ONCOLYTICS TODAY

EMPOWERING THE MEDICALLY INTEGRATED ONCOLOGY PHARMACY PRACTICE | FALL 2022

SPECIAL EDITION

TARGETING BREAST CANCER

COVERAGE BEGINS ON PAGE 50

REFERRALS MADE FROM PATHOLOGY DRAMATICALLY IMPROVE CANCER CARE
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EVERYTHING YOU NEED TO KNOW ABOUT BIOSIMILAR INTERCHANGEABILITY
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IDENTIFYING TIME TOXICITY: WHEN HOURS OF TREATMENT OUTWEIGH QUALITY OF LIFE
PAGE 73

NCODA

NCODA.ORG

Did You Know Keeping Hct <45% Is Critical for Patients With Polycythemia Vera?

In the CYTO-PV study in patients with polycythemia vera (PV), elevated hematocrit (Hct) between 45% and 50% was associated with a 4-fold higher rate of cardiovascular death and major thrombosis, compared with Hct <45%.[1]*

Quality Initiatives May Help Manage Patients With PV

Recent Quality Initiatives (QIs) are centered around keeping track of symptoms, decreasing the risk of disease complications, and focusing on monitoring lab values for patients with PV in order to determine if revisions in their care plan are necessary.[2]

MPNQuality.com offers QI resources for your practice:

Implementing Quality Initiatives

- MPN overview
- Perspectives on QIs from other practices
- Implementation tips

Perspectives on Quality Initiatives

- Best practices videos from experts and peers

Resources for Pharmacists and Practice Administrators

- Videos and downloadable PDFs that address implementation needs

Implementing QIs Affords the Potential for Impact on Quality of Care

"We need to make sure that we are aware of aspects of diseases for cancers we don't see everyday. And that elevates the importance of implementing a quality initiative for patients with MPNs, specifically MF or PV."

—Michael Reff, RPh, MBA, Founder and Executive Director of NCODA
ncoda.org

SCAN TO VISIT SITE

Visit MPNQuality.com for helpful peer perspectives on implementing a QI in your practice.

*In the CYTO-PV study of 365 adult patients with PV treated with phlebotomy, hydroxyurea, or both, patients were randomized to 1 of 2 groups—either the low-Hct group (n=182; