposures were ≥ 3 times the human exposures at the recommended dose, based on C_{max}. Advise patients of potential risks to a fetus. There are clinical considerations if MARGENZA is used during pregnancy or within 4 months prior to conception. Estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 - 4% and 15 - 20%, respectively. Clinical Considerations - *Fetal/Neonatal Adverse Reactions:* Monitor women who received MARGENZA during pregnancy or within 4 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. Data - *Animal Data:* In an enhanced pre- and post-natal development study, pregnant cynomolgus monkeys received intravenous doses of 50 or 100 mg/kg margetuximab-cmkb once every 3 weeks starting on GD 20 and until delivery. Animal exposures at doses of 50 and 100 mg/kg were 3 and 6 times, respectively, the human exposures at the recommended dose, based on C_{max}. Treatment with 50 and 100 mg/kg margetuximab-cmkb resulted in oligohydramnios beginning on GD 75. An infant mortality occurred on post-natal day 63 following maternal exposure to 100 mg/kg margetuximab-cmkb. Clinical findings included tubular degeneration/necrosis and tubular dilatation in the kidney. Maternal doses of 50 and 100 mg/kg resulted in decreased infant kidney weights and histologic immature nephrons. Measurable serum concentrations of margetuximab- cmkb were observed in infant animals, which is consistent with margetuximab-cmkb crossing the placenta. **Lactation:** Risk Summary - There is no information regarding presence of MARGENZA in human milk, effects on the breastfed child, or effects on milk production. Published data suggest human IgG is present in human milk but does not enter neonatal or infant circulation in substantial amounts. Consider developmental and health benefits of breastfeeding along with the mother's clinical need for MARGENZA treatment and any potential adverse effects on the breastfed child from MARGENZA or from the underlying maternal condition. This consideration should also take into account the MARGENZA washout period of 4 months. **Females and Males of Reproductive Potential -** MARGENZA can cause fetal harm when administered to a pregnant woman. Pregnancy Testing - Verify pregnancy status of females of reproductive potential prior to initiation of MARGENZA. Contraception - *Females:* Advise females of reproductive potential to use effective contraception during treatment and for 4 months following the last dose of MARGENZA. **Pediatric Use:** Safety and effectiveness of MARGENZA have not been established in pediatric patients. **Geriatric Use:** Of the 266 patients treated with MARGENZA 20% were 65 years of age or older and 4% were 75 years or older. No overall differences in efficacy were observed between patients ≥ 65 years of age compared to younger patients. There was a higher incidence of Grade ≥ 3 adverse reactions observed in patients age 65 years or older (56%) compared to younger patients (47%), as well as adverse reactions associated with potential cardiotoxicity (35% vs 18%).

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied - MARGENZA (margetuximab-cmkb) injection is a clear to slightly opalescent, colorless to pale yellow or pale brown solution in a single-dose vial supplied as: One 250 mg/10 mL (25 mg/mL) single-dose vial - NDC 74527-022-02; Four 250 mg/10 mL (25 mg/mL) single-dose vials - NDC 74527-022-03. **Storage -** Store vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light until time of use. **Do not freeze. Do not shake.**

PATIENT COUNSELING INFORMATION

Left Ventricular Dysfunction - Advise patients to contact a healthcare professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness. Embryo-Fetal Toxicity - Advise pregnant women and females of reproductive potential that exposure to MARGENZA during pregnancy or within 4 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with MARGENZA and for 4 months following the last dose.

Manufactured by:

MacroGenics, Inc.
9704 Medical Center Drive
Rockville, MD 20850-3343
U.S. License No. 2139

2/2022
US-COM-MGA-2200024

HOW AM I SUPPOSED TO PAY FOR THIS?
THE CHALLENGE OF ORAL CHEMO PARITY

By Allison Reed, PharmD, BCPS

You have just been diagnosed with stage III colorectal cancer.

Your oncologist tells you that there is a pretty good chance of curing you. The best part is that some of your chemotherapy can be taken as a pill at home, instead of as an infusion at a clinic. This is going to allow you to spend more time at home with your friends and family.

Allison Reed

But, wait. You have heard that oral chemotherapy is super-expensive, and you do not know if you can afford it. You want to spend more time at home, but at what cost?

ORAL CHEMOTHERAPY LEGISLATION

In the past 20 years, the development of oral oncolytics has exploded, allowing an increasingly large percentage of patients to stay out of the infusion center and spend more time at home.

However, oral chemotherapy has been around longer than most people realize, with medications such as cyclophosphamide, capecitabine and temozolomide.[1]

With older oral therapies, insurance may prefer to pay for the intravenous formulation as opposed to the oral formulation. Intravenous chemotherapy is covered under patients' medical insurance while oral chemotherapy is covered under prescription benefits.[2]

However, in 2017-2018, House Resolution 1409 was introduced, mandating that "group and individual health plans that cover anticancer medications administered by a healthcare provider to provide no less favorable cost sharing for patient-administered anticancer medications."[3] It was referred to the Subcommittee on Health, where it stayed for the remainder of the session.

Prior to this bill, more than half of the United States already had begun to create state legislation about oral chemotherapy parity.[4] During the 2019-2020 Congress, the Cancer Drug Parity Act of 2019 (House Resolution 1730) was introduced.[5] Unfortunately, it once again did not move past the referral to the Subcommittee on Health.

As of 2019, the District of Columbia and 43 states have passed oral chemotherapy parity laws (Figure 1).[6,7]

In the beginning of the 2021-2022 Congress, the Cancer Drug Parity Act of 2021 (House Resolution 4385) was introduced and sent to the House Committee on Education and Labor.[8]

ORAL CHEMOTHERAPY ISSUES

Approximately one-quarter of anticancer medications in development are oral chemotherapy.[9] However, the oral oncolytics in development, and most of the oral oncolytics that were developed in the past 20 years, do not have an intravenous formulation.

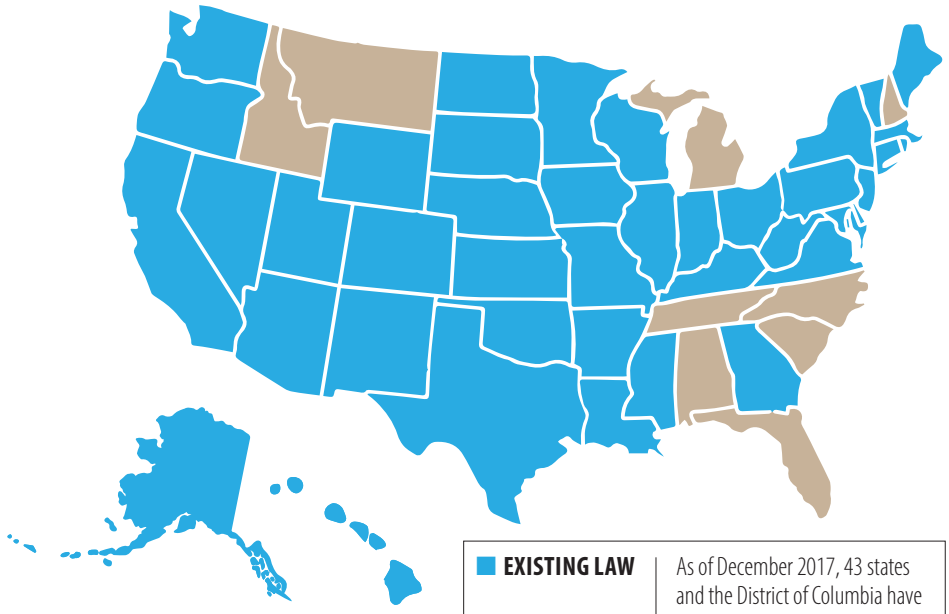
With oral chemotherapy parity laws, only oral chemotherapy with intravenous equivalents is covered. This means that patients taking oral chemotherapy that does not have an intravenous formulation can still be charged tens of thousands of dollars.

This leaves patients exposed to financial toxicity, risk of non-adherence, and potential for lapse in treatment. If clinics are unable to find ways to help patients pay for their oral chemotherapy, they will have to opt for a less favorable treatment.

Because the Cancer Drug Parity Act has not yet been signed into law on a federal level, patients must depend on the law passed at the state level, if one has been passed.[6]

CONTINUED ON NEXT PAGE

ORAL CANCER FAIRNESS LAWS AND PENDING LEGISLATION



SOURCE: COALITION TO IMPROVE ACCESS TO CANCER CARE

CHEMOTHERAPY PARITY

CONTINUED FROM PREVIOUS PAGE

While state laws have similar backbones, some states have provisions for how much the oral formulations can cost, and some states have provisions that the intravenous formulation's price cannot be increased to charge more for the oral formulation.[7]

Still, without a nationwide law, many patients remain unprotected and are still at risk of paying thousands of dollars every month for their medication if drug manufacturers increase the price of the intravenous formulation to increase the price of the oral formulation.

Patients are, in effect, at the mercy of their insurers and the drug manufacturers.

TREATMENT UNDER A PARITY LAW

After six months of therapy, you have spent considerably less time in the infusion center. You never had to worry about taking home a chemotherapy infusion, what people out in public would think about the fanny pack that you were wearing, or what would happen if the infusion pack came disconnected while you were playing with your dog.

Instead, you were present at your first granddaughter's birth, went on a second honeymoon to Hawaii and relaxed in the comfort of your own home with friends and family.

Without a nationwide law, many patients are still at risk of paying thousands of dollars every month for their medication if drug manufacturers increase the price of the intravenous formulation to increase the price of the oral formulation.

However, while you were able to do this, thousands of patients unable to afford oral chemotherapy have to spend extensive amounts of time in the infusion center.

Now that you're done with treatment, in remission and feeling 100%, you decide to volunteer and help patients gain access to these life-saving medications, in hopes that they spend less time in infusion centers and more time at home with their friends and family.

▲ **Allison Reed**, PharmD, BCPS, is an oncology/hematology pharmacy specialist float at The Ohio State University in Columbus, Ohio.

REFERENCES

1. O'Neill VJ, Twelves CJ. Oral cancer treatment: development in chemotherapy and beyond. Br J Cancer. 2002; 87: 933-937. DOI: https://doi.org/10.1038/sj.bjc.6600591.

2. Patients Rising Now. The need for oral parity. Accessed August 17, 2021. https://patientsrisingnow.org/the-need-for-oral-parity/.

3. Congress. H.R. 1409 – Cancer Drug Parity Act of 2017. Accessed August 17, 2021. https://www.congress.gov/bill/115th-congress/house-bill/1409.

4. Northern New England Clinical Oncology Society. Oral oncology parity laws. Accessed August 20, 2021. http://www.nnecos.org/Resources/Documents/Oral%20Oncology%20Parity%20Laws%20Fact%20Sheet%20AUG%202014.pdf.

5. Congress. H.R. 1730 – Cancer Drug Parity Act of 2019. Accessed August 20, 2021. https://www.congress.gov/bill/116th-congress/house-bill/1730.

6. Community Oncology Alliance. COA oral parity position Statement. Accessed August 24, 2021. https://communityoncology.org/coa-oral-parity-position-statement/.

7. Coalition to Improve Access to Cancer Care. Oral Cancer Fairness Laws and Pending Legislation. Accessed August 24, 2021. https://www.access2cancercare.org/cancer-care-access/.

8. Congress. H.R. 4385 – Cancer Drug Parity Act of 2021. Accessed August 24, 2021. https://www.congress.gov/bill/117th-congress/house-bill/4385.

9. Community Oncology Alliance. FACT SHEET: patient access to oral oncolytics. Accessed August 24, 2021. https://communityoncology.org/pdfs/fact-sheet-oral-oncolytics.pdf.

THE PAN FOUNDATION: SUPPORTING CANCER PATIENTS & ADVOCATING FOR AFFORDABILITY

By Joan Zhang, PharmD

There is nothing more important to Suzanne Cali than her family, not even her own health.

Suzanne is living with chronic lymphocytic leukemia (CLL), an illness that requires diligent medication adherence. She once paused her medications for only two weeks and saw her CLL come "roaring back" from a remission.

Joan Zhang

Unfortunately, like many people living with cancer, her medication is expensive. She is only able to afford her prescriptions with charitable assistance from the Patient Access Network (PAN) Foundation. Without that financial support, she would need to take out a mortgage on her home or drain her savings, two options she isn't willing to consider.

"If I didn't have PAN's assistance, I simply would not pay the cost of the drugs because to do so would mean that we would have to sell our home or use up our savings," she said. "How could that be helpful to my family?"

Suzanne's son-in-law is living with amyotrophic lateral sclerosis (ALS), and for Suzanne, the ability to provide some support to her family, including her teenage granddaughter, takes priority over her own health. She explained that she would rather risk her CLL "roaring back" again than become a burden to her family and eliminate her ability to pass on some money someday.

The Seattle resident has a story that is heartbreakingly familiar in the U.S. She should be focusing on enjoying her daily walks with her husband and golden retriever, not worrying about the cost at the pharmacy counter.

The PAN Foundation is proud to offer grants for nearly 70 diseases, helping people in need pay for their copays, coinsurance, and even subsidize the cost of transportation to the pharmacy or other medical care.

PAN also developed the first-of-its-kind app to alert patients, pharmacies and healthcare providers when disease-specific financial assistance becomes available at nine different charitable organizations.

PAN also focuses on advocating for Medicare reform and other common-sense legislation to ease the burden on those living with serious illnesses. Learn more about PAN at **panfoundation.org**.

PAN FOUNDATION GRANTS

PAN provides patient assistance grants for nearly 70 diagnoses, including many cancers, and chronic and rare diseases.

Healthcare providers and pharmacy staff can use our **eligibility checker** to find out whether patients qualify for any of these funds in minutes, searching by disease subtype or diagnosis code.

PAN grants often cover 100 percent of a patients' out-of-pocket prescription medication costs, including deductibles, copays and coinsurance.

We cover products that are FDA-approved or listed in official compendia or evidence-based guidelines for each disease. This includes brand and generic medications. Eligible patients also can receive transportation assistance to cover travel expenses to their doctor's offices and pharmacy.

To apply, patients — or their pharmacists applying on their behalf — complete a paperless application, get instant approval and, in most cases, can begin using their grant immediately.

You can apply online in minutes and track your grant in our online portal.

FUNDFINDER PROVIDES REAL-TIME ALERTS

Over the years, we recognized that searching the Internet for open funds, whether at PAN or another organization, was challenging and time-consuming. That's why we developed the first patient assistance app, FundFinder, which allows users to sign up for notifications for 200 funds across nine different charitable organizations.

Our award-winning app allows users to search for support organizations that may have peer support, educational resources and other helpful offerings. Anyone can use this free app, and with millions of notifications sent out in our first two years, it's connecting thousands of patients with funding opportunities. Check it out at **FundFinder.org**.

FUNDING ALERTS THROUGH THE WAIT LIST

We do our best to keep our funds open year-round. If the fund your patient needs is closed, we recommend signing them up for the wait list. Our wait list system allows prospective grantees to get the first chance to apply for assistance when funding becomes available.

Our website also tracks available funding at other charitable organizations, so even if our fund is closed, you'll be able to quickly see whether help is available somewhere else. Our goal is to help patients in need find help, regardless of the source.

▲ **Joan Zhang**, PharmD, is Manager of Medical Affairs at the PAN Foundation in Washington, D.C.

PAN Foundation

BRENDA NEVIDJON

Brenda Nevidjon, RN, MSN, FAAN, is Chief Executive Officer of the Oncology Nursing Society (ONS), a professional association of more than 35,000 members, the Oncology Nursing Foundation, and the Oncology Nursing Certification Corporations.

Her career has included clinical, academic and executive positions in oncology and general health care settings. While much of her career was at Duke University, she also worked in Switzerland and Canada as an oncology nurse.

Nevidjon was the first nurse and the first women to be Chief Operating Officer of Duke University Hospital. Immediately before joining ONS, she was a Professor Of Nursing at the Duke School of Nursing.

When she was in direct care, her clinical expertise was in medical oncology, including bone marrow transplantation.

When and why did you become involved with NCODA?

NCODA and ONS have partnered for several years in developing resources that our members need and use. I was pleased to be invited to serve on the Executive Advisory Board as I see our organizations well aligned in missions and values.

What prompted you to take a leadership role on the Executive Advisory Board?

I have served on several boards, and I always assess whether it is an organization to which I can make a positive contribution. As noted earlier, I think our two organizations are well aligned.

From your perspective at ONS, what is the most critical challenge ahead for the field of oncology?

There are numerous challenges facing the field of oncology, but the one most pressing today is the workforce, especially in nursing. The toll the COVID pandemic has taken on frontline staff is significant, not just for nurses but others on the team as well.

As headlines have shown, however, nurses left employers for contract assignments that paid much more, left the profession for other careers, or retired.

This has compounded the pre-pandemic shortages and other issues. Baby boomer nurses are retiring at a rate of 70,000 per year and this is likely to increase.

Challenges to expanding the pipeline include faculty shortages and clinical site limitations.

At ONS, we are focusing on development of resources that will assist employers to onboard novice oncology nurses as so many no longer have sufficient experienced preceptors.

What are the key challenges facing patients undergoing cancer therapy, and what can NCODA members do to help relieve their burden?

Access to care is affected by so many factors. Transportation to treatment sites is frequently the number one concern on patient surveys. It isn't a matter of distance as even in metropolitan areas, public transportation may be available, but it could take multiple bus transfers.

The financial burdens so many patients and their families experience are only worsening. All cancer care team members see the distress in patients who are facing financial toxicity. Cross-discipline problem-solving is essential today as no one profession can do it all on behalf of patients.

How can NCODA and ONS collaborate to improve patient care in the future?

I think that we can continue to build on the successes we have shared, such as the Oral Chemotherapy Education (OCE) and Intravenous Cancer Treatment Education (IVE) resources.

ONCOLOGY STATE LEGISLATION TRACKING TOOL OFFERS UNIQUE INSIGHT ON HEALTHCARE ISSUES

NCODA recently launched its new comprehensive Oncology State Legislation Tracking Tool.

The online tool is a first-of-its-kind resource within the oncology space, allowing healthcare professionals and other users to stay up-to-date on the latest state legislation pertaining to relevant issues, such as Pharmacy Benefit Managers (PBMs), Copay Accumulators and other healthcare issues.

"NCODA's Oncology State Legislation Tracking Tool is unique," said Debra Patt, MD, PhD, MBA, Executive Vice President at Texas Oncology. "It offers members the most up-to-date access available involving relevant healthcare legislation being considered in their state."

The online tool incorporates legislative updates from all 50 states in one location.

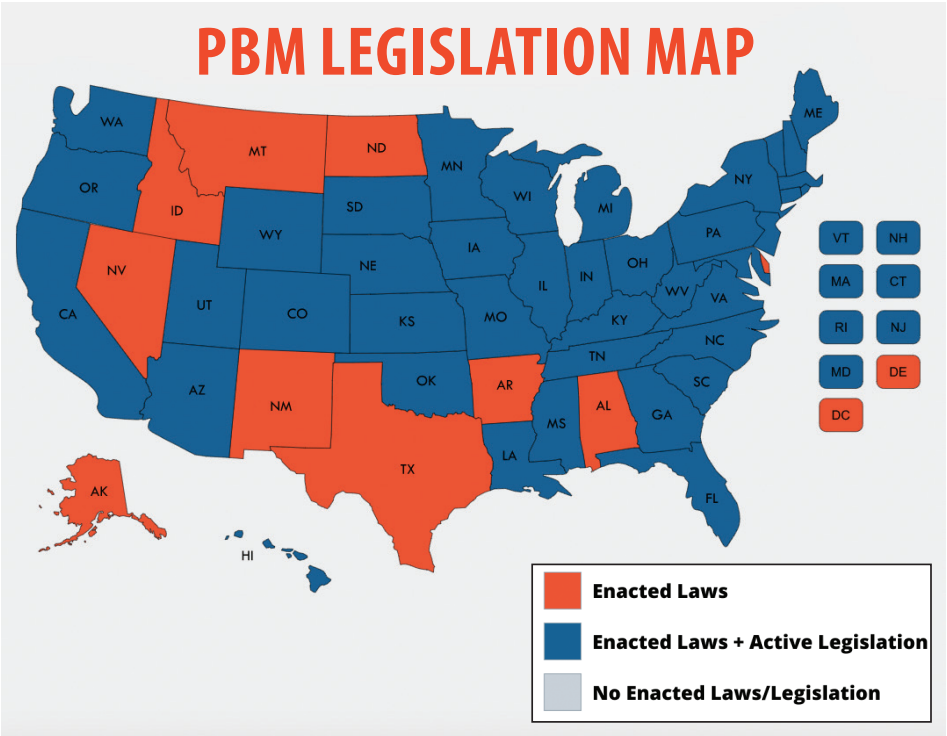
Its map-based interface provides members with simple point-and-click access to their state for concise outlines of current healthcare legislation.

Legislative outlines include relevant bill numbers, complete bill readings, as well as a brief summary and a "why it matters" section for each bill.

Timeliness is another key feature of the tool. Unlike other state legislation trackers, which typically refresh content only on a quarterly basis, the NCODA Oncology State Legislation Tracking Tool website is updated weekly.

Users viewing the website also have access to an FAQ section with concise explanations of more than three dozen specific healthcare and legislative terms.

The tool allows busy healthcare professionals to become more active participants in their state's legislative affairs that directly impact their practice and the patients they serve.



NCODA's new **Oncology State Legislation Tracking Tool** provides a simple point-and-click map interface to access current oncology-focused enacted laws and active legislation in all 50 states.

"This new tool will connect oncology professionals across the country in a way that will allow voices to be heard much more quickly, more effectively and on common ground," said Nancy Egerton, PharmD, BCOP, Director of Pharmacy at New York Oncology Hematology in Albany, New York, and Chair of the NCODA Legislative & Policy Advisory Committee (LPAC).

"Keeping our members engaged and informed of key issues relevant to their practices and patients is the goal of the committee, and this tool allows us to be much more efficient in our efforts," Egerton said.

NCODA also has launched a member-only online engagement community called NCODA CONNECT. This engagement platform provides an environment for healthcare professionals to further discuss legislative trends and updates.

In other developments, LPAC continues to collaborate with policy experts during roundtable discussions. The committee also releases statements regularly to keep the NCODA membership informed of legislative updates.

Moving forward, LPAC is planning in-person roundtable discussions, virtual days at the legislature and a virtual "legislative boot camp." The goal is to give members the opportunity to learn about the legislative process, and how to interact with their own legislators in order to help put patients first and advance the goals of medically integrated pharmacy.

If you have any questions regarding NCODA's legislative initiatives, or if you would like to get involved with LPAC, please reach out to **Kevin Scorsone** (Legislative & Policy Liaison) at **Kevin.Scorsone@NCODA.org**.

THE ROLE OF PHARMACOGENOMICS IN UNDERSTANDING DRUG ALLERGIES

HOW THIS EXPANDING SCIENCE HELPS PREDICT POTENTIAL ADVERSE EFFECTS

By Caren Hughes, PharmD, MBA, BCOP, & Michael Schuh, PharmD, MBA, FAPhA

What can we glean from the growing understanding of pharmacogenomics to unravel the genetic differences that cause drug allergies? Are we making progress?

Allergy is a general term describing undesired upregulation of the immune system in response to substances it recognizes as foreign. Allergies to medications or adverse drug reactions (ADRs) are classified by mechanism, cause, resulting adverse effect and time to occurrence.

Caren Hughes

Michael Schuh

Type A adverse reactions include approximately 90% of adverse reactions to drugs, result in predictable sequelae and are directly managed with dose reduction.[1] One example is irritation of the gastric lining resulting from chronic use of non-steroidal inflammatory medications. Type A reactions are beyond the scope of our discussion here.

Type B reactions comprise the remaining 10%. Also referred to as hypersensitivity reactions, these are more complex and most result from immune activity. These reactions are unpredictable, happening in small numbers of individuals at a dose tolerated by most patients.

The resulting effect is different or of greater magnitude from the expected side effects of the medication. These are further separated into Coombs and Gell classification Types I through IV, with I and IV being the most common.[2]

Type I is also referred to as an anaphylactic reaction. IgE antibodies are produced following the first contact to an allergen. After the second exposure, these antibodies now recognize the foreign particle subsequently binding to mast cells. These mast cells contain 500-1,500 mediators such as histamine, which are released to attack the antigen. Anaphylaxis, angioedema or urticaria can result soon after initiation of the drug.[2]

Type II is antibody mediated, caused primarily by IgG and IgM. Cell damage is caused by macrophages, neutrophils, and eosinophils, and by activation of the complement pathways resulting in cell death. The onset is rapid in patients who were previously sensitized, although clinical manifestations (infection from agranulocytosis or purpura due to thrombocytopenia) may not be evident for days.[3]

Type III is mediated by the formation of precipitating complexes formed between the antigen and antibodies (primarily IgM) in the blood vessel walls of the lungs, kidneys, and skin. The resulting inflammatory response attracts macrophages and neutrophils. Serum sickness, an example of a Type III immune complex mediated reaction, can develop in one to two weeks following administration of the causative agent.[3]

Type IV is delayed and driven by expansion of T-cells. Unlike the first three categories, Type IV reactions are not initiated by antibodies, and often are evident as skin reactions. Severity can range from

CONTINUED ON NEXT PAGE

PHARMACOGENOMICS

CONTINUED FROM PREVIOUS PAGE

contact dermatitis to Stevens-Johnson syndrome (SJS) or drug rash with eosinophilia systemic symptoms (DRESS) caused by uncontrolled expansion of T-cells.

TIME TO OCCURRENCE

The classification of drug hypersensitivity reactions supported by the World Allergy Organization (WAO) is based on time to occurrence.

Immediate reactions appear within an hour or less after drug administration, are IgE mediated and represent Type I reactions. Delayed reactions are not IgE mediated, occur later (typically one to six hours after administration or even days later) and describe Types II, III and IV reactions.[4]

A more recent classification focuses on how a drug causes a hypersensitivity reaction. The body's recognition of foreign proteins ("non-self) drives the creation of peptides that bind to major histocompatibility (MHC) molecules. MHC molecules trigger activity of the immune system.[1]

Some small molecular compounds, termed haptens (<1000 Daltons) can bind to a "self" protein, transforming it into a "non-self" antigen that will trigger activity of the immune system. Others form a noncovalent attachment with the immune receptor on antigen-presenting cells (human leucocyte antigen or HLA, also termed MHC or major histocompatibility complex molecules) or T cells, driving activation of the T cell.

These reactions are termed "pharmacologic interaction with immune receptors" or "Pi reactions." Resulting adverse events include the potential for severe or life-threatening reactions such as Stevens-Johnson syndrome and DRESS.[1,4]

In 2002, a specific MHC molecule was found to be associated with severe dermatologic adverse effects in a small number of patients. This genetic variant, or human leucocyte antigen (HLA) B*5701, was discovered in patients taking abacavir.[5,6]

Abacavir is a nucleoside reverse-transcriptase inhibitor with activity against the human immunodeficiency virus (HIV). After weeks of treatment, about 5% of patients developed worsening rash, gastrointestinal symptoms, respiratory symptoms, and fever. Subsequent research uncovered additional HLA variants driving severe reactions to dapsone, carbamazepine and allopurinol.[7]

With the identification of single nucleotide polymorphisms (SNPs), pharmacogenomics may help predict potentially serious or life-threatening hypersensitivity reactions preemptively to improve patient outcomes by avoiding medications that may precipitate these types of reactions.

ENTER PHARMACOGENOMICS

Pharmacogenomics describes the growing knowledge base detailing the impact of individual patient variances in genetic makeup that influence the metabolism and excretion of medications.

This is important because these tiny pieces of DNA, single nucleotide polymorphisms (SNPs) can result in extreme changes in drug efficacy and levels of adverse drug reactions (ADRs) if the structure is a variant from the normal version or "wild type."

Variant SNPs can be base pair substitutions, deletions, or other types of transcription variants regarding base pairs. Pharmacogenomics has focused initially on SNPs located in genes responsible for production of proteins located in the liver and small intestine (CYP family of enzymes) responsible for metabolism of medications.[7]

Technology today is focusing more on DNA sequencing because more concordance has been found in certain genes.[8]

Practitioners in oncology are constantly faced with patients exhibiting off target adverse reactions to chemotherapeutic agents. For example, platinum hypersensitivities were first recorded in workers at precious metal refineries after they experienced rhinitis, conjunctivitis and bronchospasm following exposure to platinum salts.[9]

Some hypersensitivity reactions to chemotherapy are thought to be IgE driven (experienced after sensitization), while others are more immediate. All types of allergic reactions to oncology treatments impact the patient quality of life and often choices for subsequent treatment.

Any grade hypersensitivity reactions are estimated to occur in up to 20% of patients receiving a platinum agent, 5-45% of patients on a taxane, and as high as 70% of patients treated with monoclonal antibodies.[10]

More than half of pediatric oncology protocols include the use of anthracyclines, yet we lack a method to screen for all factors that place patients at risk for anthracycline-induced cardiotoxicity (AIC), affecting 7% of patients.

A review of 86 studies of genetic polymorphisms associated with adverse effects in pediatric oncology patients noted a recommendation by one author for pretreatment screening for a specific SNP involved with ACT.[11,12]

With the knowledge that some unexpected drug reactions in small numbers of people are caused by genetic variances, we are encouraged to explore similar mechanisms for other severe drug hypersensitivities.

With the identification of these SNPs, one may use pharmacogenomics to help predict potentially serious or life-threatening hypersensitivity reactions preemptively

CONTINUED ON NEXT PAGE

PHARMACOGENOMICS

CONTINUED FROM PREVIOUS PAGE

to improve patient outcomes by avoiding medications that may precipitate these types of reactions.

This expanding science is not without challenges – for starters, the expanse of the genetic detail is enormous – each individual's genomic material contains 4-5 million SNPs.

Challenges for our future ability to predict and prevent a greater number of drug hypersensitivity reactions in our patients include education of the medical team on the complexity of pharmacogenomics.[13]

Some variances are relatively rare, requiring expansive collections of data to develop clinically actionable results. Cost has been estimated at $300 per SNP.[7] However, realization of the cost of not preventing these adverse events is much greater. Finally, not all variances predict a pathogenic affect.

There is still much to learn about medication allergies. With pharmacogenomics, new progress can be made in understanding them more fully.

▲ **Caren Lee Hughes**, PharmD, MBA, BCOP is a Hematology Oncology Pharmacy Specialist and Assistant Professor of Pharmacy. **Michael J. Schuh**, PharmD, MBA, FAPhA is an Assistant Professor of Family and Palliative Medicine. Both practice at the Mayo Clinic College of Medicine in Jacksonville, Florida.

REFERENCES

1. Bonfiglio M, Weinstein D. Allergic reactions to small-molecule drugs: Will we move from reaction to prediction? Am J Health-Syst Pharm. 2019;76(9):574-580.

2. Abbas A, Lichtman A, Pillai S. Basic immunology: functions and disorders of the immune system. 6th ed. Philadelphia, PA: Elsevier Inc.; 2020.

3. Descotes J, Choquet-Kastylevsky G. Gell and Coombs's classification: is it still valid? Toxicology, 2001;158:43-49.

4. Drug allergies. World Allergy Organization. @https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/drug-allergies. Accessed 2-7-2022.

5. Daly A. Pharmacogenomics of adverse drug reactions. Genome Med. 2013;5(1):1-12. doi: 10.1186/gm409.

6. Mallal S, Phillips E, Carosi G, Molina J, Workman C et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Eng J Med.2008;358(6):568-579. doi: 10.1056/NEJMoa0706135.

7. Jones, B. The impact of pharmacogenomics in the treatment of allergic disease and asthma. Missouri Medicine. 2011;108(5)361-365.

8. Cohn, I, Paton, T, Marshall, C, Basran R, Stavropoulos D et al. et al. Genome sequencing as a platform for pharmacogenetic genotyping: a pediatric cohort study. NPJ Genom Med. 2017;2(10). https://doi.org/10.1038/s41525-017-0021-8).

9. Pickering C. Inhalation tests with allergens: complex salts of platinum. Proc Roy Soc Med.1972;65(30272-274.

10. Lenz H. Management and preparedness for infusion and hypersensitivity reaction. The Oncologist. 2007;12(5):601-609.

11. Conyers R., Dvaraja S., Elliott D. Systematic review of pharmacogenomics and adverse drug reactions in pediatric patients. Pediatric Blood and Cancer. 2017;65(4): e26937. https://doi.org/10.1002/pbc.26937.

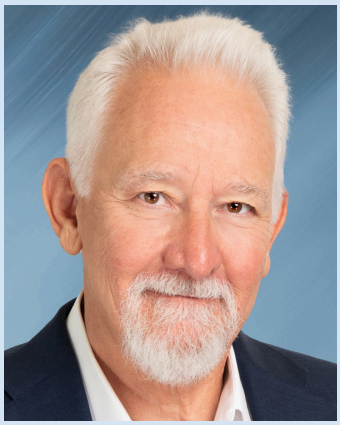
12. Aminkeng F., Bhavsar A., Visscher H. A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. Nat Genet. 2015;47(9):1079-1084.

13. Hippman C, Nislow C. Pharmacogenomic testing: clinical evidence and implementation challenges. J Pers Med. 2019;9(40). doi: 10.3390/jpm9030040.

MEET TWO OF NCODA'S EXECUTIVE COUNCIL LEADERS

Ray Bailey, BPharm, RPh, is Senior Vice President of Pharmacy at Florida Cancer Specialists & Research Institute.

Bailey has been a Clinical Pharmacist at the practice for 14 years. He manages the practice's Medical Integrated Specialty Pharmacy, RxToGo, and oversees the Pharmacy Operations team that provides support of its clinic infusion centers.



RAY BAILEY

Paul Chadwick, BA, is Chief Procurement Officer at Florida Cancer Specialists & Research Institute. He supports the pharmacy, pharmacy operations and procurement teams. Chadwick joined the practice in 2019.

His diverse background includes experience in both pathology research and business analytics.

PAUL CHADWICK

When and why did you become involved with NCODA?

Bailey: I became involved with NCODA about a year after it was initially formed. Michael Reff, who I had known previously, asked to be a part of the Executive Council and I accepted.

Chadwick: Michael Reff and I have discussed NCODA since it was first founded, but I became much more active in the last two years, and I became more engaged with the pharmacists on the team.

What prompted each of you to take a leadership role with NCODA?

Bailey: Being a part of the NCODA Executive Council has been my major leadership role at NCODA. I have always believed in the "Patient First" Mission of NCODA and saw from my own experience the importance of the medically integrated approach of pharmacy and pharmacists for patients taking oral oncology therapies.

Chadwick: It's an incredible organization with a group of leaders who are passionate about cancer patients and patient care.

In my leadership role with NCODA, I have the opportunity to support that message with our corporate partners. It has also been a very interesting time to reach out to clinicians about new and evolving therapies.

NCODA's commitment to education, not just on oral medication but infusion as well, is inspiring.

The payer model for oral oncolytics appears to be involving into a friendlier environment for dispensing pharmacies. How can oncology practices best prepare for what could be an unprecedented opportunity?

Bailey: I do believe payers are finally seeing the value to patients and the system our model brings to the table. Medically Integrated Dispensing/Pharmacy (MID/MIP) must continue to strive to bring patients the best clinical experience possible. For payers, the value is expressed in better outcomes and cost savings.

Accreditation is important to payer and that is why the NCODA Center of Excellence Medically Integrated Accreditation Program is so important. NCODA coined the term ***Going Beyond the First Fill*** many years ago. Since that time, NCODA practices have been collaborating with each other on best practices when it comes to payer pharmacy benefit strategies. We need to continue these efforts.

Chadwick: While these opportunities are coming, the environment is changing on a state-by-state level. It's going to be important for dispensing pharmacies to remain up to date on the progress of change within their own states and understand what specific changes mean to their own pharmacies.

Oral oncology is expanding at a breathtaking rate. Faced with the burgeoning selection of new treatment options, what steps must NCODA members take to ensure that patient care remains at the forefront?

Bailey: New treatments and innovation are coming at an accelerated pace in oncology. New single agent oral targeted drugs have continued to be a big part of this innovation. Combinations of oral and IV agents as new indications continue to expand as well.

NCODA's collaboration with pharmaceutical partners is essential as we look for way to partner around best practices when it comes to management of these expensive, often toxic agents inside of our practices. We must always first seek to give our patients the best clinical experience while on therapy and the best possible outcomes.

CONTINUED ON NEXT PAGE

NCODA EXPANDS EXECUTIVE COUNCIL WITH FIVE NEW MEMBERS

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

▲ **Sam Abdelghany**, PharmD, MHA, BCOP, is Executive Director of Oncology Pharmacy Services at Smilow Cancer Hospital at Yale New Haven Health. Abdelghany's current research interest areas are real-world data with cancer therapies and oncology health economic and outcomes research.

▲ **Neal Dave**, PharmD, is the Executive Director of Pharmacy Operations at Texas Oncology. Dave oversees both oral and IV medications. He joined Texas Oncology in 2005 and has previously held Pharmacy Manager and Area Pharmacy Manager roles.

▲ **Stuart Genschaw**, MHA, MBA, is the Chief Executive Officer at Cancer & Hematology Centers of Western Michigan. He serves on numerous local, state and national boards, and is an active consultant and advisor to physician practices and pharmaceutical companies.

▲ **Luis E. Raez**, MD, FACP, FCCP, is the Chief Scientific Officer & Medical Director at Memorial Cancer Institute (MCI)/Memorial Health Care System. He is also the Director of the Thoracic Oncology Program. He has expertise in medical oncology, specifically in lung cancer and head and neck cancer. He designs phase I-III clinical trials with new chemotherapeutic agents and combinations, and performs translational research and clinical research.

▲ **Stephen Ziter**, MBA, is Director of Operations at NCODA. Ziter joined NCODA in 2018. He currently oversees the development of a comprehensive patient-centered communication strategy, and coordinates with NCODA organizational leadership, team members and external stakeholders.

The Executive Council also includes:

Mary Anderson, BSN, RN, OCN, Oral Oncology Nurse Navigator | Norton Cancer Center; **Robert Ashford**, Director of Membership & Corporate Partner Strategy | NCODA; **Ray Bailey**, BPharm, RPh, Senior Vice President of Pharmacy Services, Florida Cancer Specialists & Research Institute; **Barry Brooks**, MD, Medical Director of Oncolytics | Texas Oncology; **Paul Chadwick**, Chief Procurement Officer | Florida Cancer Specialists & Research Institute; **Jonas Congelli**, RPh, Chief of Pharmacy and Ancillary Services | Hematology Oncology Associates of Central New York;

Austin Cox, PharmD, Pharmacy Manager | Alabama Oncology; **Nancy Egerton**, PharmD, BCOP, Director of Pharmacy | New York Oncology Hematology; **Randy Erickson**, RN, BSN, MBA, CEO | Utah Cancer Specialists; **Linda Frisk**, PharmD, Former Pharmacy Manager | Ironwood Cancer and Research Centers; **James Gilmore**, PharmD, BCCCP, BCPS, Chief Pharmacy & Procurement Officer, AON;

Lucio Gordan, MD, Chief Medical Officer ,Therapeutics and Analytics | Florida Cancer Specialists & Research Institute; **Kirollos Hanna**, PharmD, BCPS, BCOP, Oncology Pharmacy Manager, Clinical Assistant Professor | M Health Fairview, Mayo Clinic College of Medicine; **Dallas Lawry**, DNP, FNP-C, OCN, Oncology Nurse Practitioner | University of Californian San Diego; **Benjamin Lowentritt**, MD, Director of Minimally Invasive Surgery and Robotics and Director of the Prostate Cancer Care Program | Chesapeake Urology; **Stacey McCullough**, PharmD, Former Senior Vice President of Pharmacy | Tennessee Oncology;

Jan Montgomery, PharmD, Former Director of Pharmacy | South Carolina Oncology Associates; **Rajiv Panikkar**, MD, Chair | Geisinger Cancer Institute; **Yen Nguyen**, PharmD, Executive Director of Pharmacy | Oncology Consultants, PA; **Robert Orzechowski**, MBA, SHRM-SCP, COO | Lancaster Cancer Center; **Michael Reff**, RPh, MBA, Founder & Executive Director | NCODA; and **Jim Schwartz**, RPh, Corporate Pharmacy Manager | Texas Oncology.

EXECUTIVE COUNCIL

CONTINUED FROM PREVIOUS PAGE

NCODA has been a leader with developing Positive Quality Interventions (PQIs), focused advisory boards, clinical webinars and patient Treatment Support Kits (TSKs).

Chadwick: For several years, many practices viewed IV and oral therapies as separate. But with doublets, triplets and quad therapies now more common, the MID/MIP model is more critical than ever to manage these multimodal treatments.

The opportunity for two-way communication with the clinic staff through the MID/MIP model will be the key to persistency in the future. By taking a "one pharmacy" approach to the treatment of our patients, NCODA members are instrumental in managing patient care.

The efficacy of Medically Integrated Pharmacy is a proven success, yet getting that message across to key industry and legislative decision makers has remained a challenge. Who still needs to hear this message, and how can we get it across to them?

Bailey: All of us are ambassadors for cancer patients. Each of us has a responsibility to advocate for the value proposition our model brings for our patients. This can take the form of pharmaceutical and payer partner engagements.

It can also include legislative activities at a state and national level. NCODA has its Legislative & Policy Advisory Committee (LPAC) to help educate the membership on important policy and legislative updates. I challenge NCODA members to get involved at a state or national level to advocate and support initiatives that are important to oncology and our patients.

Chadwick: For most medications, not getting the right dose at the right time means a delay in treatment and some amount of drug waste.

In our industry, the same problem can have an exponentially higher impact on patient care. It's expensive and wasteful to delay the start of cancer therapies. It also exacerbates treatment in regimens where all medications need to start on the same day. There are too many opportunities outside of an MID/MIP for "Day 1" to mean different things. For example, Day 1 of chemo vs Day 1 of when a patient received their pills.

The best place for a properly managed therapy is a MID/MIP as the care teams have a direct connection with each other.

APPROVED FOR ADULT PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA (WM)[1]

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage
Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade occurred in 35% of patients treated with BRUKINSA monotherapy.

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

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

Infections
Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 27% of patients, most commonly pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

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

Cytopenias
Grade 3 or 4 cytopenias, including neutropenia (26%), thrombocytopenia (11%) and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 3.6% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose or discontinue treatment as warranted. Treat using growth factor or transfusions, as needed.

Second Primary Malignancies
Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 8% of patients. Other second primary malignancies included malignant solid tumors (4.0%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection, and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias
Atrial fibrillation and atrial flutter were reported in 3.2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk. Grade 3 or higher events were reported in 1.1% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

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

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

ADVERSE REACTIONS

The most common adverse reactions, including laboratory abnormalities, in ≥ 30% of patients who received BRUKINSA (N=847) included decreased neutrophil count (54%), upper respiratory tract infection (47%), decreased platelet count (41%), hemorrhage (35%), decreased lymphocyte count (31%), rash (31%) and musculoskeletal pain (30%).

DRUG INTERACTIONS

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

CYP3A Inducers: Avoid co-administration with moderate or strong CYP3A inducers.

SPECIFIC POPULATIONS

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

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

THE BTK INHIBITOR THAT DELIVERS POWERFUL AND CONSISTENT RESPONSES

BRUKINSA® (zanubrutinib) is a kinase inhibitor indicated for the treatment of adult patients with Waldenström's macroglobulinemia.

BRUKINSA vs **Ibrutinib**

The first and only head-to-head trial of BTK inhibitors in WM

A global, randomized Phase 3 trial in WM across a range of patients*[1]

- Treatment-naïve
- Relapsed/refractory
- *MYD88^{MUT} (CXCR4^{WT}, CXCR4^{WHIM})*
- *MYD88^{WT}*

Powerful Responses Across WM Patients

While the primary endpoint of superiority did not reach statistical significance, numerically higher VGPR/CR rates were achieved in the BRUKINSA treatment arm.[1]

All patients[1]

IWWM-6 criteria†
(Cohort 1)

BRUKINSA (n=102)	Ibrutinib (n=99)
78% VGPR+PR‡	78% VGPR+PR
(95% CI: 68, 85)	(95% CI: 68, 86)
16% VGPR‡	7% VGPR
62% PR	71% PR

All patients[1]

Modified IWWM-6 criteria†
(Cohort 1)

BRUKINSA (n=102)	Ibrutinib (n=99)
78% VGPR+PR‡	78% VGPR+PR
(95% CI: 68, 85)	(95% CI: 68, 86)
28% VGPR‡	19% VGPR
49% PR	59% PR

Median follow-up time was 19.4 months.[3]

The prespecified efficacy outcome measure of VGPR/CR was assessed by IRC.[1]

Safety in WM is consistent with the established BRUKINSA profile[1]

Serious adverse reactions, including fatal events, have occurred with BRUKINSA, including hemorrhage, infections, cytopenias, second primary malignancies, and cardiac arrhythmias. The most common adverse reactions (≥30%) include neutrophil count decreased, upper respiratory tract infection, platelet count decreased, hemorrhage, lymphocyte count decreased, rash, and musculoskeletal pain.

*Patients were enrolled from the United States, Europe, and Australia/New Zealand.
†IWWM-6 criteria (Owen et al, 2013) requires complete resolution of extramedullary disease (EMD) if present at baseline for VGPR to be assessed. Modified IWWM-6 criteria (Treon, 2015) requires a reduction in EMD if present at baseline for VGPR to be assessed.[4,5]
‡There were no CRs in either treatment arm.

BTK=Bruton's tyrosine kinase; CI=confidence interval; CR=complete response; IRC=independent review committee; IWWM-6=6th International Workshop on Waldenström's Macroglobulinemia; MUT=mutated; ORR=overall response rate; PBMCs=peripheral blood mononuclear cells; PR=partial response; VGPR=very good partial response; WHIM=WHIM syndrome-like somatic mutation; WT=wild type.

References: 1. BRUKINSA. Package insert. BeiGene, Ltd; 2021. **2.** Tam C, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851-859. **3.** Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. 2020;136(18):2038-2050. **4.** Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenström macroglobulinemia: update from the VIth International Workshop. *Br J Haematol*. 2013;160(2):171-176. **5.** Treon SP. How I treat Waldenström macroglobulinemia. *Blood*. 2015;126(6):721-732.

Brukinsa® zanubrutinib 80mg capsules

LEARN MORE AT **BRUKINSA.com**

BRIEF SUMMARY OF PRESCRIBING INFORMATION
FOR BRUKINSA® (zanubrutinib)
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

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

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

1.2 Waldenström's Macroglobulinemia

BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

1.3 Marginal Zone Lymphoma

BRUKINSA is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.4% of patients treated with BRUKINSA monotherapy. Hemorrhage events of any grade, excluding purpura and petechiae, occurred in 35% of patients.

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

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

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 27% of patients, most commonly pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

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

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (26%), thrombocytopenia (11%) and anemia (8%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 13% of patients, and Grade 4 thrombocytopenia occurred in 3.6% of patients.

Monitor complete blood counts regularly during treatment and interrupt treatment, reduce the dose, or discontinue treatment as warranted *[see Dosage and Administration (2.4)]*. Treat using growth factor or transfusions, as needed.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 14% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 8% of patients. Other second primary malignancies included malignant solid tumors (4.0%), melanoma (1.7%) and hematologic malignancies (1.2%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.5 Cardiac Arrhythmias

Atrial fibrillation and atrial flutter were reported in 3.2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension and acute infections may be at increased risk. Grade 3 or higher events were reported in 1.1% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate *[see Dosage and Administration (2.4)]*.

5.6 Embryo-Fetal Toxicity

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA in seven clinical trials, administered as a single agent at 160 mg twice daily in 730 patients, at 320 mg once daily in 105 patients, and at 40 mg to 160 mg once daily (0.125 to 0.5 times the recommended dosage) in 12 patients. Among 847 patients receiving BRUKINSA, 73% were exposed for at least 1 year, 57% were exposed for at least 2 years and 26% were exposed for at least 3 years.

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥ 30% of patients included neutrophil count decreased (54%), upper respiratory tract infection (47%), platelet count decreased (41%), hemorrhage (35%), lymphocyte count decreased (31%), rash (31%) and musculoskeletal pain (30%).

Mantle Cell Lymphoma (MCL)

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

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

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

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

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

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

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Blood and lymphatic system disorders	Neutropenia and Neutrophil count decreased	38	15
	Thrombocytopenia and Platelet count decreased	27	5
	Leukopenia and White blood count decreased	25	5
	Anemia and Hemoglobin decreased	14	8
Infections and infestations	Upper respiratory tract infection¶	39	0
	Pneumonia§	15	10^
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rashǁ	36	0
	Bruising*	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage†	11	3.4^
Musculoskeletal and connective tissue disorders	Musculoskeletal pain‡	14	3.4
Metabolism and nutrition disorders	Hypokalemia	14	1.7
Respiratory, thoracic and mediastinal disorders	Cough	12	0

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

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

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

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

* Based on laboratory measurements.
† Asymptomatic lymphocytosis is a known effect of BTK inhibition.

Waldenström's Macroglobulinemia (WM)

The safety of BRUKINSA was investigated in two cohorts of Study BGB-3111-302 (ASPEN). Cohort 1 included 199 patients with MYD88 mutation *($MYD88^{MUT}$)* WM, randomized to and treated with either BRUKINSA (101 patients) or ibrutinib (98 patients). The trial also included a non-randomized arm, Cohort 2, with 26 wild type MYD88 *($MYD88^{WT}$)* WM patients and 2 patients with unknown MYD88 status *[see Clinical Studies (14.2)]*.

Among patients who received BRUKINSA, 93% were exposed for 6 months or longer, and 89% were exposed for greater than 1 year.

In Cohort 1 of the ASPEN study safety population (N=101), the median age of patients who received BRUKINSA was 70 years (45-87 years old); 67% were male, 86% were White, 4% were Asian and 10% were not reported (unknown race). In Cohort 2 of the ASPEN study safety population (N=28), the median age of patients who received BRUKINSA was 72 (39-87 years old); 50% were male, 96% were White and 4% were not reported (unknown race).

In Cohort 1, serious adverse reactions occurred in 44% of patients who received BRUKINSA. Serious adverse reactions in > 2% of patients included influenza (3%), pneumonia (4%), neutropenia and neutrophil count decreased (3%), hemorrhage (4%), pyrexia (3%) and febrile neutropenia (3%). In Cohort 2, serious adverse reactions occurred in 39% of patients. Serious adverse reactions in > 2 patients included pneumonia (14%).

Permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 2% of patients in Cohort 1 and included hemorrhage (1 patient), neutropenia and neutrophil count decreased (1 patient); in Cohort 2, permanent discontinuation of BRUKINSA due to an adverse reaction occurred in 7% of patients and included subdural hemorrhage (1 patient) and diarrhea (1 patient).

Dosage interruptions of BRUKINSA due to an adverse reaction occurred in 32% of patients in Cohort 1 and in 29% in Cohort 2. Adverse reactions which required dosage interruption in > 2% of patients included neutropenia, vomiting, hemorrhage, thrombocytopenia and pneumonia in Cohort 1. Adverse reactions leading to dosage interruption in > 2 patients in Cohort 2 included pneumonia and pyrexia.

Dose reductions of BRUKINSA due to an adverse reaction occurred in 11% of patients in Cohort 1 and in 7% in Cohort 2. Adverse reactions which required dose reductions in > 2% of patients included neutropenia in Cohort 1. Adverse reaction leading to dose reduction occurred in 2 patients in Cohort 2 (each with one event: diarrhea and pneumonia).

Table 5 summarizes the adverse reactions in Cohort 1 in ASPEN.

Table 5: Adverse Reactions (≥ 10%) Occurring in Patients with WM Who Received BRUKINSA in Cohort 1

Body System	Adverse Reaction	BRUKINSA (N=101)		Ibrutinib (N=98)	
		All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infection¶	44	0	40	2
	Pneumonia§	12	4	26	10
	Urinary tract infection	11	0	13	2
Gastrointestinal disorders	Diarrhea	22	3	34	2
	Nausea	18	0	13	1
	Constipation	16	0	7	0
	Vomiting	12	0	14	1
General disorders and administration site conditions	Fatigue#	31	1	25	1
	Pyrexia	16	4	13	2
	Edema peripheral	12	0	20	0
Skin and subcutaneous tissue disorders	Bruising*	20	0	34	0
	Rashǁ	29	0	32	0
	Pruritus	11	1	6	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain‡	45	9	39	1
	Muscle spasms	10	0	28	1
Nervous system disorders	Headache	18	1	14	1
	Dizziness	13	1	12	0
Respiratory, thoracic and mediastinal disorders	Cough	16	0	18	0
	Dyspnea	14	0	7	0
Vascular disorders	Hemorrhage†	42	4	43	9
	Hypertension	14	9	19	14

* Bruising includes all related terms containing "bruise," "contusion," or "ecchymosis."
† Hemorrhage includes epistaxis, hematuria, conjunctival hemorrhage, hematoma, rectal hemorrhage, periorbital hemorrhage, mouth hemorrhage, post procedural hemorrhage, hemoptysis, skin hemorrhage, hemorrhoidal hemorrhage, ear hemorrhage, eye hemorrhage, hemorrhagic diathesis, periorbital hematoma, subdural hemorrhage, wound hemorrhage, gastric hemorrhage, lower gastrointestinal hemorrhage, spontaneous hematoma, traumatic hematoma, traumatic intracranial hemorrhage, tumor hemorrhage, retinal hemorrhage, hematochezia, diarrhea hemorrhagic, hemorrhage, melena, post procedural hematoma, subdural hematoma, anal hemorrhage, hemorrhagic disorder, pericardial hemorrhage, postmenopausal hemorrhage, stoma site hemorrhage, subarachnoid hemorrhage.
# Fatigue includes asthenia, fatigue, lethargy.
‡ Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, myalgia, bone pain, spinal pain, musculoskeletal chest pain, neck pain, arthritis, musculoskeletal discomfort.
§ Pneumonia includes lower respiratory tract infection, lung infiltration, pneumonia, pneumonia aspiration, pneumonia viral.
ǁ Rash includes all related terms rash, maculo-papular rash, erythema, rash erythematous, drug eruption, dermatitis allergic, dermatitis atopic, rash pruritic, dermatitis, photodermatosis, dermatitis acneiform, stasis dermatitis, vasculitic rash, eyelid rash, urticaria, skin toxicity.
¶ Upper respiratory tract infection includes upper respiratory tract infection, laryngitis, nasopharyngitis, sinusitis, rhinitis, viral upper respiratory tract infection, pharyngitis, rhinovirus infection, upper respiratory tract congestion.

Clinically relevant adverse reactions in < 10% of patients who received BRUKINSA included localized infection, atrial fibrillation or atrial flutter and hematuria.

Table 6 summarizes the laboratory abnormalities in ASPEN.

Table 6: Select Laboratory Abnormalities* (≥ 20%) That Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Laboratory Abnormality	BRUKINSA[1]		Ibrutinib[1]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic Abnormalities				
Neutrophils decreased	50	24	34	9
Platelets decreased	35	8	39	5
Hemoglobin decreased	20	7	20	7
Chemistry Abnormalities				
Bilirubin increased	12	1.0	33	1.0
Calcium decreased	27	2.0	26	0
Creatinine increased	31	1.0	21	1.0
Glucose increased	45	2.3	33	2.3
Potassium increased	24	2.0	12	0
Urate increased	16	3.2	34	6
Phosphate decreased	20	3.1	18	0

* Based on laboratory measurements.
[1] The denominator used to calculate the rate varied from 86 to 101 based on the number of patients with a baseline value and at least one post-treatment value.

Marginal Zone Lymphoma

The safety of BRUKINSA was evaluated in 88 patients with previously treated MZL in two single-arm clinical studies, BGB-3111-214 and BGB-3111-AU-003 *[see Clinical Studies (14.3)]*. The trials required an absolute neutrophil count ≥ 1 x 10^9/L, platelet count ≥ 50 or ≥ 75 x 10^9/L and adequate hepatic function and excluded patients requiring a strong CYP3A inhibitor or inducer. Patients received BRUKINSA 160 mg twice daily (97%) or 320 mg once daily (3%). The median age in both studies combined was 70 years (range: 37 to 95), 52% were male, 64% were Caucasian and 19% were Asian. Most patients (92%) had an ECOG performance status of 0 to 1. Eighty percent received BRUKINSA for 6 months or longer, and 67% received treatment for more than one year.

Two fatal adverse reactions (2.3%) occurred within 30 days of the last dose of BRUKINSA, including myocardial infarction and a Covid-19 related death.

Serious adverse reactions occurred in 40% of patients. The most frequent serious adverse reactions were pyrexia (8%) and pneumonia (7%).

Adverse reactions lead to treatment discontinuation in 6% of patients, dose reduction in 2.3%, and dose interruption in 34%. The leading cause of dose modification was respiratory tract infections (13%).

Table 7 summarizes selected adverse reactions in BGB-3111-214 and BGB-3111-AU-003.

Table 7: Adverse Reactions Occurring in ≥ 10% Patients with MZL Who Received BRUKINSA

Body System	Adverse Reaction	BRUKINSA (N=88)	
		All Grades %	Grade 3 or 4 (%)
Infections and infestations	Upper respiratory tract infections[a]	26	3.4
	Urinary tract infection[b]	11	2.3
	Pneumonia[c†]	10	6
Gastrointestinal disorders	Diarrhea[d]	25	3.4
	Abdominal pain[e]	14	2.3
	Nausea	13	0
Skin and subcutaneous tissue disorders	Bruising[f]	24	0
	Rash[g]	21	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[h]	27	1.1
Vascular disorders	Hemorrhage[i]	23	1.1
General disorders	Fatigue[j]	21	2.3
Respiratory, thoracic and mediastinal disorders	Cough[k]	10	0

* Includes 2 fatal events of COVID-19 pneumonia.
[a] Upper respiratory tract infections includes upper respiratory tract infection, nasopharyngitis, sinusitis, tonsillitis, rhinitis, viral upper respiratory tract infection.
[b] Urinary tract infection includes urinary tract infection, cystitis, Escherichia urinary tract infection, pyelonephritis, cystitis.
[c] Pneumonia includes COVID-19 pneumonia, pneumonia, bronchopulmonary aspergillosis, lower respiratory tract infection, organizing pneumonia.
[d] Diarrhea includes diarrhea and diarrhea hemorrhagic.
[e] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort.
[f] Bruising includes contusion, ecchymosis, increased tendency to bruise, post procedural contusion.
[g] Rash includes rash, rash maculo-papular, rash pruritic, dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, drug reaction with eosinophilia and systemic symptoms, erythema, photosensitivity reaction, rash erythematous, rash papular, seborrheic dermatitis.
[h] Musculoskeletal pain includes back pain, arthralgia, musculoskeletal pain, myalgia, pain in extremity, musculoskeletal chest pain, bone pain, musculoskeletal discomfort, neck pain.
[i] Hemorrhage includes epistaxis, hematuria, hemorrhoidal hemorrhage, hematoma, hemoptysis, conjunctival hemorrhage, diarrhea hemorrhagic, hemorrhage urinary tract, mouth hemorrhage, pulmonary hematoma, subcutaneous hematoma, gingival bleeding, melena, upper gastrointestinal hemorrhage.
[j] Fatigue includes fatigue, lethargy, asthenia.
[k] Cough includes cough and productive cough.

Clinically relevant adverse reactions in < 10% of patients who received BRUKINSA included peripheral neuropathy, second primary malignancies, dizziness, edema, headache, petechiae, purpura and atrial fibrillation or flutter.

Table 8 summarizes selected laboratory abnormalities.

Table 8: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with MZL

Laboratory Abnormality[1]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	43	15
Platelets decreased	33	10
Lymphocytes decreased	32	8
Hemoglobin decreased	26	6
Chemistry abnormalities		
Glucose increased	54	4.6
Creatinine increased	34	1.1
Phosphate decreased	27	2.3
Calcium decreased	23	0
ALT increased	22	1.1

The denominator used to calculate the rate varied from 87 to 88 based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 9: Drug Interactions that Affect Zanubrutinib

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

Males

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 847 patients in clinical studies with BRUKINSA, 53% were ≥ 65 years of age, and 20% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between younger and older patients.

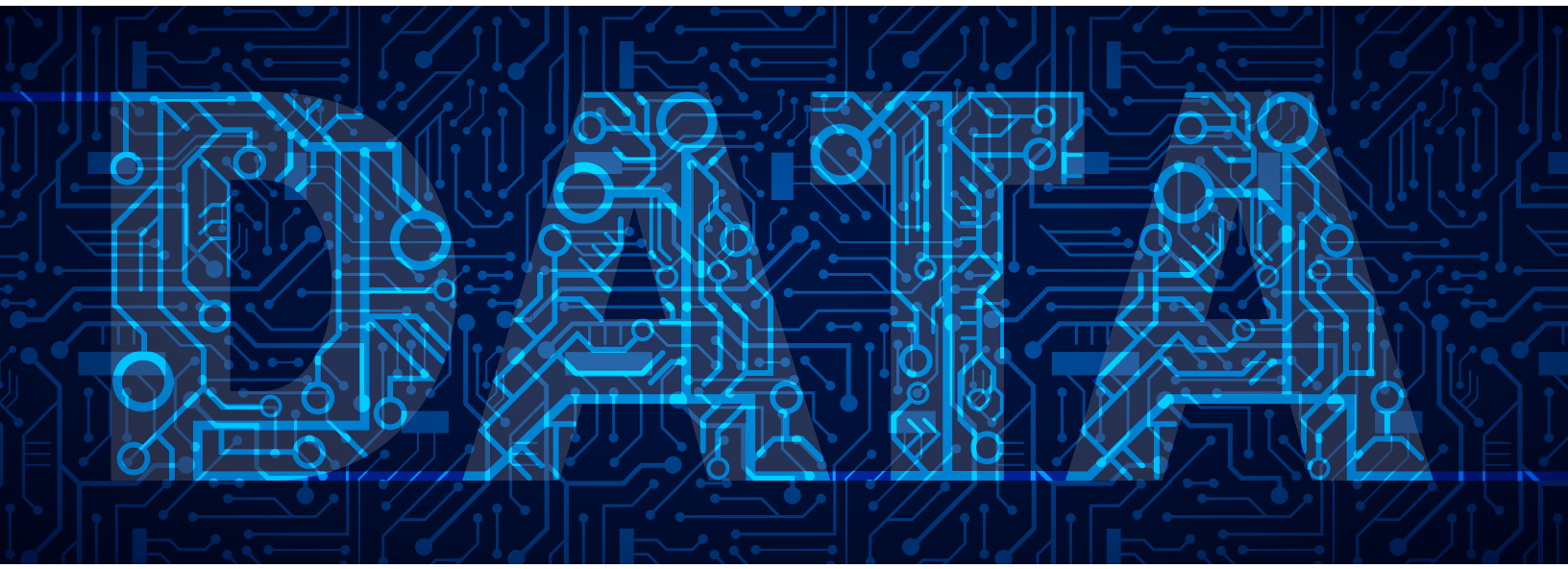
8.6 Renal Impairment

No dosage modification is recommended in patients with mild, moderate, or severe renal impairment (CLcr ≥ 15 mL/min, estimated by Cockcroft-Gault). Monitor for BRUKINSA adverse reactions in patients on dialysis *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

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

Distributed and Marketed by:
BeiGene USA, Inc.
2955 Campus Drive, Suite 200
San Mateo, CA 94403



NCODA INFORMATICS INITIATIVE PROVIDES MEMBERS WITH POWERFUL DATA PLATFORM

INTRODUCTION

NCODA has formed a new partnership with the health information technology company XIFIN, Inc. and is offering VisualStrata®, its healthcare informatics platform, as a complimentary tool to all NCODA members.

VisualStrata collates structured and unstructured clinical, diagnostic, molecular, genomic and financial data from disparate systems into a single source, enabling healthcare professionals to gain insight, make decisions and improve care and outcomes.

VisualStrata was developed to meet the unique needs and challenges of oncology practices through a four-year partnership with Utah Cancer Specialists (UCS).

By pooling clinical data into a common registry shared by all members, NCODA believes the power and potential of the platform will grow exponentially, setting new benchmarks to enhance the quality of patient care and help fill existing gaps in oncology.

PRECISION MEDICINE

NCODA's Informatics Initiative is driven by the advent of precision medicine.

Precision medicine promises to deliver more effective treatment of illnesses through individualized, targeted therapies that result in better health outcomes with fewer adverse events and at a lower cost.

The efficient delivery of precision medicine is data-driven, relying on care teams having the right information, for the right patient, at the right time. Often this information resides in multiple data systems in a variety of formats, and data integration into a single unified view has been a significant challenge.

XIFIN's VisualStrata platform overcomes this challenge through intuitive dashboards that allows users to graphically integrate disparate data, with the ability to "drill down" into a variety of subsets based on such variables as disease state, mutation, patient demographics, financial information, and much more.

BACKGROUND

San Diego-based XIFIN is a health information technology company that leverages diagnostic information to improve the quality and economics of healthcare. It was founded in 1997.

In 2019, XIFIN launched VisualStrata, the industry's only precision medicine informatics platform that uniquely integrates diagnostic, clinical, molecular, genomic, and financial data to support value-based care initiatives.

Data management is a particular challenge in the healthcare industry, noted Patricia Goede, PhD, Vice President of Clinical Informatics at XIFIN.

"That's why we created VisualStrata," Goede said. "Our goal is to help oncology practices accurately chronicle the patient's cancer journey."

For the practice, the platform simplifies what would otherwise be a complicated and sometimes insurmountable task.

"At its simplest, we organize and make it easy to find patient information," explained Sandra Greefkes, XIFIN's Vice President of Product and Partner Marketing. "As an oncology patient goes through their cancer journey, they have multiple doctors and medical specialists, and all of their information ends up in different systems."

CONTINUED ON NEXT PAGE

TECHNOLOGY

CONTINUED FROM PREVIOUS PAGE

"VisualStrata grabs the most important pieces of information and organizes it in a way that can be used by different users for different purposes. Essentially, it organizes information for healthcare professionals so that they can better understand how those pieces of data interact with each other."

DEVELOPMENT

UCS was XIFIN's key partner in the platform.

Chief Executive Officer Randy Erickson, RN, MBA, oversees strategy and vision for UCS, the largest community-based oncology and hematology practice in Utah. Erickson first approached XIFIN in 2019 regarding data access of the practice's electronic health record (EHR). Other data gaps soon came to light. He became convinced that data integration and curation was essential to both UCS and the broader field of oncology.

Randy Erickson

"We live in the greatest time in the history of oncology and medicine because we have more therapies and treatments available to patients than ever before," Erickson said. "We're embarking on a journey into a new frontier. And this new frontier is precision and personalized medicine. To make this journey possible, we must have data. Data will allow us to move forward."

Greefkes agreed. "Curated oncology data is the Holy Grail for individualized medicine," she said.

Yet the sheer magnitude of data collected by oncology practices makes aggregation a daunting task, a task further complicated by the disparate systems that the data is stored in, which includes:

- **EHR:** Contains data such as the patient's demographic information, cancer diagnosis, staging, etc.;

VisualStrata is easy to learn, easy to use and can be run on any browser-capable computer.

- **Laboratory Information Systems (LIS):** Data collected from lab tests, some highly specialized, others as simple as complete blood counts (CBC) or comprehensive metabolic panels (CMP), where the patient's biomarkers are collected; and
- **Practice Management Systems:** Systems that store financial data and associated financial dollar amounts linked to various codes or diagnoses.

Other data, such as Next-Generation Sequencing (NGS) analysis and clinical trial parameters, requires coordination of both external and internal data.

At UCS, for example, a physician seeing a patient may order an NGS test looking for mutations or variants actionable by one of the growing numbers of sequencing companies.

For clinical trials, the pharmaceutical industry is constantly searching for patients with specific disease characteristics to test new and developing treatments.

Keeping abreast of new NGS options and clinical trials, and coordinating them with current patient populations can be challenging for many practices.

Further complicating the aggregation process is the fact that key clinical data often is stored in a variety of documents and formats.

Yet identifying and integrating the data is only part of the challenge. Curating the data — that is, selecting, organizing and presenting the data in meaningful and accessible way — is an essential part of the process.

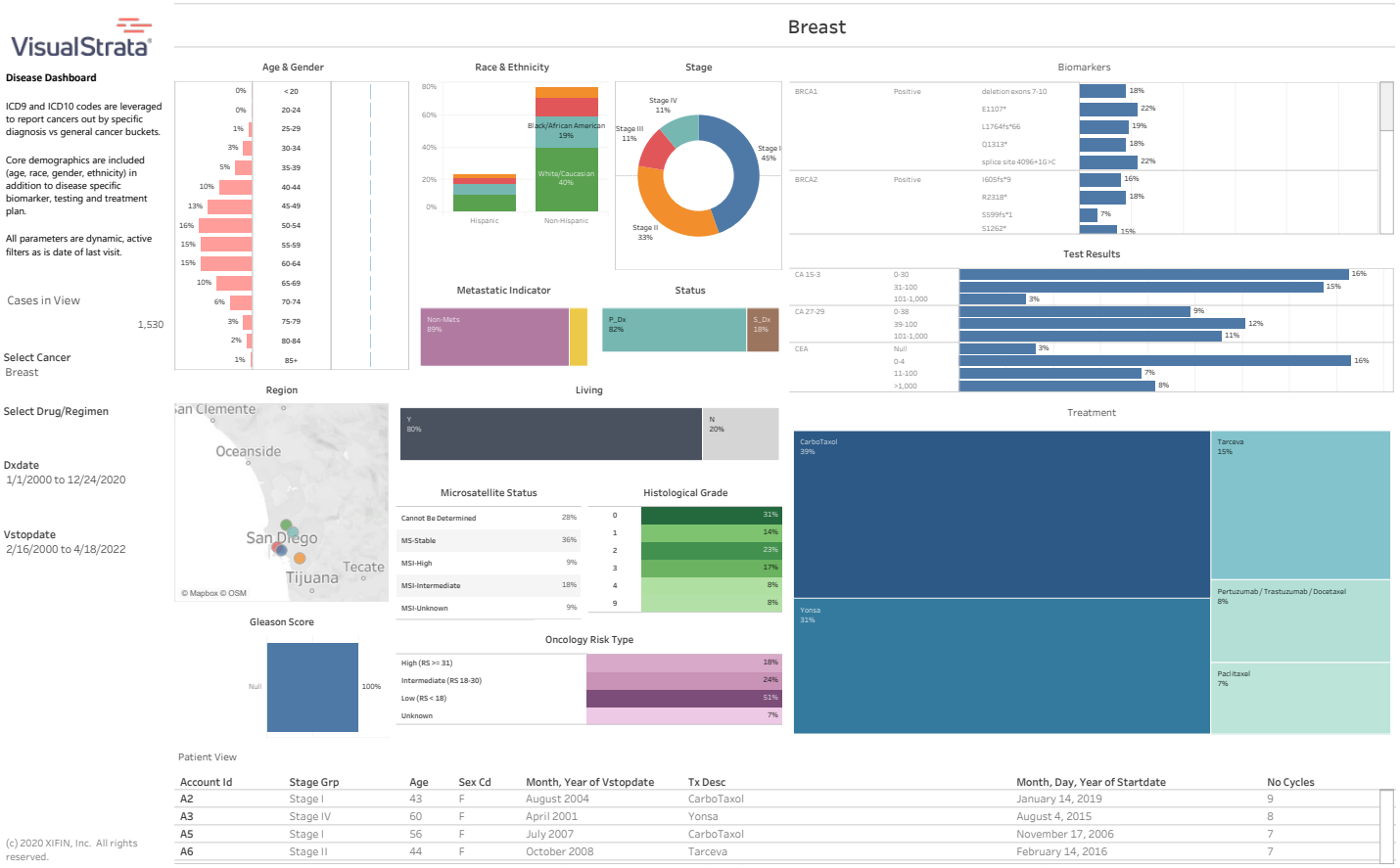
"For most practices, to take all that data and put it in one place, curate it and have it be accurate and meaningful is a huge lift," Erickson said. "It's almost impossible to do, so we have to work with other groups and entities that have like-minded goals centered around patient care and quality improvement."

"That's why we've looked to XIFIN's VisualStrata to do this heavy lifting, to integrate the data, curate it and make it meaningful and accurate."

USER EXPERIENCE

The real power of the informatics platform is achieved through graphical "dashboards" that users can generate

CONTINUED ON NEXT PAGE



VisualStrata's **Disease Dashboard** can visualize a practice's patient population in relation to disease states, staging, demographics and other variables.

TECHNOLOGY

CONTINUED FROM PREVIOUS PAGE

on their computer screens.

"We have data, but it doesn't mean much to us if we can't visualize it," Erickson explained. "VisualStrata takes the data and graphs it in any way that you would like it."

"The neat thing is that the graphs are interactive so you can start at a very high level for your initial visualization. You can then click on any of the elements and drill down."

Erickson refers to this process as "clinical insight."

"For example, your 10,000-foot view might be of all the patients in your clinic, including breast cancer, lung cancer, etc. But say you want to isolate just your colon cancer patients. You can click on 'colon cancer' and see just those patients."

"Now, let's say you only want to see a specific subset of those colon cancer patients. You then could look at a particular stage or characteristic and drill down even deeper, or sort by age, stage, etc."

"The end result is that you can use these dashboards interactively. All of these pieces of data can now be put into one source where we can visualize it, and it becomes very useful."

"We have data, but it doesn't mean much to us if we can't visualize it. VisualStrata takes the data and graphs it in any way that you would like it."

Randy Erickson, RN, MBA
CEO | Utah Cancer Specialists

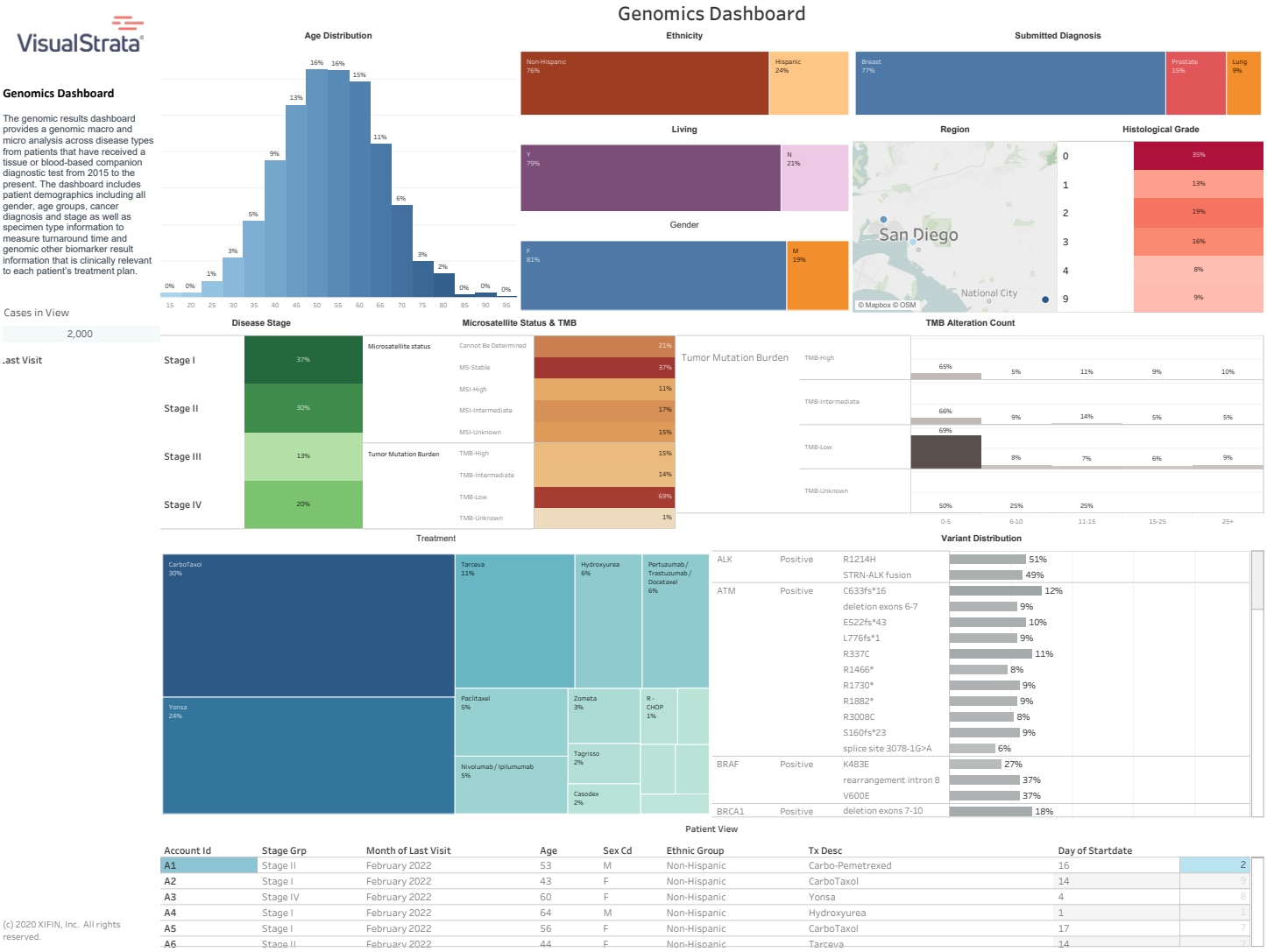
PRACTICAL APPLICATIONS

While working with XIFIN to develop VisualStrata for oncology practices, UCS quickly began to appreciate its potential in a variety of real-world practical applications:

- **Chart Pulls:** This historically manual process requires healthcare providers to access the EHR, initiate a lot of lookups, and write down or key in the results. With VisualStrata, chart pulls are simplified. The user generates a dashboard and then drills down to create a patient list.

- **Clinical Trials:** UCS Director of Clinical Research Johnny Walker oversees implementation and strategic vision of clinical trials. He uses VisualStrata on a regular basis. "A lot of times pharmaceutical manufacturers will call and ask 'Do you have this patient population?'

CONTINUED ON NEXT PAGE



The VisualStrata **Genomics Dashboard** allows users to "drill down" from an overview of a practice's patient population to specific cohorts.

TECHNOLOGY

CONTINUED FROM PREVIOUS PAGE

In the course of five minutes — while I am still on the phone — I can utilize the dashboard, drill down to the point of understanding what variants and what disease indication patients may or may not have, and determine whether we have the population to actually entertain the study. Pharmaceutical manufacturers really appreciate the fact that I can get back with them the same day, often on the same phone call."

• **NGS Options:** The platform has provided a huge lift to UCS in linking our patient population with potential treatments based on NGS results, Erickson said. "With this tool, any NGS results come into the registry, so we no longer have to go into four or five NGS company dashboards. We now have real-world data right within our practice to view.

• **Practice Patterns:** VisualStrata allows users to look at patients as they move and progress on their cancer journey from first- to second- and third-line treatments. "We can now use this tool to watch this journey and the progression of treatment," Erickson said. "That becomes very valuable information for our practice."

• **Clinical-Financial Relationships:** The financial component is an important data piece, and one of the reasons why the project evolved at UCS. "I was looking for a tool that would help a practice like ours tell its story to payers to show the quality of care that we provide to help negotiate better contracts," Erickson said. "Up until that point, without data, it's a hard story to tell." He said UCS eventually hopes to start benchmarking its total cost of care.

A SHARED VISION

On its own, VisualStrata is a powerful data integration and curation tool for oncology practices that can help improve the quality of patient care.

Yet by sharing this clinical data in a common registry accessible by all NCODA members, the potential of the platform grows exponentially, said Michael Reff, RPh, MBA, Founder and

CONTINUED ON NEXT PAGE

TECHNOLOGY

CONTINUED FROM PREVIOUS PAGE

Executive Director of NCODA.

NCODA believes that this platform will bring purposeful and improved overall operational and business outcomes to all stakeholders involved in the care of cancer patients. With a collaborative direction, the goal of this partnership is to support clinicians and researchers through:

- The identification of new patient care options,
- Optimized practice-level decision making, and
- Centralized "locked-up" patient data so that it's integrated, organized, and accessible.

NCODA's Informatics Initiative provides an enormous opportunity for NCODA members, according to Reff.

"It's going to help our members better manage their patients by giving them real-time visibility on their patient population, on what specific biomarkers these patients have and on how many patients they have in certain disease states at certain stages," he said.

Michael Reff

"For example, multi-facility practices will be able to look at their operations in different parts of the city and see if there are trends between how their doctors are treating, say, colorectal cancer. Are their similar pathways or regimens? Or are there differences, and why? It provides this visibility."

FREQUENTLY ASKED QUESTIONS

How much will this cost my practice? The VisualStrata tool is complimentary to NCODA members. If desired, additional customized options can be contracted through XIFIN.

What about data security? XIFIN understands the many methods of attempting to obtain Protected Health Information (PHI) illegally and goes to extensive lengths to protect this data. Perhaps the most foundational security concern of any entity housing PHI information is whether the data center — where the PHI is stored — meets world-class physical security requirements. Switch, XIFIN's data center partner, is the world's only Tier 5® Platinum data center.

> **"It's going to help our members better manage their patients by giving them real-time visibility on patient population, on what specific biomarkers these patients have and on how many patients they have in certain disease states at certain stages."**
>
> **Michael Reff**, RPh, MBA
> Founder & Executive Director | NCODA

Physical security does not stop at the data center. The high standard set by Switch is implemented into XIFIN's own corporate physical security. At its physical locations, XIFIN uses access control and monitoring, which includes segmenting physical areas where PHI is accessible to employees. All employees are HIPAA- and security-trained and limited to facility access by their involvement with PHI. Also, secure remote access is heavily restricted to highly encrypted virtual private networks.

Finally, XIFIN's data architecture — the governance of data collected and how it is stored, arranged, integrated and put to use — leverages world-renowned infrastructure technologies for the many data services XIFIN makes available. These industry-leading technologies enable XIFIN to monitor, alert, respond and remediate threats to data security in near-real time. On top of that is an extensive set of security tools and an internet presence that uses a heavily fortified series of firewalls and appliances to control and inspect all data through ingress and egress. Not only does this keep data safe, but it also keeps it available when needed.

Does VisualStrata have any special hardware or software requirements? No, the platform is cloud-based and can work on any system that supports an internet browser.

Is the program difficult to use? No, VisualStrata is an intuitive, point-and-click program that users can learn within a few minutes.

Can all types of data be accessed by VisualStrata? Some practices may not derive as much value as others because of limitations or availability related to source data. For example, clinical patient data, including lab results that don't reside in the EHR or need to be sourced externally, can create limitations. Some practices are challenged because they cannot get the lab's genomic testing (in bulk or real-time). Additionally, patient data and genomic and molecular results that reside only in specific formats (e.g., PDF) can further hinder the use of the data for analysis within VisualStrata. In these cases, XIFIN urges oncology practices to work with their genomic and molecular lab providers to get this patient data in a discrete format.

Who can access the program once it is implemented at the practice? Access is determined by the individual practice.

Why would I want to share my data with NCODA? By sharing HIPAA-compliant data, NCODA members can help one another improve patient care. NCODA is creating an Advisory Board to help develop this communal registry. On a broader scale, NCODA believes VisualStrata will help advance future treatment options by providing more efficient and accurate feedback about emerging precision medicines.

TO LEARN MORE ABOUT THE NCODA INFORMATICS INITIATIVE, VISIT PAGE 3

ARTIFICIAL INTELLIGENCE IS HELPING RETOOL THE WORLD OF ONCOLOGY

POWERED BY BIG DATA, AI-ENABLED TECHNOLOGY HOLDS PROMISE TO IMPROVE CANCER CARE

By Arturo Loaiza-Bonilla MD, MSEd, FACP, & Aakash Desai, MD, MPH

The field of oncology, as it stands today, has experienced two of the greatest technological revolutions: molecular "omics" (genomics, proteomics, epigenomics) and "big data."

Twenty-five years ago, cancer was diagnosed using a combination of X-ray imaging and histopathology tests. In contrast, molecular testing can now inform on changes in hundreds of genes and proteins to diagnose an individual's cancer more specifically.

Cancer treatment has similarly evolved from an indiscriminate

CONTINUED ON NEXT PAGE

ARTIFICIAL INTELLIGENCE

CONTINUED FROM PREVIOUS PAGE

"one size fits all" cytotoxic-agent treatment regimen to patient-specific and oftentimes biomarker-targeting, tissue-agnostic treatment plans and therapies that target pathways involved in tumor growth or work with the patient's immune system to attack the cancer.

These advances are indeed extending survival and improving the quality of life for hundreds of thousands of patients, yet providers face new challenges associated with implementing precision medicine, particularly as medical knowledge growth is exponential, and specialization is required to deliver highly individualized cancer care.

With almost 85% of patients treated outside NCI-designated cancer centers, providing comprehensive, state-of-the-art cancer care to millions of patients in the U.S. remains a significant challenge, particularly to suburban and rural populations.

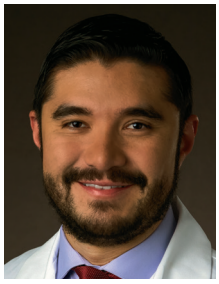
ENTER BIG DATA AND THE USE OF AI

Biomedical data are heterogeneous and difficult to classify (e.g., high dimensionality, temporal dependency, sparsity, irregularity) for Artificial Intelligence (AI) applications.[1-3] Optimized approaches to structure and standardized disparate patient-specific information (e.g., narrative text in patient medical histories and clinician notes, radiology scans, laboratory data, genomic information, pharmacogenomics, and medication lists) have yet to be developed.

These challenges are further complicated by various medical ontologies used to generalize the data (e.g., SNOMED-CT, UMLS, ICD-9, ICD-10), introducing conflicts and inconsistencies.[4]

Further, educational and case-management support systems need to be developed to ensure that the comprehensive and evidenced-based information generated from machine learning technology is truly actionable for all patients.

Potential solutions lie in effectively using comprehensive electronic health information systems, including real-world data, to guide the clinical



Arturo Loaiza-Bonilla

Aakash Desai

decision-making process. The key potential benefits of using (AI)-enabled technology to support clinical decisions include:

1. Improved prediction capabilities;
2. Real-time data updates;
3. Personalized care;
4. Better outcomes; and
5. Increased efficiency, which reduces costs.

Thus, the application of AI and machine learning — as fundamental, core-enabling technologies to assist and enable the treating oncologist — holds promise to improve cancer care.

We aimed to combine cutting-edge AI-based technology of Massive Bio's deep learning virtual tumor board (DLVTB) with high value-added services to provide evidence-based care management recommendations and implementation support to the patients and physicians in the community.

COLORECTAL ADENOCARCINOMA STUDY

To further demonstrate the feasibility, reproducibility, scalability and benefits of DLVTB, we evaluated key outcomes from incorporating DLVTB in a cohort of 35 patients with advanced colorectal adenocarcinoma (CRC). This data was presented at the recently concluded American Society of Clinical Oncology 2021 Virtual Meeting.[5]

The application of AI and machine learning — as fundamental, core-enabling technologies to assist and enable the treating oncologist — holds promise to improve cancer care.

Our core-enabling technology is a deep learning-based natural language understanding engine that employs:

- Natural language processing for medical text digestion and structuring;
- Decision trees and multilayer perception models to produce evidence-based treatment protocols; and
- Natural language-based (NLP) report generation.

The technology platform is combined with human support from oncology subspecialists to deliver a comprehensive interpretive report with a prioritized list of recommendations for each patient. These recommendations are operationalized by a case management team to ensure care implementation and monitoring of outcomes.

Thirty-five patients with CRC were referred for incorporation of DLVTB into clinical practice. Median age of patients was 57 years with 68.6% males. About 88.6% of the patients were Stage IV and 82.9% were treated by community practice oncologists. Median time since diagnosis was 17 months (1-73 months).

Overall, DLVTB-cohort demonstrated an increase in median Overall Survival of 12 months per patient in comparison with historical cohorts. More specifically, DLVTB-recommended initial and/or additional biomarker testing for 71% of the patients, with further precision oncology-guided treatment recommendation (e.g., an EGFR inhibitor) for 80% of the patients. Sixty-three percent of the patients were eligible for at least one clinical trial. Fifty-eight percent of the trials identified were within proximity (≤50 miles) of the patient's primary residence.

Thus, DLVTB was able to identify a

CONTINUED ON NEXT PAGE

ARTIFICIAL INTELLIGENCE

CONTINUED FROM PREVIOUS PAGE

trial that did not require extensive travel, but provided eligibility and actionability closer to the point of care. Fourteen percent of the DLVTB-evaluated patients subsequently enrolled in the recommended clinical trial, far surpassing the national average (3%). Moreover, DLVTB recommended treatments achieved an average savings of $39,194 per patient, which is 35% of the average drug cost per patient.

These results demonstrate the feasibility and benefits of incorporating DLVTB into clinical practice. Our results are consistent with previous studies which showed the application of virtual molecular tumor board (VMTB) with a novel scoring model for ranking therapy options.

In fact, among 1,725 patients studied, oncologists chose to implement the VMTB-derived therapies over others, thus enabling molecularly tailored treatment recommendations to clinicians through scalable informatics solutions.

A TOOL WITH TREMENDOUS POTENTIAL

As comprehensive molecular profiling tests expand beyond genomics only, to include proteomics, phosphoproteomics, metabolomics, and future molecular analyses, the complexity of the input data and treatment options available to a patient will continue to increase exponentially.

Thus, the medical oncology ecosystem already operating in an overburdened environment will need help to keep up with the ever-expanding lists of biomarkers, treatment-matching rules, cancer biology, single and combination therapies. This necessitates computationally driven clinical augmentation tools with a human-in-the-loop framework to ensure accurate and high-quality treatment matching, that clinicians, molecular labs or computational systems alone cannot provide.

Through continued development of scalable deep-learning systems, clinicians can more freely and efficiently implement outcomes-based medicine. Thus, the utilization of DLVTB has tremendous potential as a clinical trial enrollment tool and an engine for development of pathways resulting in improved clinical outcomes, in a cost-effective, and innovative care delivery model.

The future of these developments is dependent on collaboration, and we have since launched SYNERGY-AI: Artificial Intelligence-Based Precision Oncology Clinical Trial Matching and Registry — **https://clinicaltrials.gov/ct2/show/NCT03452774** — which is decentralized and may accelerate these efforts while helping cancer patients access trial options using AI.

In December 2021, we also launched the 100K SINGULARITY PROGRAM, which is an open access movement to match 100,000 cancer patients to clinical trials at no cost to patients and providers, using AI at scale for oncology clinical trials globally.[6]

▲ **Arturo Loaiza-Bonilla**, MD, MSEd, FACP, is a medical oncologist at Cancer Treatment Centers of America, Comprehensive Care and Research Center in Atlanta, and co-founder of Massive Bio in New York, New York. **Aakash Desai**, MD, MPH, is a Hematology/Oncology Fellow in the Department of Hematology and Medical Oncology at the Mayo Clinic College of Medicine in Rochester, Minnesota.

REFERENCES

1. Hripcsak, G. & Albers, D. J. Next-generation phenotyping of electronic health records. J. Am. Med. Informatics Assoc. 20, 117–121 (2013).

2. Jensen, P. B., Jensen, L. J. & Brunak, S. Mining electronic health records: towards better research applications and clinical care. Nat. Rev. Genet. 13, 395–405 (2012).

3. Luo, J., Wu, M., Gopukumar, D. & Zhao, Y. Big Data Application in Biomedical Research and Health Care: A Literature Review. Biomed. Inform. Insights 8, BII.S31559 (2016).

4. Miotto, R., Wang, F., Wang, S., Jiang, X. & Dudley, J. T. Deep learning for healthcare: review, opportunities and challenges. Brief. Bioinform. 19, 1236–1246 (2018).

5. Desai, A., Loaiza-Bonilla, A., Culcuoglu, C., Johnston, K., & Kurnaz, S. (2021). Outcomes and applicability of a deep learning virtual tumor board (DLVTB) in community-dwelling colorectal cancer (CRC) patients.

6. Massive bio launches the movement to match 100,000 cancer patients to clinical trials: 100K Singularity Program. Yahoo! https://www.yahoo.com/now/massive-bio-launches-movement-match-130000235.html?guccounter=1. Published December 7, 2021. Accessed January 31, 2022.

PRECISION MEDICINE

A PINNACLE OF INNOVATION OR A PITFALL OF IMPLICIT AND EXPLICIT BIASES?


Sonia Gill


Hirangi Mukhi


William Oh


Kashyap Patel


Prasanth Reddy


Michelle Zimmerman

By Kashyap Patel, MD, Hirangi Mukhi, BS, Prasanth Reddy, MD, MPH, FACP, Sonia Gill, BS, Michelle Zimmerman, JD, MBA, & William Oh, MD

The past five decades have seen incredible evolution in the field of science from the microcosm of our understanding of life with the Human Genome Project (HGP) to the macrocosm of commercial space travel.

While there is tremendous excitement about boundaries of science stretching beyond human imagination, realizing the real-world impact of scientific advancement on the healthcare outcomes of all patients gives us a reality check of how far we still must go.

The completion of the HGP has ushered in a new era in our understanding of cancer,[1] specifically cancer as a complex set of diseases, the possibilities of genetically targeted treatment options and how genetic variations exist leading to a high-risk for disease.[2]

The field of oncology has witnessed rapid strides and perhaps benefited most from the understanding of complex interactions of epigenetics, environmental factors, and social determinants of health (SDOH).[3] This field is now seen as "precision medicine" (PM), or to be more precise, the field of precision oncology and personalized medicine. Precision medicine holds the promise of revolutionizing cancer prevention and treatment by combining genotype, phenotype and social factors.[4-6]

Precision medicine holds the promise of revolutionizing cancer prevention and treatment by combining genotype, phenotype and social factors.

The approach of PM in cancer care permits a tailor-made approach to cancer care, increasing the chance of treatment response and reducing side effects. The application of PM stretches far beyond an individualized approach to cancer care and scales to population health with a wider application and larger impact on population health outcomes.

When it comes to oncology, PM has progressively focused on the sequencing of cancer genomes. This approach has enabled a better understanding of oncogenesis and actionable alterations. The technique of next-generation sequencing (NGS) in 2006 has reduced the cost of sequencing the cancer genome and spurred the development of targeted therapies.[7]

The depth and breadth of discoveries and innovation has enabled the detection of somatic driver mutations, resistance mechanisms, quantification of mutational burden and germline mutations. Emerging NGS technology has allowed rapid progression in the comprehensive genomic profiling (CGP), or the whole exome sequencing (WES) to optimize our understanding of molecular pathological process and appropriate therapeutic options.

In addition, NGS has catalyzed progressive developments in pharmacogenomics uncovering variance in drug metabolism, and it explains differences in the efficacy and toxicities of the same regimen in ethnically diverse populations.

PROMISES OF PRECISION MEDICINE

According to the Precision Medicine Initiative (PMI) Work group, precision medicine is "an approach to disease prevention and treatment to maximize effectiveness by

CONTINUED ON NEXT PAGE

PRECISION MEDICINE

CONTINUED FROM PREVIOUS PAGE

considering individual variability in genes, environment, and lifestyle."[8,9]

The goal of PM is to advance medical and scientific discoveries to offer more tailored, precise and accurate health interventions, and to maximize the health benefits for patients.[10,11]

Precision medicine adopts diverse strategies in cancer medicine tailored to the unique biology of a patient's disease. These strategies range from application of NGS (either CGP or WES and/or pharmacogenomics) to identify a mutation and then use targeted therapies to select a site-agnostic treatment approach.

The importance of PM is growing at a pace faster than our healthcare system can adapt. To fulfill the desired goals and objectives, the oncology ecosystem needs to carry out comprehensive strategies for success.

Precision medicine holds the promise of improved efficiency, better care and the reduction of ineffective treatments and costs. However, there are potential pitfalls and healthcare inequities that may minimize the global application and benefits of a PM-derived approach.

Pitfalls and shortcomings of precision medicine are multifactorial and include biologic, economic and psychosocial characteristics.

CHALLENGES OF IMPLEMENTING PM

The pitfalls and shortcomings of precision medicine are multifactorial and include biologic, economic and psychosocial characteristics. In addition, structural racism and implicit and explicit biases exist, and are exacerbated by unequal access to clinical trials.[12]

These factors highlight the full realization that PM requires the cooperative, multidisciplinary, global efforts of biomedical researchers, biostatisticians, community and academic clinicians, governments, the pharmaceutical industry, social scientists, population health experts and private industry. They include:

1 **Lack of Appropriate Representation of Minorities in the Genome-Wide Association Studies:** To achieve the full potential of PM, it is important to develop a comprehensive catalogue of mutations unique to each race and ethnicity representing real-world scenarios.

A 2017 study examined the populations included in Genome-Wide Association Studies, the most common type of research that detects genetic alterations that are associated with disease risk. The study found that nearly 80 percent of individuals in Genome-Wide Association Studies were of European descent, 10 percent were Asian, two percent were African, one percent were Hispanic, and less than one percent were of other populations.[12]

Failure to address systemic bias in healthcare provision and genetic databases will make existing disparities worse. For precision oncology to explain and overcome disparities, researchers will need to venture beyond the genome

CONTINUED ON NEXT PAGE

PRECISION MEDICINE

CONTINUED FROM PREVIOUS PAGE

to chart the socioeconomic landscape that governs an individual's health.

Precision medicine needs to integrate and recognize social and economic influences. Alongside its promises, PM also entails the risk of exacerbating healthcare inequalities between ethno-racial groups.

2 Lack of Uptake of NGS Testing in Advanced Cancers: In a report published in 2020, 1,007 advanced non-small cell lung cancer (NSCLC) patients showed a doubling of the use of broad-based NGS testing from 13% in 2017 to 26% in 2019 across more than 100 oncologists.[13]

However, this represents the fact that more than 75% of patients with NSCLC did not get appropriate testing to identify an actionable mutation. These figures are even worse among Black patients (14% versus 26% overall), showing that despite the promise of PM, it has not been fully adopted in the clinical setting and even less so for minority populations.

3 Payer-Related Factors — Limited Coverage / Health Policy: Payer policies are frequently a hindrance for access to testing.

In a study published in the *Journal of Precision Oncology*, Hsiao et al., reported that limited coverage and low reimbursement for the NGS testing remains a large barrier, and broader reimbursement policies are needed to adopt pan-cancer NGS testing that benefit patients in clinical practice.[14]

Additionally, NGS is not covered equally across healthcare benefits. Medicare has coverage but commercial insurance and Medicaid have more restrictions.

4 Physician and Healthcare Team Education: Rapid advances in NGS technology and molecular profiling in oncology have not been matched with appropriate provider education.

A recent survey found that community oncologists use gene profiling in 33% of lung cancer cases.[15]

Alongside its promises, precision medicine also entails the risk of exacerbating healthcare inequalities between ethno-racial groups.

The study also found a knowledge gap with regard to tumor profiling. Additionally, 69% of respondents were not familiar with matching targeted therapies with specific mutations.

Physicians also continue to struggle to manage the large amount of data with unclear therapeutic significance that are produced by comprehensive genomic profiling, such as variants of uncertain significance.

5 Social Determinants of Health: Ethnically diverse populations suffer from a lack of access to adequate cancer diagnosis and treatment, including reduced screening rates and staging at diagnosis, along with the financial challenges people often face following a diagnosis of cancer due to multiple factors.

There is a need to study the impact of social determinants of health and address them appropriately. Failure to address these will lead to drug development processes devoid of demographic diversity, including literacy, education level concerns about getting tested and how the data will be utilized in clinical trials.

This can further contribute to disparities in care and outcomes for these groups. Patients with lower literacy may not be able to comprehend the importance of testing and are also less likely to advocate for themselves due to limitations in their ability to under the consequences of being left behind.

6 Confusion Between Multiple Diagnostic Technologies: With the advent of NGS testing and the freedom of multiple LDT (lab-developed tests), as well as significant variations in the bioinformatic platforms, providers, patients and payers are somewhat disadvantaged about choosing right the test at right time.

With the single-gene testing based on immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH), a preferred test by pathologists who have the first access to tissue, leads to exhaustion of tissue for additional testing with NGS (reported as "quantity not sufficient or QNS), depriving patients right to have appropriate treatment. Of course, liquid biopsy will eventually address this challenge in many cases with concordance studies.

7 Pharmacogenomics: The rapid development of NGS testing and just-in-time trials aimed at developing targeted therapies has outpaced appropriate pharmacogenomics inclusivity. As a result, many significant problems that cancer chemotherapy encounters are the development of drug resistance and severe side effects.

The variability in therapeutic responses, even with targeted therapies, can be explained by the individual genetic variations that are specific to each person.

Pharmacogenetic progress has the potential to be a keystone to revolutionizing cancer therapy. Introducing patient genotyping into clinical settings can facilitate decision-making regarding chemotherapy regimens and drug dosages with maximal effect and minimal risk of toxicity.

Beyond chemotherapy, pharmacogenomics has the potential to inform on appropriate treatment for supportive care, including pain management and mental health considerations. Pharmacogenomics remains the key to unlock the full potential of PM in cancer patients.

8 Germline Testing: Genetic factors are important in understanding the risk of developing certain cancers. The detection of a germline predisposition can impact

CONTINUED ON NEXT PAGE

PRECISION MEDICINE

CONTINUED FROM PREVIOUS PAGE

treatment decisions, risk-reducing interventions, cancer screening and testing in patients and their relatives. Multiple studies have validated the role of germline testing and actionable interventions.[16,17] However, uptake of universal germline testing remains low across all sectors.

To fulfill the promises of precision medicine so that the right care is delivered to the right patient at the right time, actionable solutions to the barriers listed above should be addressed and implemented. Some initial suggestions for further exploration include:

▲ A universal approach to diagnostic technology, preferably whole-exome sequences or comprehensive genomic profiling, to identify both the somatic mutation and homologous repair defect;

▲ Consensus on guidelines between different specialists, pathologists, molecular scientists, and oncologists;

▲ Establishment of the clinical value, validity and utility of NGS;

▲ Establishment of an approach to universal germline testing;

▲ Establishment of concordance between tissue and liquid biopsies;

▲ Establishment of concordance between MRD and imaging studies;

▲ Applying a data-driven approach to clinical trial feasibility and patient screening;

▲ Accelerating the adoption of new drug approvals using just-in-time trials;

▲ Generating new evidence in collaboration with leading cancer centers, life sciences organizations, and the U.S. Food and Drug Administration (FDA); and

▲ Develop bioinformatic and analytics to transform real-world data into positive patient care.

Ultimately, making a meaningful change will require a multi-stakeholder team across governmental agencies and the pharmaceutical industry, as well as providers, payers and patients, to create partnerships and solutions to close the gaps in health inequalities, and fully harness the promise of precision medicine.

Meaningful change will require a multi-stakeholder team to close the gaps in health inequalities and fully harness the promise of precision medicine.

▲ **Kashyap Patel**, MD, is CEO of Carolina Blood and Cancer Care Associates and Community Clinical Oncology Research Network. **Hirangi Mukhi**, BS, is Director at Business Development of Carolina Blood and Cancer Care and Community Clinical Oncology Research Network. **Prasanth Reddy**, MD, MPH, FACP, is Senior Vice President & Global Head of Enterprise Oncology at Labcorp. **Sonia Gill**, BS, is Senior Director of Precision Oncology Partnerships at Sema4. **Michelle Zimmerman**, JD, MBA, is Chief Strategy & Transformation Officer at Sema4. **William Oh**, MD, is Chief Medical Science Officer at Sema4.

REFERENCES

1. Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. JAMA. 2001;285(5):540–4.

2. https://www.icr.ac.uk/news-features/latest-features/how-the-human-genome-project-shook-the-world-of-cancer-research. Accessed February 19, 2022.

3. Matthew Asare, PhD, Marie Flannery, PhD, RN, AOCN®, and Charles Kamen, PhD, MPH. Social Determinants of Health: A Framework for Studying Cancer Health Disparities and Minority Participation in Research. Oncol Nurs Forum. 2017 Jan 2; 44(1): 20–23.

4. National Institutes of Health. What is PM? https://ghr.nlm. nih.gov/primer/PM/definition. Published 2015. Accessed September 8, 2021.

5. Khoury MJ, Galea S. Will PM improve population health? JAMA. 2016;316(13):1357–8

6. Khoury MJ, Iademarco MF, Riley WT. Precision public health for the era of PM. Am J Prev Med. 2016;50(3):398–401.

7. Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next generation sequencing technologies. Nat Rev Genet. 2016;17(6):333–51.

8. PMI Working Group. The Precision Medicine Initiative Cohort Program - Building a Research Foundation for 21st Century Medicine [Internet]. National Institutes of Health; 2015. Available from: https://www.nih.gov/sites/default/files/research-training/initiatives/ pmi/pmi-working-group-report-20150917-2.pdf.

9. Collins FS, Varmus H. A new initiative on precision Medicine. N Engl J Med. 2015;372(9):793–5.

10. Ashley EA. Towards precision medicine. Nat Rev Genet. 2016;17:507.

11. Lester Darryl Geneviève et al. Structural racism in precision medicine: leaving no one behind, https://bmcmedethics.biomedcentral.com/articles/10.1186/s12910-020-0457-8.

12. Latrice G. Landry, Nadya Ali, David R. Williams, Heidi L. Rehm, and Vence L. Bonham; 5 Of Diversity in Genomic Databases Is a Barrier To Translating Precision Medicine Research Into Practice; Health Aff (Millwood) 2018 May;37(5):780-785.

13. Hinco J. Gierman et al. A retrospective three-year analysis using real-world data on uptake of broad-based NextGen sequencing panels in community oncology practices. JCO.Vol 38;15:e e13668.

14. Hsiao et al, Clinical Utilization, Utility, and Reimbursement for Expanded Genomic Panel Testing in Adult Oncology. JCO Precision Oncology. Volume 4; 4:1038-1048.

15. Singh BP, Britton SL, Prins P, et al. Molecular profiling (MP) for malignancies: knowledge gaps and variable practice patterns among United States oncologists (onc). Presented at: 2019 American Society of Clinical Oncology Annual Meeting; May 31- June 4, 2019; Chicago, IL. Abstract 10510.

16. Jiang W et al. Universal germline testing among patients with colorectal cancer: clinical actionability and optimized panel. http://dx.doi.org/10.1136/jmedgenet-2020-107230. Accessed September 8, 2021.

17. Edward D. Esplin, & N. Jewel Samadder. Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients with Hereditary Cancer Syndrome. AMA Oncol. 2021;7(2):230-237. doi:10.1001/jamaoncol.2020.6252. Accessed September 8, 2021.

NCODA OPTIMIZES TSK INITIATIVE TO ENSURE THE HIGHEST LEVELS OF QUALITY CONTROL

NCODA has optimized both accessibility and support for its popular Treatment Support Kits (TSKs) to further ensure that all its kits and the materials within them are of the highest quality.

The kits provide products and educational materials to help patients with medication adherence and persistence.

Based on patient and provider survey feedback, the TSK initiative has led to a longer duration of therapy and a perceived better quality of life for patients.

In 2021, NCODA distributed approximately 5,500 TSKs. Currently, more than 75 NCODA member practices participate in the TSK program.

FISHBOWL

NCODA now utilizes Fishbowl software to streamline its TSK operations. A top manufacturing and warehouse inventory management system, Fishbowl:

- Tracks product lots and expiration dates;
- Ensures timely inventory management and distribution; and
- Streamlines accounting.

It also allows NCODA to barcode and manage different products for each kit, as well as keep all customer and practice information readily available for reordering.

Fishbowl also helps NCODA members anticipate which TSKs they will need in the future based on past orders.

In the future, NCODA plans to integrate Fishbowl into a web-based ordering system for customers. The system will allow practices to order TSK products through point-and-click online shopping.

CURRENT GOOD MANUFACTURING PRACTICE

NCODA follows Current Good Manufacturing Practice (cGMP) regulations for its TSK packaging, warehousing and distribution center to ensure its kits are of the highest quality.

NCODA APPE student Michaela Sattaur assembles a Treatment Support Kit (TSK) in NCODA's production and distribution center. Sattaur is a PharmD candidate (2022) at Albany College of Pharmacy and Health Sciences.

Enforced by the U.S. Food & Drug Administration (FDA), cGMP guidelines certify consistent product quality and safety by confirming proper design, monitoring, and control of manufacturing processes and facilities.

The regulations oversee everything from proper storage and handling of materials to compliance training and tracking of orders, lot numbers and expiration dates, and implementation of Standard Operating Procedures (SOPs).

In order to comply with cGMP, NCODA maintains a myriad of quality control measures. For example, cGMPs assure that the proper products are packaged within each TSK, that no product is expired, that each product is stored in the proper place at the proper temperature and that the employees who assemble the TSKs are fully trained.

FDA REGISTRATION

NCODA regularly submits documentation to the FDA that lists relevant contents and "medical devices" contained in its TSKs to ensure compliance.

CONTINUED ON NEXT PAGE

TSK

CONTINUED FROM PREVIOUS PAGE

FDA registration means that the FDA is aware of a manufacturer and its devices, including businesses that repackage or relabel such devices.

The FDA monitors the safety of products and devices registered to them.

AVAILABLE TSKs

NCODA produces TSKs for both branded and generic oral anticancer medications.

Branded kits are produced by NCODA in collaboration with a sponsoring manufacturer. These specific TSKs are available to NCODA members as complimentary resources.

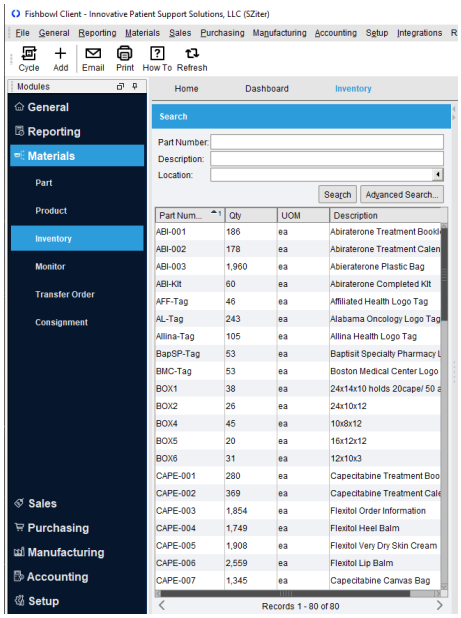
NCODA offers branded kits for the following oral oncolytics:

- **EXKIVITY™** (mobocertinib)
- **FOTIVDA®** (tivozanib)
- **INQOVI®** (decitabine and cedazuridine)
- **NERLYNX®** (neratinib)
- **STIVARGA®** (regorafenib)
- **XPOVIO®** (selinexor)

NCODA works with recommendations from members and the TSK Committee to determine which generic anticancer drugs will inspire kits. This is based on a number of factors, including which generics are frequently prescribed and which have more drastic side effects that require management. Guidelines for easing side effects greatly benefit the patient.

NCODA develops TSKs for generic drugs where there is no manufacturer support.

NCODA offers generic TSKs at minimal pricing, saving time and costs for practices that would otherwise have to commission their own kits. For example, sourcing all the products for their capecitabine kit through online vendors would cost more than $45, and not include NCODA educational materials.



NCODA utilizes Fishbowl inventory management software to oversee its TSK operations. As seen in the example above, the system tracks product lots and expiration dates, manages inventory and distribution, and streamlines accounting.

Generic TSKs, including pricing, are available for the following oral oncolytics:

- **Abiraterone acetate** | $8.99
- **Capecitabine** | $22.95
- **Temozolomide** | $8.99

TSK CONTENTS

Each TSK contains a variety of education, supportive care resources and products, and select medical devices to assist patients on a particular oncoloytic.

For example, the capecitabine TSK includes the following items:

- A comprehensive treatment booklet including a welcome letter, and an OCE educational sheet on capecitabine;
- A customizable treatment calendar;
- Twelve 2mg caplets of loperamide;
- A digital thermometer;
- A large pill container designed for twice-daily regimens; and
- Flexitol skin and lip care products: 4.4 oz. of Very Dry Skin Cream (12.5% urea), 3 oz. of Heel Balm (25% urea) and 0.35 oz. of Lip Balm (steroid-free).

The capecitabine TSKs are packaged in a canvas bag, bearing custom logo tags for the respective practice for which the TSKs were created.

PRACTICE SUPPORT

The TSKs also assist practitioners by providing them with additional support resources; in essence, guides on how to educate patients about dosage, documentation of their treatment journey, management of possible side effects, and ultimately the importance of adherence to their oral oncolytic regimen.

Certain TSKs also are paired with a relevant NCODA Positive Quality Intervention (PQI) document that is conveniently packaged within the shipping box. The PQI provides additional education to the healthcare team surrounding the specific drug or disease state, adding yet another touchpoint in the journey to providing enhanced patient care.

SMART CAP SYSTEM DESIGNED TO TRACK DISPENSING, RECORD VITAL SIGNS & SHARE DATA WITH PROVIDERS

A New Jersey-based healthcare solutions developer is creating a system to better assess medication and treatment protocol efficiency, while improving the level of remote treatment monitoring and support for cancer patients taking oral oncolytics.

ModoScript is developing a tamper-alert lock-dispensing cap with fingerprint biometric authentication and an oxygen saturation (SpO2) sensor.

The cap will record the patient's medication dispensing, as well as their heart rate and oxygen saturation level. It also will record a patient's heart rate variability and respiratory rate.

The device will include an LCD screen display that allows patients to access vital sign readings. It also will provide personalized educational content. This function is especially useful for supporting patients with mental health and cognitive decline, according to Modoscript CEO and Founder David Zuleta.

The lock-dispensing cap will only allow the authorized patient access to the prescription bottle. It will also only dispense the prescribed dosage of the patient's medication.The cap will integrate with standard orange and white prescription bottles.

All medication adherence and vital sign health data from the lock-dispensing cap will be shared through a ModoScript mobile application.

The app will allow cancer patients to perform remote health assessments (i.e., pain score), access a symptom tracker and integrate health data from other wearables to enable ModoScript to create a more holistic image of the patient's current remote health status.

All data collected will be shared with healthcare providers via a real-time online dashboard. The dashboard will give

providers access to real-world patient health data and analytics to better assess and assist their patients, as well as improve efficiency in the prescription refill process and monitor medication tapering.

The device is still in the prototype phase. It will undergo its first clinical study at Memorial Sloan Kettering Cancer Center in New York in October. The anticipated market release date is Q3 2023.

While the system will be marketed primarily to pharmaceutical and health insurance companies, ModoScript also plans to offer it as a "freemium" service to patients and healthcare providers, Zuleta said.

Ultimately, analytics collected from the device, mobile application and healthcare provider dashboard will be shared with authorized industry stakeholders, including The Centers for Medicare & Medicaid Services (CMS), health insurance companies, health systems and provider networks, and pharmaceutical companies.

"The goal is to further support research and development of more personalized oral therapies and to gain deeper insight into effective population health management strategies," Zuleta said.

The system will be fully secured

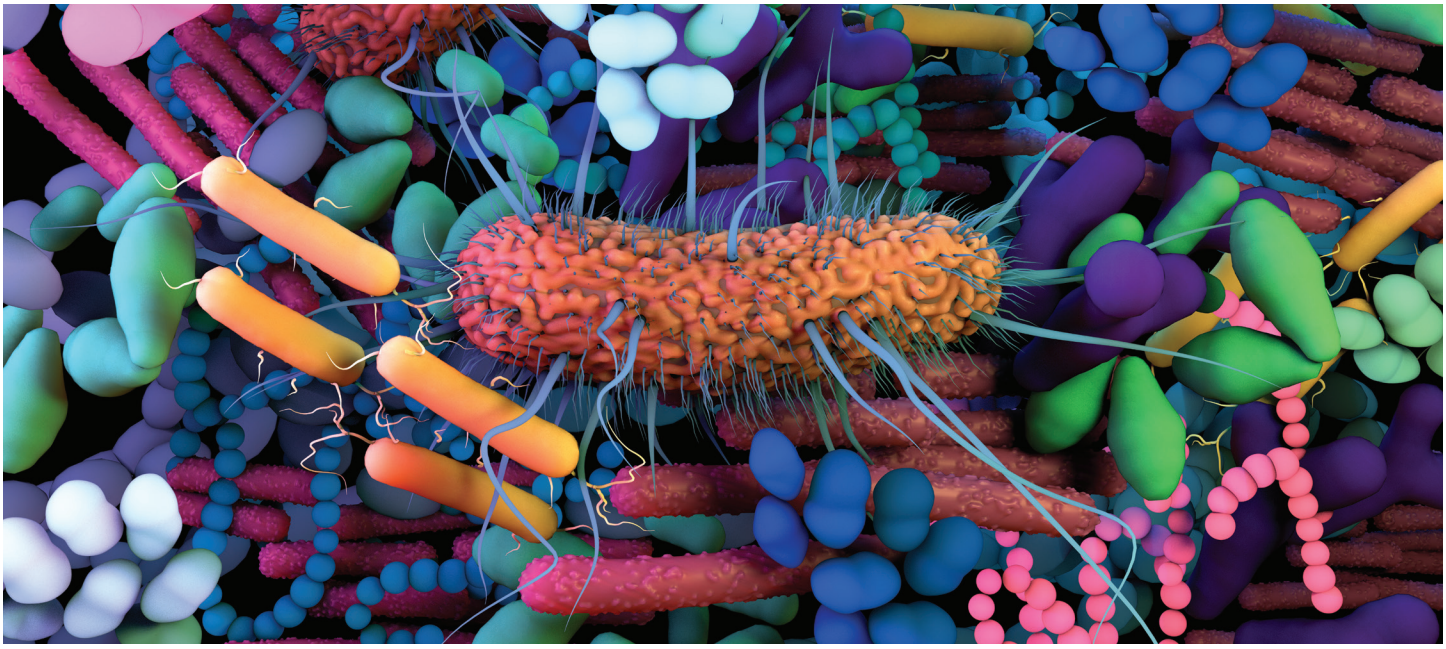
ModoScript is developing a tamper-alert lock-dispensing cap with fingerprint biometric authentication and an oxygen saturation (SpO2) sensor.

to protect the data and assure patient confidentiality.

"Patient health data security is our utmost priority," Zuleta said. "We are committed to following the proper HIPAA compliance and regulatory procedures to build an ecosystem of trust and transparency."

For more information on ModoScript's smart cap system, contact David Zuleta at **David@ModoScript.com**.

THE HUMAN MICROBIOME



A computer rendering of the human microbiome, which contains genetic material of all the microbes that live on and inside the human body.

By Samuel H. Cass, MD & Nadim J. Ajami, PhD

The human microbiota consists of trillions of microbes, including bacteria, archaea, fungi and viruses which outnumber our own native human cells.

These organisms typically work symbiotically by contributing a protective barrier to injury and pathogenic microbes and by priming our innate and adaptive immune systems – the multitude of functions their collective genomes encode to complement many aspects of human physiology.

For instance, these microbes aid in metabolism of food and interact with local host tissues and immune cells, resulting in important contributions to normal human health and function.

However, disturbances in the diversity, composition and function of the microbiome, known as dysbiosis, has been implicated in numerous autoimmune, inflammatory and neoplastic conditions.

A NEW DIMENSION & HALLMARK OF CANCER

There are a multitude of factors influencing cancer development. Pathogenic microbes recently have been implicated as newer pieces of the puzzle due to their ability to produce chronic inflammatory states and/or pro-carcinogenic genotoxins.

In the gut, generalized dysbiosis has also been implicated in tumorigenesis for both gastrointestinal (GI) and non-GI cancers, findings supported by a large retrospective study that suggested recurrent antibiotic exposure was associated with increased cancer risk.[1]

In addition to its potential role in the modulation of cancer development, recent evidence from the past decade now suggests an important role of the gut microbiota in affecting treatment responses to cancer therapies, including chemotherapeutics, radiation therapy and immunotherapy.[2-5]

Revolutionary progress has been made in cancer treatment due to the advent of immune checkpoint inhibitors (ICIs). Tumor cells can express immune checkpoint molecules, enabling them to evade anti-tumor responses from T-cells. ICIs block these signals, allowing circulating host immune cells to mount appropriate anti-tumor responses. However, only a subset of cancer patients ultimately responds to ICIs and often, significant treatment-related adverse events can necessitate ICI discontinuation.

Over the past two decades, numerous studies have described the potential role of the gut microbiota in modulating response to ICIs. Across different cancer types, many investigations have described differences among gut microbiota signatures and the relative abundance of

CONTINUED ON NEXT PAGE

MICROBIOME

CONTINUED FROM PREVIOUS PAGE

specific bacterial taxa between responders and non-responders to ICIs.

Several studies utilizing preclinical mouse models have demonstrated that the "responder" phenotype could be reconstituted in antibiotic-treated or germ-free mice via fecal microbiota transplant (FMT). These studies have led to the opportunity to utilize gut microbial ma-nipulation to achieve or enhance treatment response, as shown recently in two independent FMT trials in melanoma patients that previously failed ICI therapy. [6,7]

MICROBIOME MANIPULATION STRATEGIES

In recent years, much research effort has been given towards understanding the optimal gut microbiome and strategies of microbiome manipulation.

The gut microbiome's structure and function are significantly altered by environmental exposures, especially diet and medications, according to Carrie Daniel-MacDougall, PhD, MPH, Associate Professor in the Department of Epidemiology and Director of the MD Anderson Cancer Center (MDACC) Bionutrition Research Core.

"We know that nutrition is a key tool across the cancer continuum from primary prevention to survival after cancer," Daniel-MacDougall said. "Beyond meeting calorie and protein needs to maintain strength through the cancer treatment journey, we are also beginning to see that how diet interacts with the gut microbiome and the immune system may be an important piece of the puzzle toward achieving more 'optimal' responses to cancer therapy. MD Anderson has made it a priority to support state-of-the-art nutrition research in our patients and our community through the establishment of the Bionutrition Research Core."

Because response to ICIs and treatment-related toxicity has been shown to be dependent on the gut microbiome, a few dietary intervention trials have demonstrated successful modulation of the gut microbiome and its function through changes in dietary composition.

Samuel Cass

Nadim Ajami

Based on this understanding, a study recently published in *Science* **(www.science.org/doi/10.1126/scitranslmed.aap9489)** by our group at MDACC investigated whether factors such as dietary fiber intake or probiotic use could affect immunotherapy responses in patients with metastatic melanoma.[8]

In this study, fecal microbiome profiling, clinicopathologic features and outcome data were collected among 438 melanoma patients at MDACC. Patients treated with ICIs completed a comprehensive lifestyle survey that included assessments of dietary habits and probiotic use.

First, evaluation of gut microbial taxa associated with response to immunotherapy demonstrated enriched relative abundance of bacteria from the Ruminococcaceae family, the *Faecalibacterium* genus, as well as *Faecalibacterium prausnitzii* among responders. Enrichment of these fiber-fermenting bacteria has been previously described by our group and was supported here in a larger patient cohort.[8]

Given that many of the abundant bacteria utilize fiber-fermenting functions, the effect of dietary fiber intake on ICI response was then evaluated.

Sufficiently high-fiber intake, defined as > 20 g/day was met by ~30% of melanoma patients on ICIs. Patients with sufficient dietary fiber intake demonstrated improved progression-free survival (PFS) and odds of response compared to patients with insufficient fiber. Furthermore, every 5g increase in dietary fiber intake corresponded with a 30% reduction in risk of progression or death.

DIETARY HABITS MATTER

Due to the growing interest in probiotic use in gastrointestinal health, use of commercially available probiotics was queried and it was found that 31% of melanoma patients on ICB reported probiotic use within the past month. However, there was no statistically significant difference in PFS or odds of response among patients who reported probiotic supplementation.

Interestingly, when dietary fiber and probiotic use were assessed in conjunction, significantly longer PFS was observed in patients with sufficient dietary fiber and no probiotic used compared to all groups.

Next, these findings were supported in preclinical models, which demonstrated impaired treatment responses to immunotherapy in mice receiving low-fiber diets or probiotics.

While a causal role of dietary fiber cannot be proven from this observational human cohort, this preclinical model supports the hypothesis that dietary fiber can modulate the microbiome and enhance immunotherapy response in mice.

Ultimately, these exciting data have important implications, including the potential predictive value of the microbial signatures and dietary habits for treatment response, as well as the potential utility of noninvasive, dietary interventions to improve patients' cancer treatments.

MICROBIOME ASSESMENT IN CANCER CARE

In modern cancer care, patients undergo mutational analyses as well as profiling of the tumor immune microenvironment to manage patients with personalized, targeted therapies.

For example, microsatellite-instability in colorectal tumors corresponds with more robust tumor immune cell infiltrates, which leads to increased efficacy of ICIs in this tumor type compared to microsatellite-stable tumors. In addition to evaluating tumor characteristics, patient-centric cancer care utilizes individualized treatment options that are adapted based on genetic, environmental and lifestyle factors.

To advance personalized cancer care,

CONTINUED ON NEXT PAGE

MICROBIOME

CONTINUED FROM PREVIOUS PAGE

further patient assessment via profiling of the gut microbiome can be utilized to define the diversity, composition and functionality of the microbiome, and its contribution to a patient's cancer.

MICROBIOME ASSESSMENT IN CANCER CARE

As we learn more about the role of the gut microbiota in cancer development and treatment response, efforts are being made to understand the setting and clinical value of microbiome and metabolome assessment as part of routine cancer care.

Furthermore, for patients with unfavorable microbiomes, FMT or next-generation probiotics could be potentially utilized to reconstitute healthy microbiomes that favor treatment response. For those with favorable microbiomes, dietary intervention or pre/pro-biotic maintenance could be utilized to enhance treatment responses and decrease rates of treatment-related toxicities.

Similarly, screening and early detection is the cornerstone of cancer prevention and management. Fecal microbiome profiling may represent an important adjunct to traditional screening methodologies.

For example, fecal immunochemical tests (FIT) are utilized for the detection of colorectal cancerous polyps. The relative abundance of *Fusobacterium nucleatum* has been shown to be increased in numerous studies focused on the gut microbiome of colorectal cancer patients.[9]

Based on this finding, one study demonstrated the predictive value of *F. nucleatum* screening, as its use combined with the FIT led to improved sensitivity and specificity of CRC detection.[10]

In prostate cancer, chronic inflammation correlates with the risk of prostate cancer development and tumor progression. Circulating inflammatory markers assessed in patients either at the time of cancer diagnosis or in high-risk patients, could serve as an important adjunct for cancer risk assessment.

Furthermore, modulation of systemic inflammation through dietary and/or exercise programs is being investigated in clinical trials, with hopes that it can help prevent prostate cancer or slow tumor progression in low-risk prostate cancer patients on active surveillance.

A CORNERSTONE OF RESEARCH

Here at MDACC, microbiome research has evolved into a cornerstone of cancer research — it is a new piece of the puzzle with exceptional potential.

To this end, MDACC has invested in the development of a program to help coordinate and augment new and existing translational microbiome research, — the Program for Innovative Microbiome and Translational Research (PRIME-TR).

Insights from observational human cohorts as well as preclinical cancer models are being used to better profile and describe the interplay between microbes and the host, and the impact of those interactions on treatment outcomes.

Researchers here have been working on microbiome science from different perspectives and cancer types, and investigators at MDACC have developed numerous trials aimed to unlock the power of the microbiome and optimize cancer treatment through microbiome manipulation.

"The interplay of the microbiome and immune response represents an area of tremendous potential for us to maximize the benefit of immunotherapy for patients," explained Michael Overman, MD, a Professor in the Department of Gastrointestinal Medical Oncology at MDACC.

"However, this requires well-conducted clinical trials of microbiome modulation in patients. This has led to our clinical trial, NCT04729322, investigating microbiome modulation to reignite an immune response in patients with solid tumors characterized by a deficiency in mismatch repair or high in microsatellite instability solid tumors that are previously resistant to PD1-based immunotherapy."

In Overman's phase II clinical trial, FMT and reintroduction of anti-PD1 therapy are being investigated for the treatment of metastatic colorectal cancer in anti-PD1 non-responders.

FMT FOR CANCER PATIENTS

Merve Hasanov, MD, Medical Oncology Fellow, and Florencia McAllister, MD, Associate Professor in the Department of Clinical Cancer Prevention and Gastrointestinal Medical Oncology, are examining the safety and efficacy of FMT in treating patients with pancreatic cancer.

Pancreatic cancer is a third leading cause of cancer death with limited treatment options and dismal outcomes.

"More effective treatment strategies are desperately needed," Hasanov said. "We studied the tumor microbiome of long- and short-term pancreatic cancer survivors and found differences in their tumor microbiome composition."

Preclinical studies with FMTs from healthy controls and long-term survivors in mice showed an increase in gut and tumor microbiome diversity and tumor-immune microenvironment activation compared to FMTs from short-term survivors.

"To translate these findings to clinical setting with the ultimate goal of providing new treatment strategies to pancreatic cancer patients, we opened our clinical trial, NCT04975217," Hasanov explained.

"With this trial, we will be testing the safety and feasibility of FMT from healthy controls to resectable pancreatic cancer patients and monitor the changes in the gut, tumor and periodontal microbiome and switch in the tumor microenvironment. The successful implications of this trial will lead to follow-up combination treatment strategies with immunotherapies, chemotherapies, and FMTs from long-term survivors, opening up a new chapter in the management of pancreatic cancer patients."

Yinghong Wang, MD, PhD, Associate Professor in the Department of Gastroenterology Hepatology and Nutrition, Division of Internal Medicine, has been using FMT to treat patients that develop

CONTINUED ON NEXT PAGE

MICROBIOME

CONTINUED FROM PREVIOUS PAGE

colitis, one of the most common immune-mediated toxicities resulting from ICI treatment, with outstanding results.

Wang has provided evidence that modulation of the gut microbiome may abrogate colitis with early insights into potential mechanisms.[11]

Justin Gregg, MD, an Assistant Professor in the Department of Urology, has an ongoing clinical trial that is investigating the role that a feeding program may have on high-risk factors known to influence prostate cancer.

For low-risk prostate cancer, active surveillance is a safe management strategy, yet 35% of men ultimately undergo definitive treatment within four years, mostly due to disease progression. Obesity and increased lipid levels correlated with prostate cancer risk, and in a recent prospective study, men with prostate cancer who had higher quality diets had lower risk of disease progression.[12,13]

DIETARY SOLUTIONS

The Mediterranean diet specifically may be beneficial due to its anti-inflammatory, antilipidemic and chemopreventative properties, as well as its ability to decrease proinflammatory gut microbial taxa. Identifying noninvasive means to lower risk of disease progression in prostate cancer could ultimately spare men the quality-of-life issues associated with radical prostate treatment.

At MDACC, investigators are investigating whether personalized nutrition, an often-ignored component of personalized care, can be employed to improve outcomes in cancer care.

Gregg's trial is investigating the use of a very strict Mediterranean diet-based intervention in men with prostate cancer scheduled to undergo radical prostatectomy. The study involves the provision of all calorie-containing meals and snacks for four weeks prior to surgery.

"The primary outcome is to assess feasibility of enrollment onto and initiation of the dietary study," Gregg said. "We are also investigating changes in circulating metabolism-related biomarkers and the gut microbiome that may be relevant in men diagnosed with localized prostate cancer."

Similarly, given the known influence of diet on the microbiome and the association of high-fiber diet intake with treatment response to ICIs, Jennifer McQuade, MD, MS, MA, Assistant Professor in the Department of Melanoma Medical Oncology, is currently running a clinical trial investigating the role of a high-fiber dietary intervention on patients with metastatic melanoma treated with immunotherapy.

"Recently published studies and our own research show us that microbiome modulation has great potential in improving cancer outcomes," McQuade said.

"To this end, we studied the effects of diet in patients with a history of melanoma by providing participants with all food during a period of six weeks (NCT03950635) to carefully measure the effects of a controlled diet in gut microbiome composition and function."

"We initiated a phase II trial (NCT04645680) where we are investigating the effects of two different diets in patient with stage III-IV melanoma receiving standard of care immunotherapy and we are hopeful these results will provide us with a roadmap to develop dietary solutions to improve the outcome of our patients."

CONCLUSION

There is wide and genuine interest in exploring the impact of the human microbiome on the onset, progression, and therapeutic responses across numerous cancer types with hopes of unraveling underlying mechanisms that could lead to novel strategies to improve cancer care and prevention.

As a group, we look forward to generating information with valuable translational potential that can be brought to the clinic and offered to our patients.

▲ **Samuel H. Cass**, MD, is a T32 Research Fellow in the Department of Surgical Oncology and **Nadim J. Ajami**, PhD, is Executive Director of Scientific Research for the Program for Innovative Microbiome and Translational Research (PRIME-TR) at The University of Texas, MD Anderson Cancer Center.

REFERENCES

1. Boursi, B., et al., Recurrent antibiotic exposure may promote cancer formation--Another step in understanding the role of the human microbiota? Eur J Cancer, 2015. 51(17): p. 2655-64.

2. Iida, N., et al., Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science, 2013. 342(6161): p. 967-70.

3. Yu, T., et al., Fusobacterium nucleatum Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy. Cell, 2017. 170(3): p. 548-563.e16.

4. Kim, Y.S., J. Kim, and S.J. Park, High-throughput 16S rRNA gene sequencing reveals alterations of mouse intestinal microbiota after radiotherapy. Anaerobe, 2015. 33: p. 1-7.

5. Crawford, P.A. and J.I. Gordon, Microbial regulation of intestinal radiosensitivity. Proc Natl Acad Sci U S A, 2005. 102(37): p. 13254-9.

6. Baruch, E.N., et al., Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science, 2021. 371(6529): p. 602-609.

7. Davar, D., et al., Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science, 2021. 371(6529): p. 595-602.

8. Spencer, C.N., et al., Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. Science, 2021. 374(6575): p. 1632-1640.

9. Yu, J., et al., Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. Gut, 2017. 66(1): p. 70-78.

10. Wong, S.H., et al., Quantitation of faecal Fusobacterium improves faecal immunochemical test in detecting advanced colorectal neoplasia. Gut, 2017. 66(8): p. 1441-1448.

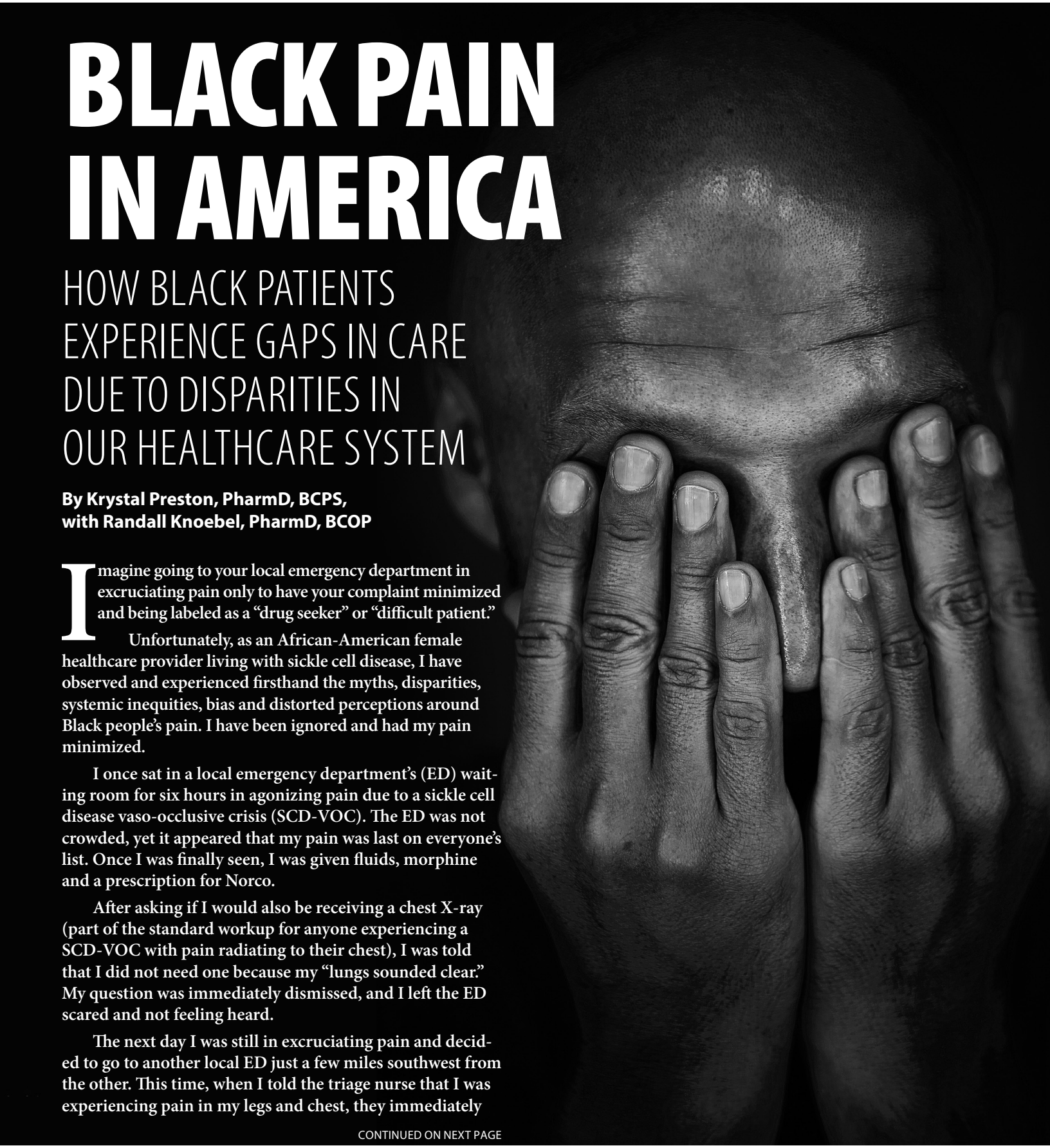
11. Wang, Y., et al., Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. Nat Med, 2018. 24(12): p. 1804-1808.

12. Gregg, J.R., et al., Adherence to the Mediterranean diet and grade group progression in localized prostate cancer: An active surveillance cohort. Cancer, 2021. 127(5): p. 720-728.

13. Gregg, J.R., et al., Diet quality and Gleason grade progression among localised prostate cancer patients on active surveillance. Br J Cancer, 2019. 120(4): p. 466-471.

BLACK PAIN IN AMERICA

HOW BLACK PATIENTS EXPERIENCE GAPS IN CARE DUE TO DISPARITIES IN OUR HEALTHCARE SYSTEM



By Krystal Preston, PharmD, BCPS, with Randall Knoebel, PharmD, BCOP

Imagine going to your local emergency department in excruciating pain only to have your complaint minimized and being labeled as a "drug seeker" or "difficult patient."

Unfortunately, as an African-American female healthcare provider living with sickle cell disease, I have observed and experienced firsthand the myths, disparities, systemic inequities, bias and distorted perceptions around Black people's pain. I have been ignored and had my pain minimized.

I once sat in a local emergency department's (ED) waiting room for six hours in agonizing pain due to a sickle cell disease vaso-occlusive crisis (SCD-VOC). The ED was not crowded, yet it appeared that my pain was last on everyone's list. Once I was finally seen, I was given fluids, morphine and a prescription for Norco.

After asking if I would also be receiving a chest X-ray (part of the standard workup for anyone experiencing a SCD-VOC with pain radiating to their chest), I was told that I did not need one because my "lungs sounded clear." My question was immediately dismissed, and I left the ED scared and not feeling heard.

The next day I was still in excruciating pain and decided to go to another local ED just a few miles southwest from the other. This time, when I told the triage nurse that I was experiencing pain in my legs and chest, they immediately

CONTINUED ON NEXT PAGE

BLACK PAIN

CONTINUED FROM PREVIOUS PAGE

addressed my concerns and sent me for an X-ray. Sure enough, as I suspected, the doctor told me that I would be receiving antibiotics to treat pneumonia seen on the X-ray. While I am glad that I was ultimately treated well and with proper care, this outcome might not have happened had I not advocated for myself.

Additionally, another factor that played a role in my positive outcome was access. Had I been inadequately insured, I would not have had the option to go to another facility for care.

Sadly, this story is not unique and is the plight of many Black patients living with chronic pain in our country. Many Black patients have experienced gaps in their care due to disparities in our healthcare system. Ideally, treatment decisions are informed by evidence and are unbiased by characteristics such as gender, race, socioeconomic status, education level and other social determinates of health.

However, observation after observation demonstrates that this is simply not the case. Some examples include:

▲ White medical trainees that endorsed false beliefs or stereotypes (~50%) recorded lower pain ratings and ultimately suboptimal treatment for Black subjects versus White subjects.[1]

▲ White medical trainees that were implicitly primed with either a Black or White subject's face were more likely to respond more to the White subject's needs when compared to the Black subject.[2]

▲ Providers were more dominant in conversations with Black HIV patients compared to White HIV patients.[3]

▲ Compared with White patients, Black patients had 2.54 times the odds of having at least one negative descriptor (e.g., challenging, aggressive, refuse/resist, non-adherent, non-compliant) in the history and physical notes.[4]

▲ A total of 31% of African American cancer pain patients received analgesics at insufficient strength to manage their pain compared to White cancer patients. Additionally, 74% of physicians underestimated African American's cancer pain severity.[5]

Krystal Preston

Randall Knoebel

▲ A total of 22% of physicians provide care to roughly 80% of African Americans in the United States, and these physicians report limited access to health care resources, such as specialists and diagnostic imaging.[6]

▲ Clinics serving at least 30% racial minority patients have fewer supplies, fewer examination rooms per physician and fewer referrals to specialists, and are more likely to be covered by Medicaid and have more medically and psychologically complex patients. Physicians at these clinics report less control over their work environments, lower job satisfaction levels and higher rates of burnout.[7]

▲ Black children with appendicitis were less likely to receive pain medication for moderate pain or opioids for severe pain compared to White children.[8]

▲ In the primary care setting, patients from low socioeconomic areas were more likely to receive opioid-only therapy and not receive referrals to physical therapy for back pain when compared to patients from high socioeconomic areas.[9]

▲ In the emergency department setting, Black patients were less likely to receive opioid analgesics for moderate-to-severe pain.[10]

We believe that being a true patient advocate means listening to our patients and not minimizing their experiences, especially when it comes to pain. Empathy can be taught.

AN ETHICAL DILEMMA

These disparities represent an ethical dilemma, and the problems are both broad and complex. As healthcare providers, we must do the hard work and recognize and address all barriers that prevent us from achieving optimal and equitable pain care. The six steps below were proposed in a recent article by Knoebel et al.:[11]

1. Acknowledge the pervasive presence and pernicious effects of implicit bias.

2. Avoid stereotypes. Deploy targeted strategies such as stereotype replacement using a consciously adjusted response or counter-stereotypic imaging in which the patient is framed as the stereotypic opposite.

3. Adopt an "individuation" approach focusing on each patient's unique personal history and context for their care.

4. Empathize with each patient — incorporate cognitive empathy of "putting yourself in your patient's shoes" and affective empathy of sharing in the experience of their illness and pain.

5. Establish meaningful partnerships in which the patient/provider exchange is a collaboration between equals and forms the basis of shared decision-making.

6. Engage in an ongoing critique of our behaviors, attitudes and biases through patient feedback and self-reflection.

These steps help us, as healthcare providers, to recognize that these disparities do exist and to address them properly.

However, truly addressing them means advocating for all patients, which will ultimately minimize these gaps in care. We believe that being a true patient advocate means listening to our patients

CONTINUED ON NEXT PAGE

BLACK PAIN

CONTINUED FROM PREVIOUS PAGE

and not minimizing their experiences, especially when it comes to pain. Empathy can be taught.

▲ **Krystal M. Preston**, PharmD, BCPS, is an Oncology Clinical Pharmacist Specialist at the Amita Health St. Joseph Hospital Presence Center for Advanced Care Cancer Center as well as a Clinical Pharmacist at the University of Chicago Comer Children's Hospital in Chicago. **Randall W. Knoebel**, PharmD, BCOP, is Pharmacy Director of Health Analytics and Drug Policy, a Research Assistant Professor in the Department of Medicine, PGY1 Pharmacy Residency Program Director, and Pharmacy Director of Pain Stewardship at UChicago Medicine in Chicago.

REFERENCES

1. Hoffman KM, Trawalter S, Axt JR, Oliver MN. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. Proc Natl Acad Sci. 2016;113(16):4296-4301. doi:10.1073/pnas.1516047113.

2. Mathur VA, Richeson JA, Paice JA, Muzyka M, Chiao JY. Racial bias in pain perception and response: Experimental examination of automatic and deliberate processes. J Pain. 2014;15(5):476-484. doi:10.1016/j.jpain.2014.01.488.

3. Beach MC, Saha S, Korthuis PT, et al. Patient-provider communication differs for black compared to white HIV-infected patients. AIDS Behav. 2011;15(4):805-811. doi:10.1007/s10461-009-9664-5.

4. Sun M, Oliwa T, Peek ME, Tung EL. Negative Patient Descriptors: Documenting Racial Bias In The Electronic Health Record. https://doi.org/101377/hlthaff202101423. Published online January 19, 2022. doi:10.1377/HLTHAFF.2021.01423.

5. Anderson KO, Mendoza TR, Valero V, et al. Minority cancer patients and their providers: pain management attitudes and practice. Cancer. 2000;88(8):1929-1938. Accessed August 8, 2018. http://www.ncbi.nlm.nih.gov/pubmed/10760771.

6. Bach PB, Pham HH, Schrag D, Tate RC, Hargraves JL. Primary Care Physicians Who Treat Blacks and Whites. N Engl J Med. 2004;351(6):575-584. doi:10.1056/NEJMsa040609.

7. Varkey AB. Separate and Unequal. Arch Intern Med. 2009;169(3):243. doi:10.1001/archinternmed.2008.559.

8. Goyal MK, Kuppermann N, Cleary SD, Teach SJ, Chamberlain JM. Racial Disparities in Pain Management of Children With Appendicitis in Emergency Departments. JAMA Pediatr. 2015;169(11):996-1002. doi:10.1001/jamapediatrics.2015.1915.

9. Gebauer S, Salas J, Scherrer JF. Neighborhood Socioeconomic Status and Receipt of Opioid Medication for New Back Pain Diagnosis. J Am Board Fam Med. 2017;30(6):775-783. doi:10.3122/jabfm.2017.06.170061.

10. Joynt M, Train MK, Robbins BW, Halterman JS, Caiola E, Fortuna RJ. The impact of neighborhood socioeconomic status and race on the prescribing of opioids in emergency departments throughout the united states. J Gen Intern Med. 2013;28(12):1604-1610. doi:10.1007/s11606-013-2516-z.

11. Knoebel RW, Starck J V., Miller P. Treatment Disparities Among the Black Population and Their Influence on the Equitable Management of Chronic Pain. Heal Equity. 2021;5(1):596. doi:10.1089/HEQ.2020.0062.

FDA ANNOUNCES 8 ORAL ONCOLYTIC APPROVALS IN 4TH QUARTER 2021 AND 1ST QUARTER 2022

By Elizabeth Engel, Carter Friedt, Kirollos Hanna, PharmD, BCPS, BCOP, & Derek Gyori, PharmD, BCOP

Eight oral oncolytic approvals were announced by the U.S. Food & Drug Administration (FDA) during Q4 2021 and Q1 2022 (Aug. 31, 2021 through March 11, 2022).

In the following charts, **+** stands for new formulations; ***** stands for new indications. Further information can be found on the FDA website and/or in the medication-specific prescribing information.

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
BRUKINSA® (zanubrutinib)[1-3]	9/1/2021*	• Waldenström macroglobulinemia • 160mg orally twice daily or 320mg orally once daily	**ASPEN Study** **Cohort 1:** • N=201 • Patients with $MYD88^{L265P}$ • Assigned 1:1 to receive ibrutinib 420mg once daily or zanubrutinib 160mg twice daily • No patients achieved a complete response (CR) • Very Good Partial Response: 29 (28%) zanubrutinib vs. 19 (19%) ibrutinib patients (P= 0.09) • Median DoR and PFS was not reached **Cohort 2:** • N=28 • Patients with MYD88 ($MYD88^{WT}$) disease or with undetermined MYD88 mutation received zanubrutinib 160mg twice daily • Median follow-up: 17.9 months • Seven $MYD88^{WT}$ patients (27%) had a VGPR and 50% a major response (partial response or better) • No CRs reported • At 18 months: Estimated PFS and OS rates were 68% and 88%, respectively, while the median DOR had not been reached	• ≥20%: neutrophil count decreased, upper respiratory tract infection, platelet count decreased, rash, hemorrhage, musculoskeletal pain, hemoglobin decreased, bruising, diarrhea, pneumonia and cough	• Administer with or without food • Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia and other infections according to standard of care in patients at increased risk for infections • Available in 80mg tablets
BRUKINSA® (zanubrutinib)[3-6]	9/14/2021*	• Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen • 160mg twice daily or 320mg daily	**MAGNOLIA Study** • (N=66, zanubrutinib 160mg twice daily) • Overall Response Rate (ORR): 68.2% (95%CI, 55.6-79.1%) • Complete response (CR): 25.8% • Median DoR and PFS was not reached **BGB-3111-AU-003 Study** • (N=14 zanubrutinib 160mg twice daily, N=18 zanubrutinib 320mg daily) • ORR: 84.4%(95% CI, 67.2-94.7% • CR: 25% • Median DoR: 18.5 months [95%CI, 12.6-Not Estimable(NE)] • PFS: 21.1 months (95% CI, 13.2-NE)	• ≥30%: decreased neutrophil count, upper respiratory tract infection, decreased platelet count, hemorrhage, decreased lymphocyte count, rash and musculoskeletal pain	• Administer with or without food • Consider prophylaxis for herpes simplex virus, pneumocystis jirovecii pneumonia and other infections according to standard of care in patients at increased risk for infections • Available in 80mg tablets

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
EXKIVITY® (mobocertinib)[7-9]	9/15/2021+	• Advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy • 160mg daily	**NCT02716116 Trial** • (N=114) • ORR: 28% (95%CI, 20-37) • Median DOR: 17.5 months (95%CI, 7.4-20.3)	• ≥20%: diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin and musculoskeletal pain • **Boxed warnings: boxed warning for QTc prolongation and Torsade de Pointes, interstitial lung disease/pneumonitis, cardiac toxicity**	• Administer at approximately the same time each day, with or without food • Available in 40mg tablets
CABOMETYX® (cabozantinib)[10-12]	9/17/2021*	• Advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are ineligible or refractory to radioactive iodine • 60mg daily	**COSMIC-311 Trial** • (N=187) • Randomized 2:1 cabozantinib vs placebo • Objective Response rate: 9% for cabozantinib(95%CI, 4.5-15.2) and 0% for placebo (95% CI 0,5.8) • PFS not reached for cabozantinib (96%CI, 5.7-NE) and 1.9 months for placebo (1.8-3.6)	• ≥20%: diarrhea, palmar-plantar erythrodysesthesia (PPE), fatigue, hypertension, stomatitis, hypocalcemia	• Do not administer with food; administer on an empty stomach (at least one hour before or two hours after eating) • Antiemetics are recommended to prevent nausea/vomiting • Available in 20mg, 40mg and 60mg tablets
JAKAFI® (ruxolitinib)[13-15]	9/22/2021*	• Chronic graft-vs-host disease (cGVHD) • 10mg orally twice daily	**REACH3 Trial** • (N=329) • 1:1 randomized Ruxolitinib vs Best Available Therapy (BAT) • Overall response rate (ORR) Ruxolitinib 49.7% vs BAT 25.6%; OR, 2.99; P < 0.001	• ≥20%: infections and viral infections • >35% hematologic adverse events: anemia and thrombocytopenia	• Administer with or without food • Substrate of CYP3A4, avoid grapefruit juice • Available in 5mg, 10mg, 15mg, 20mg and 25mg tablets

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
VERZENIO® (abemaciclib)[16-18]	10/12/2021*	• Adjuvant treatment of adult patients with hormone receptor positive, human epidermal growth factor receptor 2 (HER-2)-negative, node positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% • 150mg orally taken twice daily in combination with tamoxifen or an aromatase inhibitor	**monarchE Trial** • (N=2003) • 1:1 randomized two years abemaciclib + physician's choice of standard therapy or standard therapy alone • Invasive disease-free survival (IDFS) Abemaciclib + standard therapy: Abemaciclib plus ET demonstrated superior IDFS vs ET alone (P = .01; hazard ratio, 0.75; 95% CI, 0.60 to 0.93), with two-year IDFS rates of 92.2% vs 88.7%, respectively	• >20%: diarrhea, infections, neutropenia, fatigue, leukopenia, nausea, anemia and headache	• Diarrhea typically occurs five to 10 days after initiation, encourage loperamide • Available in 50mg, 100mg, 150mg and 200mg
SCEMBLIX® (asciminib)[19-21]	10/29/2021+	• Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) • 40mg orally daily twice daily or 200mg orally twice daily with a T315I mutation	**ASCEMBL Trial** • (N=233) 2:1 Randomized Asciminib vs bosutinib • Major Molecular Response (MMR) Asciminib 25.5% (95% CI, 2.19-22.30 vs Bosutinib 13.2% **CABL001X2101 Study** • (N=45) • 45 patients with the T315I mutation received asciminib 200mg twice daily • Major molecular response (MMR) was achieved by 24 weeks in 42% (19/45, 95% CI: 28% to 58%) of the patients • MMR was achieved by 96 weeks in 49% (22/45, 95% CI: 34% to 64%) of the patients • Median duration of treatment was 108 weeks	• ≥20%: upper respiratory tract infections, musculoskeletal pain, fatigue, nausea, rash and diarrhea • Lab abnormalities: decreased platelet counts, increased triglycerides, decreased neutrophil counts and hemoglobin, and increased creatine kinase, alanine aminotransferase, lipase and amylase	• Administer on an empty stomach • Avoid food for at least two hours before and one hour after asciminib administration. • Administer at approximately the same time each day • Available in 20mg and 40mg tablets
LYNPARZA® (olaparib)[22-24]	03/11/2022	• Adjuvant treatment of deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative high-risk early breast cancer • 300mg orally twice daily for up to a year	**OlympiA Trial** • (N=1836) • 1:1 Randomized olaparib vs placebo • IDFS: 85.9% for olaparib and 77.1% for placebo (95% CI 0.46-0.74)	• ≥10%: nausea, fatigue (including asthenia), anemia, vomiting, headache, diarrhea, leukopenia, neutropenia, decreased appetite, dysgeusia, dizziness and stomatitis	• Administer with or without food • Available in 50mg capsules and 100mg 150mg tablets

▲ **Elizabeth Engel** is a 2023 PharmD Candidate at the University of Toledo College of Pharmacy and Pharmaceutical Sciences. **Carter Friedt** is a 2023 PharmD Candidate 2023 at the University of Toledo College of Pharmacy and Pharmaceutical Sciences. **Kirollos Hanna**, PharmD, BCPS, BCOP, is the Oncology Pharmacy Manager at M Fairview Health and an Assistant Professor of Pharmacy at the Mayo Clinic College of Medicine. **Derek Gyori**, PharmD, BCOP, is a Clinical Assistant Lecturer at the University of Toledo College of Pharmacy and Pharmaceutical Sciences and a Clinical Pharmacy Specialist at the Eleanor N. Dana Cancer Center at the University of Toledo Medical Center.

REFERENCES

1. FDA. Hematology/Oncology (Cancer) Approvals & Safety Notifications; 2021. www.fda.gov. Available from https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-zanubrutinib-waldenstroms-macroglobulinemia.

2. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström's macroglobulinemia: the ASPEN study. Blood. 2020:136(18)2038-50.

3. Brukinsa (zanubrutinib) [prescribing information]. San Mateo, CA: BeiGene USA Inc; November 2019.

4. FDA. Hematology/Oncology (Cancer) Approvals & Safety Notifications; 2021. www.fda.gov. Available from https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zanubrutinib-marginal-zone-lymphoma.

5. Opat S, Tedeschi A, Linton K, et al. The MAGNOLIA Trial: Zanubrutinib, a next-generation bruton tyrosine kinase inhibitor, demonstrates safety and efficacy in relapsed/refractory marginal zone lymphoma. Clin Cancer Res. 2021 Dec 1;27(23):6323-6332.

6. Tam CS, Opat S, Simpson D, eta al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. Blood Adv. 2021 Jun 22;5(12):2577-2585.

7. FDA. Hematology/Oncology (Cancer) Approvals & Safety Notifications; 2021. www.fda.gov. Available from https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mobocertinib-metastatic-non-small-cell-lung-cancer-egfr-exon-20.

8. Exkivity (mobocertinib) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals America Inc: September 2021.

9. Zhou C, Ramalingam SS, Kim TM, et al. Treatment outcomes and safety of Mobocertinib in platinum-pretreated patients with EGFR exon 20 insertion-positive metastatic non-small cell lung cancer: a phase 1/2 open-label nonrandomized clinical trial. JAMA Oncol. 2021 Dec 1;7(12):e214761.

10. FDA. Hematology/Oncology (Cancer) Approvals & Safety Notifications; 2021. www.fda.gov. Available from https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-cabozantinib-differentiated-thyroid-cancer.

11. Cabometyx (cabozantinib) tablet [prescribing information]. Alameda, CA: Exelixis Inc; September 2021.

12. Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2021 Aug;22(8):1126-1138.

13. FDA. Hematology/Oncology (Cancer) Approvals & Safety Notifications; 2021. www.fda.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ruxolitinib-chronic-graft-versus-host-disease.

14. Jakafi (ruxolitinib) [prescribing information]. Wilmington, DE: Incyte Corporation; September 2021.

15. Zeiser R, Polverelli N, Ram R, et al; REACH3 Investigators. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. N Engl J Med. 2021;385(3):228-238.

16. FDA. Hematology/Oncology (Cancer) Approvals & Safety Notifications; 2021. www.fda.gov. Available from https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abemaciclib-endocrine-therapy-early-breast-cancer.

17. Verzenio (abemaciclib) [prescribing information]. Indianapolis, IN: Lilly USA, LLC; October 2021.

18. Johnston SRD, Harbeck N, Hegg R, et al; monarchE Committee Members and Investigators. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol. 2020;38(34):3987-3998.

19. FDA. Hematology/Oncology (Cancer) Approvals & Safety Notifications; 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-asciminib-philadelphia-chromosome-positive-chronic-myeloid-leukemia.

20. Rea D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of Asciminib, a STAMP inhbitor vs Bosutinim in CML after ≥2 prior TKIs. Blood 2021, Aug 18.

21. Scemblix (asciminib) tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; October 2021.

22. FDA. Hematology/Oncology (Cancer) Approvals & Safety Notifications; 2021. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-adjuvant-treatment-high-risk-early-breast-cancer.

23. Tutt ANJ, Garber B, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2- mutated breast cancer. N Engl J Med. 2021 Jun 24;384(25):2394-2405.

24. Lynparza (olaparib) tablets [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; June 2021.

NCODA & ONCOLOGY NURSING SOCIETY

SHARING INTERPROFESSIONAL EXPERTISE THROUGH ORGANIZATIONAL COLLABORATION

By Mary Anderson, BSN, RN, OCN

From its inception, the guiding values of NCODA have been to remain patient-centered and always collaborative. Since 1975, the Oncology Nursing Society (ONS) has a rich history of advancing excellence in oncology nursing and quality cancer care.

As the missions of both organizations promote the advancement of quality care for cancer patients, NCODA and ONS have formed a relationship that exhibits interprofessional collaboration and development of resources that ensure patients receive quality care. Over the years, that relationship has continued to strengthen.

Mary Anderson

As a multidisciplinary organization, NCODA recognizes the value of combining efforts with all members of the medically integrated oncology team to advocate for quality patient care.

"The medically integrated oncology team has proven to be vital in delivering the highest quality of patient care," said Michael Reff, RPh, MBA, Founder and Executive Director of NCODA.

ONS also exhorts the value of working together.

"Collaboration is often the key to success, especially in healthcare," said Brenda Nevidjon, MSN, RN, FAAN, Chief Executive Officer of ONS. "Many voices speaking as one, particularly on a single effort, can make a difference professionally, personally and politically."

With increasing demands brought on by the COVID-19 pandemic and resulting staffing shortages, nurses are challenged more than ever to provide superior care in a demanding, fast-paced environment.

"Nurses are at a crossroads," noted Kris LeFebvre, MSN, RN, NPD-BC, AOCN, Oncology Clinical Specialist for ONS. "It is imperative that organizations who support oncology care providers develop resources that help nurses and the entire healthcare team succeed in their daily practice. Michael Reff and NCODA recognized the need for a resource to address the education gap for patients taking oral oncolytics and sought to fill this gap with the Oral Chemotherapy Education (OCE) initiative."

While OCE was an NCODA-conceived educational resource for patients undergoing treatment with different oral anticancer medications, its growth and adoption were driven by the collaboration with its partners in the Association of Community Cancer Centers (ACCC), the Hematology/Oncology Pharmacy Association (HOPA) and ONS.

"Each organization reaches unique stakeholders within the oncology care continuum, and the collective efforts of all organizations have helped grow OCE into a resource that is accessed more than 60,000 times monthly by oncology care professionals around the world," Reff said.

The OCE sheets are especially valuable to nurses in the practice setting, Nevidjon said.

"ONS staff and members bring their nursing expertise to this collaboration, ensuring that the nursing standards are respected and incorporated," Nevidjon said. "Rather than creating redundant resources, we are realizing the benefits of shared interprofessional expertise."

NCODA has been committed to providing educational resources to nurses for several years. It created the Nursing Committee so that its nursing membership had a place to come together and discuss current best practices.

The Nursing Committee's mission is to inspire nurses caring for individuals with cancer, share ideas, collaborate interprofessionally and promote quality standards and best practices.

For more than three years, the Nursing Committee has developed resources to assist oncology nurses caring for individuals taking oral anticancer medications, including an oral oncology welcome letter, medication fill tracking forms and a plan of care treatment guide for patients.

Many committee members also are members of ONS, bridging the relationship between the two organizations once again. ONS, in turn, has embraced the resources developed by the NCODA Nursing Committee. For example, the ONS Oral Anticancer Medication Toolkit references the committee's recent Treatment Plan Initiative as a valued tool in caring for patients.

▲ **Mary K. Anderson**, BSN, RN, OCN, is an Oral Oncolytic Nurse Navigator at Norton Cancer Institute in Louisville, Kentucky. She is co-chair of NCODA's Nursing Committee, a member of ONS and Past President of the Greater Louisville ONS Chapter.

"Collaboration is often the key to success, especially in healthcare. Many voices speaking as one, particularly on a single effort, can make a difference professionally, personally and politically."

Brenda Nevidjon, MSN, RN, FAAN, Chief Executive Officer | ONS

1L aRCC

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

EFFICACY IN BALANCE[1]

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

*Superior OS vs sunitinib in patients with previously untreated aRCC. Primary analysis OS results: 40% reduction in risk of death with CABOMETYX + OPDIVO vs sunitinib (HR=0.60; 98.89% CI: 0.40-0.89; *P*=0.001); median OS was not reached in either arm. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and the clinical significance is unknown.[1,2]

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

INDICATIONS

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

CABOMETYX is indicated for the treatment of patients with advanced RCC.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

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

Superior PFS and ORR results in the ITT population[1]

Median follow-up time of 18.1 months; range: 10.6-30.6 months[2]

MEDIAN PFS WAS DOUBLED[1]*

16.6 months CABOMETYX + OPDIVO (95% CI: 12.5-24.9; n=323)

vs

HR=0.51 (95% CI: 0.41-0.64) *P*<0.0001

8.3 months sunitinib (95% CI: 7.0-9.7; n=328)

ORR WAS DOUBLED[1]*

55.7% CABOMETYX + OPDIVO (95% CI: 50.1-61.2; n=323)

vs

P<0.0001

27.1% sunitinib (95% CI: 22.4-32.3; n=328)

CR

8% (n=26/323) CABOMETYX + OPDIVO vs **4.6%** (n=15/328) sunitinib

PR

48% (n=154/323) CABOMETYX + OPDIVO vs **23%** (n=74/328) sunitinib

*PFS and ORR were assessed by BICR.[1]

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

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

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

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

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

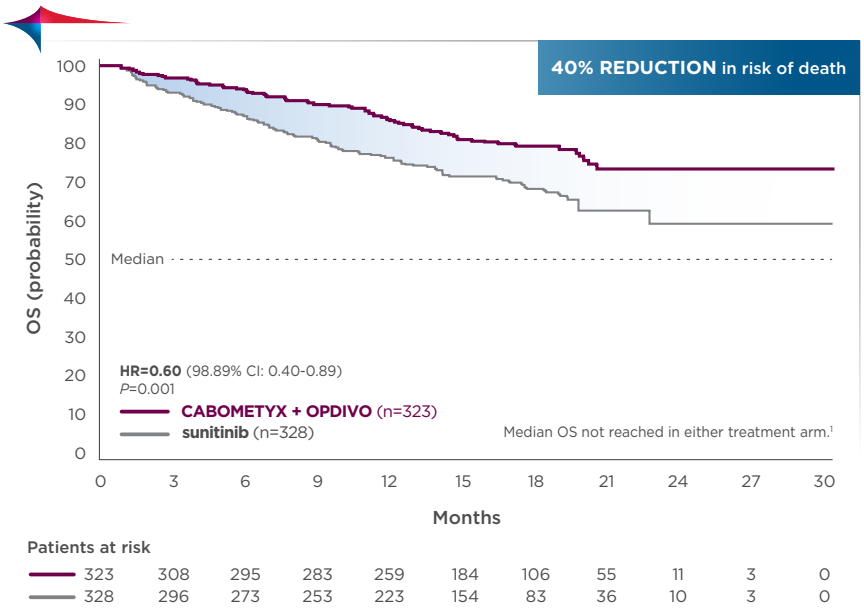
Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

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

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

Early and sustained separation of OS curves[1]



CheckMate-9ER study design[1,2,5]

A randomized (1:1), open-label, Phase 3 trial vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO 240 mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) PO once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. PFS and ORR were assessed by BICR. Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and the clinical significance is unknown. Other exploratory endpoints included biomarkers, PK, immunogenicity, and PFS-2.

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

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

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

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

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

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

ADVERSE REACTIONS

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

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

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

DRUG INTERACTIONS

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

BICR=blinded independent central review; CR=complete response; ITT=intent to treat; IV=intravenous; PFS-2=progression-free survival after subsequent therapy; PK=pharmacokinetics; PO=by mouth; PR=partial response.

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis Inc; 2021. **2.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384(9):829-841. **3.** Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial. Presented at The European Society for Medical Oncology (ESMO) Virtual Congress 2020; September 19-21, 2020. Presentation 6960. **4.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [supplementary appendix]. *N Engl J Med*. 2021;384(9):829-841. **5.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [protocol]. *N Engl J Med*. 2021;384(9):829-841.

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

DISCOVER MORE AT CABOMETYXhcp.com

CABOMETYX® (cabozantinib) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

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

1 INDICATIONS AND USAGE

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

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

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

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Renal Cell Carcinoma

METEOR

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

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

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

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

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

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

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

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

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

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

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

CABOSUN

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

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

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

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

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

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

CHECKMATE-9ER

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

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

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

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

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

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

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

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

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

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

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

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

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

[h] Includes primary hypothyroidism.

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

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis

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

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

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

Hepatocellular Carcinoma

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

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

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

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

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

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

[2] NCI CTCAE Version 4.0

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

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

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

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

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

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

Differentiated Thyroid Cancer

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

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

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

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

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

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

[2] NCI CTCAE Version 5.0

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

[4] Includes the following terms: fatigue, asthenia

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

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

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

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

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

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

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CABOMETYX

Strong CYP3A4 Inhibitors

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

Strong CYP3A Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

Infertility

Females and Males

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

8.4 Pediatric Use

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

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

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

Juvenile Animal Toxicity Data

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

8.5 Geriatric Use

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

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Embryo-fetal toxicity:

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

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

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

Important administration information

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

This brief summary is based on the CABOMETYX Prescribing Information

Revision 10/2021

Distributed by Exelixis, Inc. Alameda, CA 94502

EXELIXIS®

Printed in USA 10/2021 CA-1121-4

PATIENTS ON ORAL ONCOLYTICS ARE ENTITLED TO THE SAME NURSING CARE AS THOSE ON IV TREATMENTS ...

SO WHERE ARE THE NURSES?

By Suzanne Hinman, RN, OCN

Oncology nurses are very familiar with the "deer in the headlights" look of a brand-new patient as they walk with fear and trepidation towards the infusion area for their first treatment.

But it doesn't take long before this same patient is sharing hugs, parental advice and photos of pets with their infusion nurse.

Suzanne Hinman

During the intravenous (IV) infusion, there is plenty of time for the patient to develop a relationship of trust and understanding with their nurse. At each visit, the nurse does a physical and emotional assessment, fills education gaps, and offers support to the patient.

Additionally, there is built-in social support that often occurs between patients as they chat with other people going through chemotherapy treatments in the infusion area.

In contrast, a patient on oral chemotherapy may feel isolated at home, unaware that others are undergoing similar treatments and challenges and unsure of whom to ask for help.

Every patient receiving anticancer treatment needs education, support and nursing care regardless of whether their treatment is administered in the infusion center or via pills they are prescribed to take at home.

The oncology community is well aware of the tremendous increase in oral anticancer agents over the past ten years, a trend that will only continue given that approximately 30% of all oncology drugs in the research pipeline are oral in formulation.[1]

This means that a significant percentage of oncology patients are receiving treatment at home, rather than an IV infusion in a hospital or outpatient setting. But has there been a corresponding increase in the percentage of oncology nurses who are taking care of these patients?

A TEAM APPROACH

As Shawn Costanzo, BSN, RN, OCN, noted in her article "Managing Adherence in Oral Chemotherapy Patients: A Team-Based Approach for Outpatient Clinics," managing patients on oral treatments must be a team effort.[2] The basic team triad in oncology treatment is the oncologist, the pharmacist and the nurse — each with a complimentary — but distinct role.

In 2013, the American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards were updated to include oral oncolytics and the need for patient monitoring for adherence and toxicity.[3]

In the intervening years, oncologists have incorporated new oral anticancer drugs into treatment plans and their medical practices.

Medically integrated pharmacies have been created or expanded and now include excellent education, financial assistance, and monitoring programs for oral oncolytics.

Yet while skilled and knowledgeable oncology nurses have been administering IV anticancer therapies for years in the outpatient setting, Oral Oncolytic Nurse Navigators are still not considered essential at many oncology practices.

NURSE-PATIENT RELATIONSHIP IS KEY

Without a close relationship with a nurse, patients may be reluctant to call

CONTINUED ON NEXT PAGE

NURSES

CONTINUED FROM PREVIOUS PAGE

the clinic with questions and concerns. The challenge is how to develop a trusting relationship when patients are not spending significant time in the clinic. Building relationships with patients is more important than ever, and such relationships are fundamental to ensuring management and adherence to treatment regimens.[4]

Ideally, the Oral Oncolytic Nurse Navigator meets with the patient when the physician prescribes a new oral medication. The nurse explains the process of obtaining insurance authorization, co-pay assistance, and the role of the medically integrated pharmacy team.

Then a teaching visit is scheduled. If possible, doing a "pill-in-hand" education session means the nurse can review the "rights" of medication administration with the patient and family members as they verify the information on the bottle together. The patient is going to be administering their own medication, so this is an important first step to making them feel that they are part of the team.

The teaching session includes not just education about safe handling, administration, and side effects, but also a full baseline assessment to determine if a symptom is a new side effect of the medication or a preexisting condition. Most importantly, the teaching visit is the time for the nurse to begin the process of developing a supportive relationship with the patient.

Once the patient starts on the new treatment, having ongoing contact with the nurse through telephone calls or office visits furthers this relationship. Every patient visit is an opportunity to assess and adjust educational needs based on the assessment.

No matter how consistent we are with our handouts and teaching tools, every patient absorbs information differently and each patient has their own interpretation (or misinterpretation) of the volumes of printed material they received along with their new medication.

Creating a good relationship with the patient is as important as helping the patient obtain their oral oncolytic. Ongoing support and education are crucial for oncology patients to remain adherent to their oral anticancer medication. When patients can effectively identify, manage, and report side effects, their ability to continue the medication for a longer duration improves, as does the potential for maximized patient outcomes.[5]

THE ADHERENCE ISSUE

When patients receive IV treatment, we know they are receiving 100% of their treatment because we are administering it. But are patients adhering to their regimen when they are taking their medication at home?

Studies show that overall adherence to any oral medication ranges from 17% to 80%, with an average of about 50%.[6] Adherence is the single most important part of managing patients on oral anticancer medications and is directly correlated with patient outcomes.[7]

Side effects can impact a patient's adherence to their regime. The first step in managing side effects is having patients call to report them, and they need to know who to call. Patients are more likely to report side effects to someone they know and trust.

Patients are often fearful of "looking bad," so they do not want to report missed doses to their provider or call and bother their doctor with any side effects they may be experiencing.

Pharmacists know the drugs and provide detailed education, but do not typically have face-to-face contact nor do they perform physical assessments of the patients.

Oncology nurses, on the other hand, are in a unique position to ensure that patients are adhering to their regime and receiving optimal treatment. The oncology nurse who sees the patient on a regular basis can recognize changes in their physical or emotional status, can get to know their family and caregivers and can better advocate and care for them.

WHAT'S IN A NAME?

I have been working at an ambulatory oncology clinic in Northwestern Connecticut since 2000, initially as an infusion nurse then as a Clinical Research Coordinator.

In 2012, our small, private practice was acquired by the large healthcare system, Yale New Haven Health. I transitioned into a new position of Practice Nurse at a time when oral oncolytics were receiving FDA approval at an increasingly rapid rate. Since then, while my primary focus is patients on oral treatments, my daily activities do not necessarily reflect it.

The role of the infusion nurse is clear; they educate, treat, and take triage calls from patients on IV treatments. However, there are myriad tasks in any oncology/hematology clinic beyond administering cancer treatments.

For example, there are supportive care treatments such as darbepoetin, B12 or denosumab injections, port maintenance flushes, and PICC line dressing changes. Paperwork includes FMLA, visiting nurse forms, prior approval appeals and faxes from pharmacies.

In addition, there are triage calls from non-treatment patients and refill requests for prescription medications.

Often these tasks fall to the Practice Nurse as the infusion nurses have a full schedule of IV treatments to administer.

When I introduce myself as a Practice Nurse, some patients think I am a Nurse Practitioner, others think I am still practicing to become a nurse. If my title was Oral Oncolytic Care Coordinator it would clearly identify me as the point person for patients on oral oncolytics.

When patients and caregivers know that there is a nurse specifically for oral treatments, it underlines the importance of their treatment and identifies who will be their contact person for their questions and concerns.

CONTINUED ON NEXT PAGE

NURSES

CONTINUED FROM PREVIOUS PAGE

BEHIND-THE-SCENES WORK

Part of the problem with recognizing the amount of work involved with oral treatments is that this work often takes place behind the scenes. A patient receiving an IV treatment is scheduled with the infusion nurse for the length of their treatment, whereas most of the work with oral treatment patients does not happen during clinic visits.

Marlene Lichatz, BSN, RN, OCN, a Practice Nurse at the Smilow Cancer Hospital Care Center in Waterbury, Connecticut, describes a typical day. Her tasks include tracking patients starting new treatments, coordinating with the pharmacy to obtain prior approval, seeking financial assistance for the frequent, overwhelmingly high copays, coordinating care for patients on concurrent oral/IV treatment regimens, or oral treatment and radiation, coordinating care with nursing homes or visiting nurses, registering a new patient to REMS (Risk Evaluation & Mitigation Strategy), and fielding calls from medically integrated pharmacies looking for prescription refills.

Help NCODA by scanning this QR code to take a brief survey about Oral Oncolytic Nurse Navigators

Then there are the multiple triage calls from patients with issues that may need to be addressed urgently.

"While I'm on hold on the phone with an insurance company, I'm replying to a patient in MyChart, checking that the physicians have signed the treatment plans for oral refills, sending a message to the radiation nurse about a new concurrent treatment, working on FMLA paperwork, noting an urgent call from a patient's daughter about her mom's new symptoms, talking to the infusion nurse about her patient who hasn't received his pills yet, and reviewing the labs for the patient who is waiting for my evaluation," Lichatz explained. "And only one of those patients is actually on my schedule."

WHO WILL ADVOCATE FOR THE NURSES?

Lichatz has taken the initiative to make oral treatment patients her priority and makes sure that every oral treatment patient scheduled for a clinic visit is also scheduled for a visit with her.

"I've been asked why I need to see patients if they have a physician visit, but this contact every time is how I build relationships with them," Lichatz said. "Sometimes they just stop in my room to see me after their office visit with the doctor, and I can ask them if they have their pills for the next cycle, if they have missed any doses, if their insurance has changed, or if they have any new side effects."

"If there is no change to their status, this may only take a few minutes. But then, when they have a new symptom, or if their grant for financial assistance has run out, they know to call me immediately so I can address the problem and avoid a potential delay in their treatment, or possible serious toxicity."

Without a dedicated nurse to ensure patients are adhering to therapy, it is likely, as Costanzo said, that patients will fall through the cracks. They may stop taking their medications, or take them incorrectly, not report side effects, develop toxicities, and experience potential progression that could have been avoided.

While many clinics cannot afford an Oral Oncolytic Nurse Navigator, or don't recognize the value of this position, these events could ultimately prove more costly to the healthcare system.

A recent pilot study demonstrated a reduction in emergency department, urgent care, and hospital visits using an innovative oral antineoplastic nurse navigator role. Proactive engagement of patients and their caregivers, prompt identification and mitigation of adverse events, and tailored follow-up to reinforce learning effectively reduced the number of patients needing emergency services.[8]

It is time for the oncology community to advocate for dedicated Oral Oncolytic Nurse Navigators at every site to ensure that patients who are taking their medications at home have as much nursing support as those receiving IV treatments in the clinic.

▲ **Suzanne Hinman**, RN, OCN, is a Practice Nurse at the Smilow Cancer Hospital Care Center, part of Yale New Haven Health in Torrington, Connecticut. She is also a member of NCODA's Nursing Committee.

REFERENCES

1. Lisi, D., Oral Chemotherapeutic Agents and the Role of Specialty Pharmacies, U.S. Pharmacist, Jan 2022.

2. Costanzo, Shawn, Managing Adherence in Oral Chemotherapy Patients: A Team-Based Approach for Outpatient Clinics, Oncolytics Today, Fall 2021.

3. Neuss, MN., Polovich, M., McNiff,K., Esper, P., Gilmore, T. R., Lefebvre, K. B., Jacobson, J.O. (2013) 2013 updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, including standards for the safe administration and management of oral chemotherapy. Oncology Nursing Forum, 40, 225 – 233.

4. Yagasaki, K., and Komatsu, H., The Need for a Nursing Presence in Oral Chemotherapy, Clinical Journal of Oncology Nursing, Volume 17, Number 5, October 2013.

5. Anderson, M., Reff, M., McMahon, R., Walters, D., The Role of the Oral Oncology Nurse Navigator, ACCC-Cancer.org, September-October 2017.

6. Wimbiscus, B., Patient Adherence, a Challenge of Oral Chemotherapy, Targeted Oncology, January 21, 2019.

7. Winkeljohn, D., Adherence to Oral Cancer Therapies: Nursing Interventions, Clinical Journal of Oncology Nursing, Volume 14, Number 4.

8. Barkett, N., Weiss, G., High, B., Kurtin, S., Implementation of an Oral Antineoplastic Therapy Program: Results From a Pilot Project, Clinical Journal of Oncology Nursing, Volume 26, Number 1, February 2022.

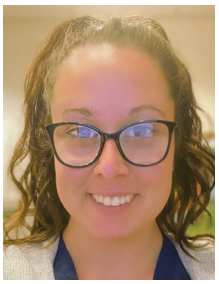
PHARMACY BOTTLENECKS

COVID-RELATED CHALLENGES STILL LINGER IN WAKE OF THE PANDEMIC

By Jennifer Berni, CPhT

When the COVID-19 pandemic hit the United States in 2020, it was impossible to understand the full magnitude of the challenges that our healthcare system would face.

Our hospitals were inundated. Our staffs overworked. Our inventory of medication and critically-needed isolation supplies was drained. And, if that weren't enough, healthcare providers were further challenged to isolate COVID patients while at the same time protecting their own staff from infection.



Jennifer Berni

It came as no surprise, then, when a new problem developed.

SUPPLY SHORTAGES

In an effort to keep the virus from spreading, the federal government ordered nonessential businesses to suspend operation. So, while hospitals and oncology clinics remained open, many of the factories, companies and businesses that served them remained closed.

And now, two years after the pandemic began, medical facilities still face critical shortages of equipment, supplies and drugs.

I started working for Stockton Hematology Oncology Medical Group (SHOMG) in June 2020, during the heart of the pandemic. SHOMG is a physician-owned practice that specializes in oncology/hematology disorders and some autoimmune diseases. Our practice is managed by eight doctors with locations in Stockton, Lodi, Tracy and Manteca, California. We remained open through the entirety of the pandemic.

As a pharmacy technician at SHOMG, my job involves (but is not limited to) mixing intravenous medications, managing drug inventory, managing supplies for both the pharmacy and nursing staff, dispensing some oral chemotherapy medications, and following up with patients regarding their care.

Working in the healthcare field requires vast amounts of medical equipment for both patients and staff. For example, when mixing chemo we use specific gowns, special N95 masks, chemotherapy-tested gloves, shoe covers and head covers. Our nurses use specific tubing to administer these types of medications along with their own forms of protective equipment.

However, with "nonessential" factories and manufacturers shutting down all over the world, SHOMG's supply resources were stretched thin. When nonessential businesses were allowed to reopen, we hoped to replenish our supplies.

Fast-forward to present day (Spring 2022): Instead of seeing replenished supplies, we are seeing more scarcity. The worker shortages and supply chain bottlenecks generated by COVID-19 have continued to hamper both the manufacture and distribution of medical supplies in critical need. While COVID continues to challenge the healthcare system in many ways, it's the resulting supply shortage that has affected us most here at SHOMG.

Throughout the COVID crisis, we've had to come up with creative solutions to unexpected supply challenges. And that process still goes on today as we continue to struggle with drug allocations, supply allocations and manufacturer backlogs.

DRUG ALLOCATIONS

ABRAXANE® is a chemotherapy drug used to treat non-small cell lung cancer, pancreatic cancer, and metastatic breast cancer. SHOMG's first shortage occurred when this drug was put on allocation at our clinic.

CONTINUED ON NEXT PAGE

BOTTLENECKS

CONTINUED FROM PREVIOUS PAGE

"Allocation" is defined as an amount or portion of a resource assigned to a particular recipient. SHOMG orders drugs based on a patient schedule for the upcoming weeks. However, if that amount or dose ordered exceeds the amount the wholesaler has assigned to us, we will not receive the amount needed.

I remember ordering ABRAXANE® in mid-2021. I needed six vials to cover the dose of each patient coming in for treatment. Our drugs are usually received overnight, so when I came in the next day I was surprised to receive only two vials. I had my manager call our wholesaler. We learned that ABRAXANE® would be on allocation until further notice.

SUPPLY ALLOCATIONS

We soon started seeing other items on allocation, including sterile gloves, normal saline, heparin flushes, face masks and sanitary wipes. All these items are crucial in our line of work with patients. We mix most of our chemotherapy and immunotherapy drugs in normal saline bags. Heparin flushes are used to flush out port placements and face masks, and sanitary wipes are extremely important to to prevent our patients and employees from COVID infection.

When nurses start IV infusions for our patients, they use sterile gloves. Sterile gloves are usually sized. Some brands use traditional sizing (small, medium, large, etc.), while others size by a particular number. Glove size is important because extra room at the end of fingertips can create errors or distractions. Gloves should fit the hand perfectly for the best patient care, but when certain sizes go on back order or allocation, nurses must use gloves that might be too big or even too small.

As a chemotherapy clinic, SHOMG also handles many port flush procedures. A port-a-cath is a central line that generally requires flushing every 30 days to prevent clotting and maintain vascular access. When handling routine port flushes for patients who are no longer on chemotherapy, the quick procedure usually consists of using normal saline followed by heparin.

With both the normal saline flushes and heparin flushes being on backorder, our pharmacy technicians started to draw up normal saline in 10 ml syringes themselves. The nurses would have to use it all within the same day before discarding, so it was crucial to be aware of what our patient population looked like each day.

Routine port flushes are starting to be pushed out as far as scheduling because now we often cannot get heparin in at all.

MANUFACTURER BACKORDERS

Though allocations are far from ideal, they are a lot easier to deal with than items being placed on a manufacturer back order and not coming in at all. Such was our experience with bacteriostatic water.

Bacteriostatic water is a diluent used to reconstitute certain drugs. The main drug used with bacteriostatic water at our practice is Kanjinti (trastuzumab-anns). Kanjinti is used to treat metastatic, HER2-positive breast cancer and to reduce the risk of early-stage, HER2-positive disease coming back after surgery and other treatments as part of a regimen with chemotherapy medicines.

Kanjinti is weight-based when it comes to dosing, so the vial comes as a multiuse vial. Multiuse vials usually contain preservatives to keep the drug stable for a longer period of time, allowing pharmacy technicians to use the same vial for multiple patients. When bacteriostatic water is used with Kanjinti, the drug is stable for up to 28 days when refrigerated.

When bacteriostatic water went on a manufacturer back order, we had to quickly come up with an alternative. One of my coworkers took it upon herself to email the manufacturer of Kanjinti to see if normal saline might be a possibility for reconstituion; however, it was not because it does not contain preservatives. When mixed with sterile water, Kanjinti goes from being stable for 28 days to a mere 24 hours.

We quickly realized that if we didn't see all our Kanjinti patients within a certain time frame, we would be wasting much of the drug. To make matters worse, this alternative then created another problem: sterile water became short in supply as well.

SOLUTIONS

Dealing with COVID-related shortages has proven to be far from easy, but as a healthcare practice, we had no choice but to work together and figure out our options.

When first dealing with allocations and shortages, the easiest solution we came up with was to distribute supplies and drugs between our four clinics. Stockton is by far our largest clinic, so they tend to have a larger inventory of supplies and drugs. We have been able to share items from Stockton among our other clinics to avoid shortages until the next shipment arrives.

Another option is contacting manufacturers and drug companies to see what other mixing options are available, such as we did in the case of bacteriostatic water for reconstituting Kanjinti.

That solution, in turn, required more precise patient scheduling to avoid unnecessary waste. At SHOMG, we've found that these shortages take great communication between nurses, the pharmacy team, and administration.

SHOMG takes pride in being able to provide for our patients. The last thing we want to do is turn patients away because of shortages on supplies and drugs. Yet healthcare systems only have so much room for shortcuts and emergencies before it starts to affect patient care.

It is important that we in the healthcare system come together to review the COVID-related challenges of the past two years and share our best practices and work solutions now, ahead of any potential future pandemic.

▲ **Jennifer Berni**, CPhT, is a pharmacy technician in the Oral Medication Center at Stockton Hematology Oncology Medical Group in Stockton, California.

PATIENT ASSISTANCE & THE ESSENTIAL ROLE PHARMACY TECHS PLAY IN ONCOLOGY CARE

By Alicia Barnes, CPhT

Patients dealing with a cancer diagnosis have a lot on their plate.

First are the many fears and questions — Am I going to live to see my grandchildren graduate high school? Am I going to live to celebrate our 50th wedding anniversary? How are we financially going to afford treatment on a fixed income?

Cancer generally, though not exclusively, affects older individuals, many of whom are approaching or are in their retirement years. According to the American Cancer Society, 54% of cancer patients are covered under Medicare.[1]

Alicia Barnes

And while Medicare is a healthcare blessing for older Americans, it can be difficult to understand, let alone navigate. This is especially true for patients undergoing expensive cancer treatments.

Medicare Part D plans follow standard Medicare prescription drug guidelines. Plans can differ based on which drugs they cover, the tier in which a drug is placed for coverage, step therapy processes and standard copay vs coinsurances, but they all follow the same general guidelines.

Patient costs are fixed in the Deductible, Initial Coverage and Coverage Gap ("the donut hole") phases, but can skyrocket in the Catastrophic Coverage Phase, where patients are on the hook for approximately 5% of the prescription price for the rest of that year.

For oral oncolytics costing hundreds — if not thousands — of dollars per pill, financial toxicity can quickly become an added stress for the patient.

THE 2022 MEDICARE PART D "DONUT HOLE"

DEDUCTIBLE PHASE
You pay until your deductible amount reaches **$480 in 2022**

INITIAL COVERAGE PHASE
You pay copay and/or co-insurance **$4,430 in 2022** (enter "The Donut Hole")

COVERAGE GAP PHASE
"The Donut Hole"
You pay 25% of the cost of brand-name drugs and 25% of the cost of generic drugs **$7,050 in 2022** (exit "The Donut Hole")

CATASTROPHIC COVERAGE PHASE
You pay approximately 5% of drug price upon reaching the out-of-pocket limit

PLAN RESETS JAN. 1, 2023

Patients already don't feel well because of their disease. Now, due to financial concerns, many fear they are becoming a burden to their spouse or family. They wonder how they will cover their rent or mortgage if they must pay $3,000 a month for a medication.

The cancer patient then begins to wonder: Is this medication going to work? Will it be a waste of money that I don't have?

RESOLVING FINANCIAL CONCERNS

When considering all of these hardships, oncology patients are now also burdened with planning how to pay for treatment. As pharmacy technicians specializing in patient assistance, it is our job to help them resolve these financial issues.

Patients often don't realize that they are eligible for assistance with the cost of cancer medications through third-party foundations as well as manufacturer rebates.

For patients who are privately or commercially insured, manufacturers offer copay cards that can be billed as a secondary to insurance and cover the medication, leaving the patient with little to no out-of-pocket cost.

Medicare patients, however, are not eligible for copay cards. Social Security rules make it illegal for pharmaceutical companies to offer discounts for medications that could be purchased through Medicare. Because of these restrictions, the pharmacy technician must turn to third-party foundations.

Foundations such as HealthWell, The PAN Foundation and the Leukemia & Lymphoma Society have funds available based on diagnosis and financial qualifications.

Most patients automatically think they don't qualify for these programs because they make too much money. Yet, these programs are very generous, with income limits generally at 400% to 500% over the Federal Poverty Level.

In 2022, the Federal Poverty Level is $17,420 for a household of two. This means that a couple living on a fixed

CONTINUED ON NEXT PAGE

PATIENT ASSISTANCE

CONTINUED FROM PREVIOUS PAGE

income can bring in anywhere between $69,680 and $87,100 annually and still qualify for assistance depending on the limits of that specific program.

BEST PRACTICES

In the oncology space, working as a pharmacy technician involves more duties than one might expect. We process prior authorizations. We perform benefit investigations. We work with mail-order pharmacies all over the country to make things fall into place.

But oftentimes, once all of these boxes are checked, we find out that the medication is going to cost the patient $2,376, and we hit a brick wall. Now it is our job to help this patient obtain this medication at an affordable cost.

FundFinder.org (www.fundfinder.org) is an online tool put together by The Patient Access Network Foundation. The portal allows users to quickly search by disease state and see all foundations with available funding at the time.

Foundations are the first choice for assistance. The process is usually easier with a quicker turnaround time than manufacturer options.

We want to get assistance as soon as possible to prevent any delay in therapy. Most foundations have online portals with a relatively simple application process, requiring only annual income and household size, along with diagnosis and medication prescribed.

Unfortunately, not all foundations or manufacturers use the same criteria to determine eligibility. These discrepancies can often lead to dead ends and change of therapy in hopes of finding assistance. This can make it very difficult on us as pharmacy technicians to ensure we are helping our patients the best we can in a timely fashion.

FINANCIAL STRESS AND COMPLIANCE

As with any medication, compliance with oral oncolytics is key. And making sure there is funding for these drugs plays a big role in patient compliance.

When patients aren't sure if they will be able to afford their next refill, corners are cut. Patients start splitting tablets that shouldn't be split, skipping doses, or discontinuing therapy altogether.

Removing financial stress, therefore, makes for more effective therapy. Pharmacy technicians can help achieve this by:

- Monitoring grant balances each month with refills to secure funding before it is needed; and
- Keeping track of renewal dates with manufacturers to ensure there is no enrollment gap.

OBSTACLES TO PATIENT ASSISTANCE

The struggles and hurdles that we as pharmacy technicians encounter along with patients are all too common.

For example, JT, a 61-year-old female, was diagnosed with lung cancer. Upon diagnosis, she was forced to sell her business where she was self-employed. Being self-employed, she doesn't have a retirement plan, and she has a Christian Health Share plan. The sale of her business, while it reflects as income, also is the basis of her retirement for the rest of her life.

During first-line therapy with oral medication, we were able to show the manufacturer that she was technically "uninsured" and provide a letter of financial hardship showing that the income she has is not expendable.

The manufacturer continued to provide the medication at no cost until the patient progressed on therapy and was advanced to second-line therapy.

Again, we were able to show that she was uninsured and gain assistance from the manufacturer.

Now the patient is rapidly progressing and forced to move on to a third-line therapy.

Unfortunately, working with the third manufacturer was not as simple. A health share plan is considered "insured" even though reimbursement is not guaranteed. They did not accept letters of financial hardship or take into consideration that the income did not truly reflect the patient's financial need.

This patient was then left with the only option of paying $8,000 monthly out of pocket from her savings and hoping that she qualified to be reimbursed through her health share.

Yet, while this is a very daunting and time-consuming process, the impact of the pharmacy technician regarding financial assistance can have unparalleled impact on patient care.

Alicia Barnes, CPhT, is a Patient Assistance Technician at AON Pharmacy in Spokane, Washington.

REFERENCE

1. Lifeline: Why Cancer Patients Depend on Medicare for Critical Coverage. Accessed on August 30, 2021. Available from: https://www.fightcancer.org/sites/default/files/2013-Medicare-Chartbook-Online-Version.pdf.

KIM SMITH | AstraZeneca

"I can't understand why anyone in the oncology space wouldn't be a partner with NCODA. The relationships we create by coming to their events and being able to talk to the pharmacy leaders and to have conversations with people you wouldn't get to see, particularly during COVID, have been extremely valuable."

Kim Smith, RN, BSN, is the National Oncology Account Director at AstraZeneca, a global, science-led biopharmaceutical business with innovative medicines used by millions of patients worldwide. Her group works with the largest accounts in the United States to ensure that patients have access to AstraZeneca's medications, and that patients know how to use them appropriately.

A former ICU and home health nurse, Smith has worked in the pharmaceutical industry for the past 20 years.

How have AstraZeneca and NCODA collaborated over the years?

I started collaborating with NCODA very early on in their history. Michael Reff had just started NCODA, and he was collaborating with pharmacy directors from across the country to share the idea of building out educational support resources for oral oncology and Medically Integrated Pharmacy (MIP) teams. At the time I was working for Bayer Pharmaceuticals.

NCODA was just starting to partner with pharmaceutical manufacturers on different initiatives. As a young organization, many folks in the industry had not yet heard about NCODA. I started educating Bayer executives on who NCODA was, and how they were helping to educate healthcare providers on oncology products, particularly oral oncolytics. Bayer was very supportive of NCODA from the start, and decided to become one of NCODA's first corporate sponsors.

I replicated this same process when I assumed a new role with AstraZeneca. Initially, AstraZeneca had a relatively small oncology portfolio, but we had a large pipeline. We knew that oncology was going to be a growing field for us. I brought the NCODA team to the AstraZeneca office and introduced them to all of our brand teams and market access teams. They were able to talk about the organization and what they were doing, and our team was able to understand the importance of partnering with NCODA, specifically by providing support for projects such as the development of **Positive Quality Intervention (PQI)** documents for our oral oncology products.

AstraZeneca now has PQIs across our entire oncology portfolio, along with two interactive assessment tools that can be used by providers to assess side effect management.

Can you tell us more about the oral oncolytics produced by AstraZeneca?

We currently have three oral oncolytics:

- **CALQUENCE® (acalabrutinib)**, a BTK inhibitor which is used in mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).
- **LYNPARZA® (olaparib)** for maintenance treatment of BRCA-mutated advanced ovarian cancer in adults, as well as prostate cancer, pancreatic cancer and breast cancer.

CONTINUED ON NEXT PAGE

PROFILE

CONTINUED FROM PREVIOUS PAGE

• **TAGRISSO® (osimertinib)**, which is utilized in non-small cell lung cancer with patients who have an EGFR mutation.

How has the COVID pandemic affected AstraZeneca's educational efforts?

AstraZeneca has had more than 13 FDA approvals in the last four years (which is unheard of) — several during the COVID pandemic.

Access has been relatively hard for our teams; we really needed to have a good partner. So, as new medications are FDA-approved, we work closely with NCODA to provide education and create unique resources, such as PQIs, nurse education tools, and assessment tools.

It's difficult when you have a new medication that's changing the standard of care; if the clinicians don't know about it, they can't use it appropriately. We recognized NCODA as a good partner to help us educate oncology healthcare providers since their membership was growing so rapidly.

Are there any other NCODA resources that have been useful for AstraZeneca?

We've hosted educational breakfast and lunch product theaters at several NCODA meetings. We've also developed interactive assessment tools to assess interstitial lung disease and side effects when providers use LYNPARZA®.

Are there any other ways that NCODA can help support AstraZeneca's mission and vision?

We would definitely like to pursue the creation of **PQI in Action** articles and **Treatment Support Kits (TSK)** for patients. We also appreciate the continued feedback from NCODA's Executive Council. On multiple occasions, the Council has given us feedback on areas such as how we package our products, formulation of products, and on access issues due to financial toxicity.

Financial toxicity seems to be a constant challenge for both the patients on oral oncolytics and the practices that serve them. How is AstraZeneca dealing with this issue?

Utilizing some of the feedback that NCODA members have given to us related to financial toxicity, we've been able to find solutions. For example, we established vouchers for our CALQUENCE® product line that have been helpful. We've also created some value-based contracting strategies that work well for the accounts as well as the patients.

What other challenges does AstraZeneca see on the horizon?

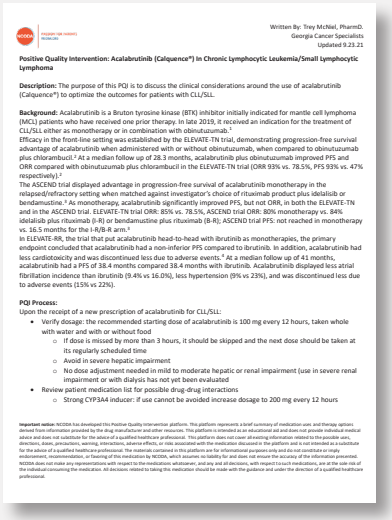
COVID has changed how we interact with customers and this will have a long-lasting impact. We are now transitioning to more of a digital world where we interact virtually. We've had to adapt some of our tools to be more electronic-based for accessibility.

Whether it's a podcast or other form of "simplified education," we are trying to be more digitally aligned than in the past. The message that we've received from our customers is "stop the paper, stop sending things to our practice that we are just going to recycle. Provide us with more digital-based resources."

That's been part of the transition we've started with NCODA, and we will continue moving in that direction in the future.

Positive Quality Interventions Sponsored by AstraZeneca

CALQUENCE® (acalbrutinib)



Written By: Trey McNiel, PharmD.
Georgia Cancer Specialists
Updated 9.23.21

Positive Quality Intervention: Acalabrutinib (Calquence®) in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Description: The purpose of this PQI is to discuss the clinical considerations around the use of acalabrutinib (Calquence®) to optimize the outcomes for patients with CLL/SLL.

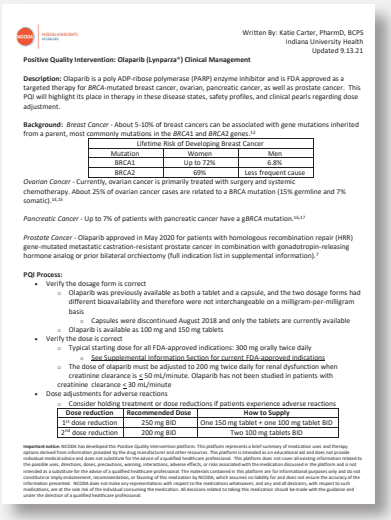
Background: Acalabrutinib is a Bruton tyrosine kinase (BTK) inhibitor initially indicated for mantle cell lymphoma (MCL) patients who have received one prior therapy. In late 2019, it received an indication for the treatment of CLL/SLL either as monotherapy or in combination with obinutuzumab.[1]
Efficacy in the front-line setting was established by the ELEVATE-TN trial, demonstrating progression-free survival advantage of acalabrutinib when administered with or without obinutuzumab, when compared to obinutuzumab plus chlorambucil.[2] At a median follow up of 28.3 months, acalabrutinib plus obinutuzumab improved PFS and ORR compared with obinutuzumab plus chlorambucil in the ELEVATE-TN trial (ORR 93% vs. 78.5%, PFS 93% vs. 47% respectively).[2]
The ASCEND trial displayed advantage in progression-free survival of acalabrutinib monotherapy in the relapsed/refractory setting when matched against investigator's choice of rituximab product plus idelalisib or bendamustine.[3] As monotherapy, acalabrutinib significantly improved PFS, but not ORR, in both the ELEVATE-TN and in the ASCEND trial. ELEVATE-TN trial ORR: 85% vs. 78.5%, ASCEND trial ORR: 80% monotherapy vs. 84% idelalisib plus rituximab (I-R) or bendamustine plus rituximab (B-R); ASCEND trial PFS: not reached in monotherapy vs. 16.5 months for the I-R/B-R arm.[3]
In ELEVATE-RR, the trial that put acalabrutinib head-to-head with ibrutinib as monotherapies, the primary endpoint concluded that acalabrutinib had a non-inferior PFS compared to ibrutinib. In addition, acalabrutinib had less cardiotoxicity and was discontinued less due to adverse events.[4] At a median follow up of 41 months, acalabrutinib had a PFS of 38.4 months compared 38.4 months with ibrutinib. Acalabrutinib displayed less atrial fibrillation incidence than ibrutinib (9.4% vs 16.0%), less hypertension (9% vs 23%), and was discontinued less due to adverse events (15% vs 22%).

PQI Process:
Upon the receipt of a new prescription of acalabrutinib for CLL/SLL:

- Verify dosage: the recommended starting dose of acalabrutinib is 100 mg every 12 hours, taken whole with water and with or without food
  - If dose is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time
  - Avoid in severe hepatic impairment
  - No dose adjustment needed in mild to moderate hepatic or renal impairment (use in severe renal impairment or with dialysis has not yet been evaluated
- Review patient medication list for possible drug-drug interactions
  - Strong CYP3A4 inducer: if use cannot be avoided increase dosage to 200 mg every 12 hours

Important notice: NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.

LYNPARZA® (olaparib)



Written By: Katie Carter, PharmD, BCPS
Indiana University Health
Updated 9.13.21

Positive Quality Intervention: Olaparib (Lynparza®) Clinical Management

Description: Olaparib is a poly ADP-ribose polymerase (PARP) enzyme inhibitor and is FDA approved as a targeted therapy for *BRCA*-mutated breast cancer, ovarian, pancreatic cancer, as well as prostate cancer. This PQI will highlight its place in therapy in these disease states, safety profiles, and clinical pearls regarding dose adjustment.

Background: *Breast Cancer* - About 5-10% of breast cancers can be associated with gene mutations inherited from a parent, most commonly mutations in the *BRCA1* and *BRCA2* genes.[12]

Lifetime Risk of Developing Breast Cancer		
Mutation	Women	Men
BRCA1	Up to 72%	6.8%
BRCA2	69%	Less frequent cause

Ovarian Cancer - Currently, ovarian cancer is primarily treated with surgery and systemic chemotherapy. About 25% of ovarian cancer cases are related to a BRCA mutation (15% germline and 7% somatic).[34,35]

Pancreatic Cancer - Up to 7% of patients with pancreatic cancer have a g*BRCA* mutation.[16,17]

Prostate Cancer - Olaparib approved in May 2020 for patients with homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer in combination with gonadotropin-releasing hormone analog or prior bilateral orchiectomy (full indication list in supplemental information).[7]

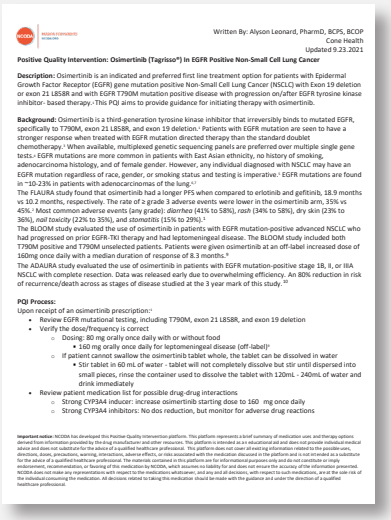
PQI Process:

- Verify the dosage form is correct
  - Olaparib was previously available as both a tablet and a capsule, and the two dosage forms had different bioavailability and therefore were not interchangeable on a milligram-per-milligram basis
    - Capsules were discontinued August 2018 and only the tablets are currently available
  - Olaparib is available as 100 mg and 150 mg tablets
- Verify the dose is correct
  - Typical starting dose for all FDA-approved indications: 300 mg orally twice daily
    - See Supplemental Information Section for current FDA-approved indications
  - The dose of olaparib must be adjusted to 200 mg twice daily for renal dysfunction when creatinine clearance is ≤ 50 mL/minute. Olaparib has not been studied in patients with creatinine clearance ≤ 30 mL/minute
- Dose adjustments for adverse reactions
  - Consider holding treatment or dose reductions if patients experience adverse reactions

Dose reduction	Recommended Dose	How to Supply
1st dose reduction	250 mg BID	One 150 mg tablet + one 100 mg tablet BID
2nd dose reduction	200 mg BID	Two 100 mg tablets BID

Important notice: NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.

TAGRISSO® (osimertinib)



Written By: Alyson Leonard, PharmD, BCPS, BCOP
Cone Health
Updated 9.23.2021

Positive Quality Intervention: Osimertinib (Tagrisso®) In EGFR Positive Non-Small Cell Lung Cancer

Description: Osimertinib is an indicated and preferred first line treatment option for patients with Epidermal Growth Factor Receptor (EGFR) gene mutation positive Non-Small Cell Lung Cancer (NSCLC) with Exon 19 deletion or exon 21 L858R and with EGFR T790M mutation positive disease with progression on/after EGFR tyrosine kinase inhibitor- based therapy.[1]This PQI aims to provide guidance for initiating therapy with osimertinib.

Background: Osimertinib is a third-generation tyrosine kinase inhibitor that irreversibly binds to mutated EGFR, specifically to T790M, exon 21 L858R, and exon 19 deletion.[1] Patients with EGFR mutation are seen to have a stronger response when treated with EGFR mutation directed therapy than the standard doublet chemotherapy.[1] When available, multiplexed genetic sequencing panels are preferred over multiple single gene tests.[2] EGFR mutations are more common in patients with East Asian ethnicity, no history of smoking, adenocarcinoma histology, and of female gender. However, any individual diagnosed with NSCLC may have an EGFR mutation regardless of race, gender, or smoking status and testing is imperative.[2] EGFR mutations are found in ~10-23% in patients with adenocarcinomas of the lung.[3]
The FLAURA study found that osimertinib had a longer PFS when compared to erlotinib and gefitinib, 18.9 months vs 10.2 months, respectively. The rate of ≥ grade 3 adverse events were lower in the osimertinib arm, 35% vs 45%.[3] Most common adverse events (any grade): *diarrhea* (41% to 58%), *rash* (34% to 58%), dry skin (23% to 36%), *nail toxicity* (22% to 35%), and *stomatitis* (15% to 29%).[3]
The BLOOM study evaluated the use of osimertinib in patients with EGFR mutation-positive advanced NSCLC who had progressed on prior EGFR-TKI therapy and had leptomeningeal disease. The BLOOM study included both T790M positive and T790M unselected patients. Patients were given osimertinib at an off-label increased dose of 160mg once daily with a median duration of response of 8.3 months.[3]
The ADAURA study evaluated the use of osimertinib in patients with EGFR mutation-positive stage 1B, II, or IIIA NSCLC with complete resection. Data was released early due to overwhelming efficiency. An 80% reduction in risk of recurrence/death across as stages of disease studied at the 3 year mark of this study.[37]

PQI Process:
Upon receipt of an osimertinib prescription:[1]

- Review EGFR mutational testing, including T790M, exon 21 L858R, and exon 19 deletion
- Verify the dose/frequency is correct
  - Dosing: 80 mg orally once daily with or without food
    - 160 mg orally once daily for leptomeningeal disease (off-label)[3]
  - If patient cannot swallow the osimertinib tablet whole, the tablet can be dissolved in water
    - Stir tablet in 60 mL of water - tablet will not completely dissolve but stir until dispersed into small pieces, rinse the container used to dissolve the tablet with 120mL - 240mL of water and drink immediately
- Review patient medication list for possible drug-drug interactions
  - Strong CYP3A4 inducer: increase osimertinib starting dose to 160 mg once daily
  - Strong CYP3A4 inhibitors: No dos reduction, but monitor for adverse drug reactions

Important notice: NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.

SCAN QR CODE TO VIEW OR DOWNLOAD ASSOCIATED PQI

NCODA

CENTER OF EXCELLENCE

MEDICALLY INTEGRATED PHARMACY ACCREDITATION

An Accreditation Program That Finally Meets Your Unique Needs!

About The Program:

- Compliant with ASCO/NCODA Patient-Centered Standards as published in the *Journal of Clinical Oncology*
- Focused on enhanced integrated patient care and quality of services
- Supports *Going Beyond the First Fill*
- Designed to produce positive patient outcomes
- Preferred accreditation for Prime Therapeutics' IntegratedRx® Oncology Program

"The NCODA CoE MIP Accreditation Program focuses on real-world medically integrated pharmacy processes and documentation. The program provides guidance on what high-quality care looks like, and it helps us demonstrate that we are providing high-quality care with every single patient that comes through our pharmacy."

Paul Forsberg, PharmD
Director of Pharmacy | Minnesota Oncology

For More Information Or To Request A Quote,
Scan QR Code Or Visit: **www.ncoda.org/accreditation**

AN OVERVIEW OF CURRENT FDA-APPROVED PARP-INHIBITORS FOR PROSTATE CANCER

By Kristen Farnet, PharmD, MBA, Lillian Higgins & Kelly Brunk, PharmD, BCOP,


Kristen Farnet


Lillian Higgins


Kelly Brunk

Prostate cancer is the second most common cancer diagnosis in the United States, accounting for 13.1% of all new cases in 2021.[1]

With 248,530 new cases and 34,140 deaths from prostate cancer in 2021 alone, it is the second leading cause of cancer-related deaths in men with a five-year overall survival rate of 97.5%.[1,2]

Prostate cancer is most commonly found in men over the age of 65, in African Americans with a family history of prostate cancer, or in those with a genetic predisposition.[3]

TARGETABLE DNA REPAIR GENE MUTATIONS IN PROSTATE CANCER

About one in 10 patients with prostate cancer have a germline mutation linked to an increased risk of developing cancer.[4]

An example of this is the association between prostate cancer and hereditary breast and ovarian cancer syndrome caused by homologous DNA repair gene germline mutations. These DNA repair genes commonly include BRCA2, ATM, and CHEK2.

A prospective clinical sequencing infrastructure study showed that in metastatic castration-resistant prostate cancer (mCRPC), mutations in BRCA1, BRCA2, and ATM were observed in 19.3% of cases.[5] Other studies suggest BRCA1 or BRCA2 mutations in prostate cancer lead to poor outcomes, including increased risk of progression and decreased overall survival.[6,7]

Germline testing is recommended for individuals who have positive family history of certain cancers. This includes individuals with a first-, second- or third-degree relative with breast, colorectal, endometrial, ovarian, pancreatic or prostate cancer.[3]

Guidelines also recommend testing family members with pathogenic or likely pathogenic germline mutations associated with familial cancer risk, such as BRCA1 or BRCA2 mutation.[8]

Other indications for germline genetic testing include: having a personal history of breast cancer, being of Ashkenazi Jewish descent, having high-risk, very high-risk, regional or metastatic prostate cancer.[3]

Somatic mutations also represent a connection to mCRPC and guidelines recommend tumor testing in select patients. Tumor testing is recommended in those with metastatic disease and may be considered in regional disease. Those with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) with mCRPC are also recommended to be tested along with consideration of those with hormone-sensitive prostate cancer (HSPC).[3]

Approximately 89% of mCRPC tumors have mutations that can be targeted by available anticancer treatments, but only 9% of these are germline. Metastatic patients are more likely than localized prostate tumors to contain somatic mutations (23% versus 19%).[9] Additionally, mutations to BRCA2 and ATM are the most common in both mCRPC and localized tumors.[9,10]

THE ROLE OF PARP-INHIBITORS

Poly-ADP Ribose Polymerase (PARP) inhibitor targeted therapy has received U.S. Food and Drug Administration (FDA) approval in the United States, as well as approval in Europe and other countries in treating patients with mCRPC.[9]

There are four FDA-approved PARP inhibitors: olaparib, niraparib, rucaparib and talazoparib. Outside of prostate cancer, agents in this class carry indications for ovarian, breast and pancreatic cancers.[11]

PARP inhibitors work through disruption of DNA repair and may be more beneficial in patients with underlying DNA damage repair (DDR) gene mutations.[12] PARP inhibitors cause accumulation of damaged cells leading to cell cycle arrest through prevention of repairing DNA single-stranded breaks. This leads to conversion of double-stranded breaks and permanent DNA damage.[13]

These agents are used for patients with mCRPC after traditional androgen deprivation therapy, taxane therapy and other castrate-resistant pharmacotherapy options (including therapies such as Radium-223 and Sipuleucel-T) have failed.[3]

Currently, olaparib and rucaparib are the only two FDA-approved PARP inhibitors in prostate cancer. Both were approved in May 2020 in the mCRPC setting. Approval was

CONTINUED ON NEXT PAGE

PARP-INHIBITORS

CONTINUED FROM PREVIOUS PAGE

based on evidence showing benefit in patients with germline and somatic mutations in homologous recombination repair (HRR) genes.[3]

Olaparib is specifically approved for patients with germline or somatic HRR gene-mutated mCRPC who have progressed on prior treatment with new hormonal therapies (i.e., abiraterone or enzalutamide).[3,11] It was studied in the randomized, phase III PROfound trial comparing olaparib 300mg twice daily versus physician's choice of enzalutamide or abiraterone.

Trial patients had previously been on a new hormonal agent and/or taxane therapy and were divided into one of two cohorts (A or B).

Patients in cohort A included genetic alterations in BRCA1, BRCA2, or ATM. Cohort B had at least one of the following genetic alterations: BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RA51D, or RAD54L.

In cohort A, median radiographic progression free survival (PFS) was 7.4 months in the olaparib group versus 3.6 months in the control group (HR, 0.34; 95% CI, 0.25-0.47; p <0.001). The objective response rate (ORR) was 33% in the olaparib group and 2% in the control (OR, 20.86; 95% CI, 4.18-379.18; p<0.001). Median overall survival (OS) was 18.5 months in the olaparib group versus 15.1 months in the control (HR, 0.64; 95% CI, 0.43-0.97; p=0.02).

Overall, there was a 66% reduction in progression of disease and 81% of patients in the control group who experienced progression switched over to the olaparib group.

Tolerability and side effect profiles for olaparib were similar to previous studies. Grade 3 events were higher with olaparib than the control group at 21%. The most common side effects of any grade included anemia (46%), nausea and fatigue (41%), decreased appetite (30%), diarrhea (21%), and vomiting and constipation (18%).[14]

PARP inhibitors, alone or in combination with other therapies, are on the horizon & may soon find their way into standard-of-care therapy for various stages of prostate cancer.

Rucaparib was originally approved under accelerated approval status for treatment of adults with a BRCA1 or BRCA2 mutation and mCRPC previously treated with taxane and new hormonal therapies.[3,11]

Evidence was based on the phase II TRITON-2 study in patients with mCRPC and somatic or germline alterations in HRR genes who previously progressed on one to two new hormonal therapies and at least one prior taxane therapy. All patients received rucaparib 600mg twice daily as a 28-day cycle in combination with a gonadotropin-releasing hormone analog or bilateral orchiectomy.

The primary endpoint was ORR in patients who had measurable disease. ORR was 43.5% (95% CI, 31.0%-56.7%) in the BRCA1 and BRCA2 population. Median radiographic PFS was 9.0 months (95% CI, 8.3-13.5 months).[15]

The guidelines do not usually recommend using rucaparib in mCRPC patients with BRCA1 or BRCA2 unless they have already been treated with a taxane therapy.3 The range for duration of response (DOR) was 1.7 months to more than 24 months. More than 50% had a DOR greater than or equal to six months.[15]

The most common adverse events of any grade included fatigue (62%), nausea (52%), anemia (44%), increased ALT/AST (33%), decreased appetite (32%), constipation (27%), thrombocytopenia and decreased platelets (25%), vomiting (22%) and diarrhea (20%).[16]

FUTURE DIRECTIONS AND ONGOING TRIALS

Many ongoing clinical trials continue to evaluate the use of PARP inhibitors, alone or in combination with other therapies, in various stages of prostate cancer.

In early-stage prostate cancer, olaparib and niraparib are being studied in the neoadjuvant setting (NCT03432897-BrUOG 337, NCT04030559), and rucaparib and olaparib plus or minus durvalumab are being studied in non-metastatic biochemically recurrent prostate cancer (NCT03533946-ROAR, NCT03047135, NCT03810105, NCT04336943).

In HSPC, TRIUMPH (NCT03413995) is evaluating rucaparib for patients with germline mutations in at least one recombination DNA-repair gene. ZZ-First (NCT04332744) is studying talazoparib in combination with enzalutamide in patients with HSPC regardless of aberrations in homologous recombination repair genes.

In regard to mCRPC, many trials are underway. Ongoing studies for the first-line treatment of mCRPC include olaparib plus or minus abiraterone (NCT03012321-BRCAAway, NCT03732820-PROpel), niraparib plus or minus abiraterone (NCT03748641-MAGNITUDE), and rucaparib plus or minus enzalutamide (NCT04455750-CASPAR).

All four currently FDA-approved PARP inhibitors are being studied, alone or in combination with other therapies, for the subsequent-line treatment of mCRPC.

Combination therapies with PARP inhibitors include immune checkpoint inhibitors (i.e., durvalumab, nivolumab, pembrolizumab), radiopharmaceutical Radium-223, new hormonal therapy, taxanes (i.e., docetaxel, cabazitaxel), ataxia telangiectasia and rad3-related kinase (ATR) inhibitor AZD6738, vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor cediranib,

CONTINUED ON NEXT PAGE

PARP-INHIBITORS

CONTINUED FROM PREVIOUS PAGE

and protein kinase B (PKB, AKT) inhibitor ipatasertib.

Currently, when the terms "prostate cancer" and "PARP inhibitor" are searched on clinicaltrials.gov, 42 trials result. Indeed, PARP inhibitors, alone or in combination with other therapies, are on the horizon and may soon find their way into standard-of-care therapy for various stages of prostate cancer.

CONCLUSION

Prostate cancer remains a prevalent diagnosis among men and has many guideline-directed treatment options.

When standards-of-care fail, emerging evidence suggests using the PARP inhibitors olaparib and rucaparib in patients with germline or somatic genetic mutations.

Ongoing studies are investigating the role of PARP inhibitors, alone or in combinations with other standards-of-care, in various stages of prostate cancer, including nonmetastatic prostate cancer, mHSPC, and mCRPC.

▲ **Kristen Farnet**, PharmD, MBA, is a PGY2 Oncology Resident, **Lillian Higgins** is an Oncology Pharmacy Intern and **Kelly Brunk**, PharmD, BCOP, is an Oncology Clinical Pharmacist. All three are employed at The University of Kansas Health System.

REFERENCES

1. Cancer of the Prostate - Cancer Stat Facts. SEER. Accessed March 24, 2022. Available from:https://seer.cancer.gov/statfacts/html/prost.html?msclkid=15ff001eab2211ec-9f33e08356e3f86f.

2. CDC Prostate Cancer Statistics. Centers for Disease Control and Prevention. Published June 8, 2021. Accessed March 24, 2022. Available from: https://www.cdc.gov/cancer/prostate/statistics/index.htm?msclkid=68c71861ab3311ec-87e68fa222ba1384.

3. National comprehensive cancer network clinical practice guidelines in oncology. Prostate cancer v3.2022,www.nccn.org (accessed March 14, 2022).

4. Pilié PG, Johnson AM, Hanson KL, et al. Germline genetic variants in men with prostate cancer and one or more additional cancers. Cancer. 2017;123(20):3925-3932.

5. Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol. 2015;68(2):186-193.

6. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol. 2013;31(14):1748-1757.

7. Beebe-Dimmer JL, Kapron AL, Fraser AM, et al. Risk of prostate cancer associated with familial and hereditary cancer syndromes. J Clin Oncol. 2020;38(16):1807-1813.

8. Sokolova A, Cheng H. Germline testing in prostate cancer: when and who to test. Oncology (Williston Park). 2021;35(10):645-653.

9. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015; 161:1215-1228.

10. Cancer Genome Atlas Research N. The molecular taxonomy of primary prostate cancer. Cell. 2015;163:1011-1025.

11. Rose M, Burgess JT, O'Byrne K, et al. PARP inhibitors: Clinical relevance, mechanisms of action and tumor resistance. Front Cell Dev Biol. 2020;8:564601.

12. Zhen JT, Syed J, Nguyen KA, et al. Genetic testing for hereditary prostate cancer: Current status and limitations [published correction appears in Cancer. 2019 Jul 1;125(13):2325]. Cancer. 2018;124(15):3105-3117.

13. Teyssonneau D, Margot H, Cabart M, et al. Prostate cancer and PARP inhibitors: progress and challenges. J Hematol Oncol. 2021;14(1):51.

14. de Bono J, Mateo J, Fizazi K, Saad F, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020;382(22):2091-2102.

15. FDA grants accelerated approval to rucaparib for BRCA-mutated metastatic castration-resistant prostate cancer. FDA. Published online June 11, 2021. Accessed March 25, 2022. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate?msclkid=1d87f87aabd111ec9350180e2ea0fc9b.

16. Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 Gene Alteration. J Clin Oncol. 2020 Nov 10;38(32):3763-3772.

CONE HEALTH CANCER CENTER AT WESLEY LONG

VISION/MISSION STATEMENT:

Our vision is to provide an exceptional, unsurpassed healthcare experience at the Cone Health Cancer Care program. Our mission is to create a patient-centered, safe, high-quality, comprehensive program to meet the needs of our community. Through an empowered team, we will provide outstanding, collaborative, coordinated care with empathy and compassion that will exceed our patients', customers' and communities' expectations.

LOCATIONS:

- **Cone Health Cancer Center at Wesley Long**
  Greensboro, North Carolina
- **Cone Health Cancer Center at Annie Penn**
  Reidsville, North Carolina
- **Cone Health Cancer Center at Alamance Regional**
  Burlington, North Carolina
- **Cone Health Cancer Center at MedCenter High Point**
  High Point, North Carolina
- **Cone Health Cancer Center at MedCenter Mebane**
  Mebane, North Carolina
- **Cone Health Cancer Center at Asheboro**
  Asheboro, North Carolina
- **Cone Health Cancer Center at Drawbridge Parkway**
  Greensboro, North Carolina

PRACTICE DETAILS:

- 19 medical oncologists/hematologists, five gynecologic oncologists, one neuro-oncologist
- 14 advanced practice providers
- 13 oncology pharmacists
- One director of oncology pharmacy services
- One oncology informatics pharmacist
- Two oral chemotherapy pharmacists
- Two oral oncology specialty patient advocates
- Two IV drug assistance patient advocates
- One ambulatory Hematology/Oncology pharmacy resident

QUALIFICATIONS/CREDENTIALS:

- Quality Oncology Practice Initiative (QOPI) certified
- Accreditation Commission for Health Care (ACHC)
- Utilization Review Accreditation Commission (URAC)
- Radiation Oncology — American College of Radiology (ACR) accredited

DISPENSING TYPE:

- Retail pharmacy (Medically Integrated Pharmacy)
- Seven medical offices with chemotherapy infusion suites

SERVICES PROVIDED:

CHCC offers outpatient chemotherapy (oral and infusion) services, inpatient chemotherapy, radiation oncology, specialty pharmacy services, genetic testing and counseling, as well as nutrition support, clinical social workers, financial counselors, patient support and cancer survivorship programs. Our pharmacy team supports learners from four colleges of pharmacy and two PGY1 pharmacy residency programs. Our pharmacists are dedicated preceptors to our ASHP-accredited, PGY2 Ambulatory Hematology/Oncology Pharmacy Residency. We have an active clinical trials program receiving NCI and ASCO recognition for high-quality clinical research and excellence in patient enrollments among community oncology practices.

WHY DID YOU JOIN NCODA?

We joined NCODA to collaborate with similar oncology practices dedicated to excellence in patient care and to participate in the numerous educational opportunities including PQIs, Oral Chemotherapy Education (OCE) sheets and NCODA webinars.

HOW CAN NCODA HELP YOU?

NCODA offers a national oncology resource team too share knowledge, best practices, valuable experience and educational opportunities. NCODA provides engaging, up-to-date education for patients and colleagues.

HOW WOULD YOU LIKE TO BE MORE INVOLVED WITH NCODA?

Our passion is to educate and empower patients, colleagues and future colleagues to provide the highest quality, personalized, cancer care. We would like to see our students and residents involved in NCODA activities including Student Educational Talks (SETs), oncology journal clubs, etc. We also would like to expand and promote NCODA's Intravenous Cancer Treatment Education (IVE) sheets.

WHAT ONCOLOGY CHALLENGES ARE YOU FACING NOW OR ENVISION IN THE FUTURE?

1. Financial barriers to oral oncology agents.
2. Excessive out-of-pocket costs for IV chemotherapy medications.
3. Creating and maintaining oncology treatment plans in our electronic medical record.
4. Staying current with payer requirements for biosimilars.

SCAN QR CODE TO VIEW PRACTICE IN FOCUS WEBINAR FEATURE

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 International Monthly Webinar as the featured practice.

For an application, visit:
www.ncoda.org/practice-in-focus

PHARMACIST WHO BEAT CANCER TO START A FAMILY NOW FIGHTS FOR CO-SURVIVORS

When diagnosed with advanced stage classical Hodgkin's lymphoma in 2013, Joshua Raub quickly realized that more than just his own life was at stake.

Raub and his wife, Krystle, were in the second year of their marriage and planning to raise a family. But as clinical pharmacists, the couple knew that his therapy options at the time were harsh and limited. Raub's survival, let alone his ability to father children, were anything but guaranteed.

"A diagnosis like that turns your world upside down," Raub said.

Ultimately, their decision to take part in a clinical trial changed the course of their lives, both personally and professionally.

Up until the diagnosis, Raub's life had been one of continual success.

After receiving a PharmD from Wayne State University in Detroit and finishing a PGY1 Residency at The Johns Hopkins Hospital in 2010, he went on to become a clinical specialist in internal medicine at Detroit Medical Center (DMC). In 2012 he was named director of the center's PGY1 Residency Program.

"My career was in high gear; I was 29 years old, and I thought I was invincible," Raub recalled.

But everything changed in 2013.

"In January I began to feel really off. I was experiencing cyclical fevers, night sweats and severe fatigue. It would come and go every few weeks and hit me in waves," Raub said.

Raub consulted his physician about his condition, yet his labs and physical exam came back as normal.

In July 2013, he was diagnosed with pulmonary tuberculosis because he had been exposed to a patient a few months prior at DMC.

Joshua and Krystle Raub today, with their children, Mila and Eliana. Retaining the ability to have children was a key consideration in his therapy selection.

"I was happy that I finally had a diagnosis," Raub said. "I went home for awhile and began to feel better."

But within a few weeks his lymph nodes became enlarged around his collarbone. A biopsy was ordered to determine whether the swelling was caused by the tuberculosis or a lymphoma.

A SECOND DIAGNOSIS

On Aug. 19, 2013, Raub's pathology report came back. The diagnosis: classical Hodgkin's lymphoma.

Raub said it was the worst day of his life. "There's nothing you can do to prepare for it," he said. "Even for a pharmacist, with all our training and everything we know about the disease, your mind basically goes blank. Because when you're a patient, you become extremely vulnerable."

Further scans and testing staged Raub's condition as advanced.

The couple reviewed available treatments with his oncologist at the Karmanos Cancer Institute in Detroit. Preserving his ability to father children was a key consideration.

Raub credits the multidisciplinary care team at Karmanos for working with him and suggesting he take part in a clinical trial.

"As a clinical pharmacist, I think they approached my treatment a little differently than they would a typical patient," he said. "They allowed me to have

CONTINUED ON NEXT PAGE

PATIENT SUCCESS

CONTINUED FROM PREVIOUS PAGE

a week to digest all the data on my own (before enrolling in the clinical trial)."

For the Raubs, it was a defining moment. "The biggest question that went through both our minds was 'Am I going to live and, if I can live, can I still be a father?'" he said.

"The clinical trial we were presented with provided both those options. But, of course, there's also an experimental arm to every clinical trial and I decided to enroll because I saw this as an opportunity to help other patients besides myself."

Raub was randomized to the brentuximab vedotin plus doxorubicin, vinblastine and dacarbazine treatment arm. All four agents were given by IV every 14 days for 12 rounds.

"It was really the gold standard for Hodgkin's lymphoma at the time," he said.

Yet the therapy was an exhausting process. Each session took about 10 hours. Due to enlarged lymph nodes in his chest, doctors opted for a PICC line rather than an infusion port.

"It was a very long, grueling day," Raub recalled. "It's basically like going into a ring to have someone beat you up, because that's how you feel ultimately when you receive chemotherapy, and voluntarily at that."

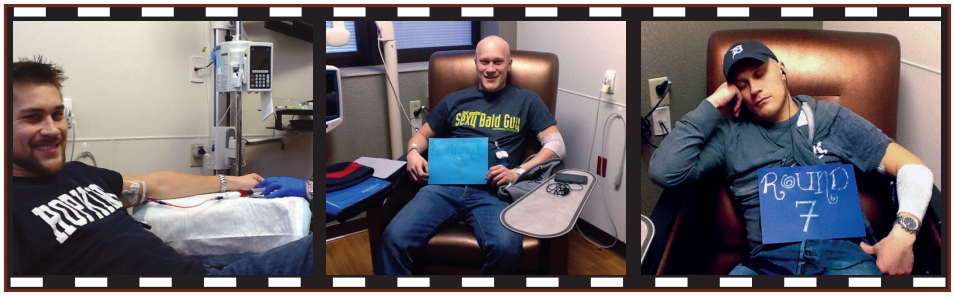
"The side effects began to come on worse and worse. It was after the second cycle that I knew I was going to lose my hair ... it started falling out as soon as I took a shower that day."

One major benefit for Raub was that the treatment center was in the adjacent building from his office, so he was able to continue working while receiving treatment.

RETURN TO 'NORMALCY'

After receiving his final treatment cycle in February 2014, Raub's cancer was declared to be in complete remission. "It was a huge turning point," he said. "It was a return to normalcy."

Or so he thought at the time.



Joshua Raub underwent a grueling 12 rounds of infusion therapy of brentuximab vedotin plus doxorubicin, vinblastine and dacarbazine. Each infusion session took about 10 hours. Photos (from left) depict the physical toll that the therapy took on Raub at the beginning, Round 4 and Round 7.

Because Raub, like many other cancer survivors, discovered he didn't really know what "normal" was anymore.

"Soon after my last dose, I began struggling with post-traumatic stress disorder and anxiety," he said. "Anytime I got sick, I felt that I was relapsing. It was very hard to control the anxiety and the fear and it came in waves for the next few years."

Raub's oncologist eventually recommended counseling.

"I was a little reluctant because I thought I could conquer it on my own, but I was exhausted," he said. "So, I met with a Karmanos social worker and counselor who only specializes in cancer patients recovering. It was probably one of the best decisions I made."

"I realized that when you beat cancer it's this huge accomplishment, but that accomplishment of remission is just the harbinger for the fear of relapse and it follows you wherever you go."

Raub also came to understand that while post-treatment counseling was an important part of the healing process, it's often beyond the scope of many practices.

"As oncologists, it's really out of their hands with what they're supposed to do," Raub explained. "You need to bring in other individuals to help with that process."

PATIENT ADVOCACY

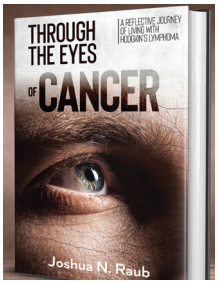
Raub became so committed to post-therapy counseling that he eventually became a patient advocate himself.

"It's good to have a patient advocacy support network, because it's a tough journey," he said. "For me, it was harder going through recovery than it was the chemotherapy."

He encourages patients that he advocates for to journal their experience.

"Throughout my entire journey, I kept a journal. It was a good reflection, but I also wanted to learn from the experience and possibly share it with others."

In 2021, he was inspired to publish a memoir: "Through the Eyes of Cancer: A Reflective Journey Of Living With Hodgkin's Lymphoma."



Raub published the book "Through the Eyes of Cancer" in 2021. It is available for purchase online.

"For years, I tried to find the silver lining to having a cancer diagnosis; I still have not found it," he said. "But the one lesson I gained was the most important one: cancer doesn't have to define you. You decide how you want the disease to be part of your life. It is not the disease controlling you. Ultimately, that lesson led me to write the book."

Raub, now 37, has been cancer-free for eight years. The experience has changed both his outlook on life and his career path. Now a medical science liaison for a global biotechnology company, his mission is to help as many people as he can.

"I think the experience opened a lot of doors for me personally and professionally," he said. "Having both the clinical knowledge as a pharmacist and the personal experience as a patient put me in a unique position to relate to many people."

A SEASON OF GROWTH: NCODA PROGRAMS & INITIATIVES OFFER GREAT OPPORTUNITIES

Winter has finally given way to Spring, and with Spring comes new life, new hope and new growth.

Spring 2022 is also proving to be a time of new growth at NCODA, where several exciting new opportunities and initiatives are now underway.

Our membership continues to flourish, and now exceeds 4,700 members and 800 unique practices.

NCODA continues to empower the future generation of oncology leaders. Our **Professional Student Organization (PSO)** has grown steadily in both student participation and student programs.

Michael Reff

And our new initiatives — including the **NCODA Center of Excellence (CoE) Medically Integrated Pharmacy (MIP) Accreditation** program and our **Informatics Initiative** — offer outstanding opportunities to improve both the quality of patient care and practice efficiency.

EDUCATIONAL OPPORTUNITIES

Our PSO has grown to include more than 1,200 students in 41 chapters. That number is expected to rise even higher by the end of the year.

In 2021 alone, we added 14 new PSO chapters, including three new chapters in Canada. And plans for additional international chapters are currently in the works.

PSO students now participate in a variety of academic, professional and community projects, including:

▲ **Advanced Pharmacy Practice Experience (APPE):** Ten more schools have opted to affiliate with our six-week onsite and remote elective oncology APPE rotation;

▲ **Positive Quality Intervention (PQI) Competition:** We've developed new and meaningful PSO programming, such as this competition, in which 35+ two-student teams use their medical writing and research skills in competition for a professional publishing opportunity;

▲ **Student Educations Talks (SETs):** Student participation at our monthly presentations given by clinical and industry professionals has more than tripled in the last year; and

▲ **Fellowships:** While NCODA continues to offer our Oncology Association Management Fellowship to future pharmacy leaders, we're also expanding our fellowship opportunities with the first-ever Oncology, Advocacy, and Health Policy and Equity Fellowships in collaboration with Bristol Myers Squibb and Pharmacyclics. NCODA's fellowship program provides an opportunity to receive a teaching certification through St. John Fisher College — Wegmans School of Pharmacy in New York.

NCODA CoE MIP ACCREDITATION

Our new accreditation program was launched Jan. 3, 2022, following pilot programs last year at Minnesota Oncology in Minneapolis, Minnesota, and Ocala Oncology in Ocala, Florida.

Several practices have since contracted with NCODA and started the formal accreditation process, including Mission Cancer & Blood in Des Moines, Iowa, Urology Cancer Center in Omaha, Nebraska, New York Oncology Hematology in Albany, New York, and New Jersey Hematology Oncology Associates in Brick, New Jersey.

Visit **Page 8** to view a comprehensive list of practices committed to starting the program in 2022.

And while NCODA CoE MIP Accreditation currently focuses on oncology, we are planning to expand it into a multispecialty accreditation by year's end.

INFORMATICS INITIATIVE

Finally, NCODA has partnered with health information technology company XIFIN, Inc., to launch our **Informatics Initiative**, offering XIFIN's new healthcare platform VisualStrata® as a complimentary service to all NCODA members.

Developed over the last four years in collaboration with NCODA member practice Utah Cancer Specialists, VisualStrata® is designed to meet the unique needs and challenges of oncology practices.

This intuitive platform integrates, organizes and collates data from a practice's electronic health record, laboratory information and practice management systems and other "data silos" into a simple electronic dashboard.

Users can quickly and easily view relationships between patient populations, disease states, treatment options, financial considerations and a myriad of other variables — with the option of "drilling down" to individual data points — all at the touch of a finger. The system offers extraordinary potential to improve both the quality of patient care and practice efficiency.

Yet, this is just the beginning.

By sharing clinical data through NCODA's Informatics Initiative, the power of this platform will grow exponentially for all participants.

That's because in the new world of precision and personalized medicine, data is important. And by working together, we can utilize that data to improve patient care.

Michael J. Reff, RPh, MBA
Executive Director & Founder | NCODA

BE THE MATCH®

NCODA

ENDING BLOOD CANCER *STARTS WITH US*

TOGETHER WE CAN MAKE A LIFE-SAVING IMPACT

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 NCODA 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 281 new registry members and raised over $27,300.

Emily, stem cell donor, with her Dad, Bob, former stem cell transplant recipient

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.

STRIVING TO LOWER TOTAL COST OF CARE ON A GLOBAL SCALE

BeiGene is committed to a thoughtful approach to drug pricing and is looking to partner with access stakeholders across the US healthcare ecosystem

- We engage customers in meaningful partnerships that drive access and affordability
- We focus on bringing important new medicines to areas of high unmet need
- We believe in demonstrating and proving value through HEOR and real-world customer data

How can BeiGene help bring value to you? Learn more about BeiGene at BeiGene.com and the treatment areas we are focused on at BeiGeneVirtualExperience.com.

BeiGene MARKET ACCESS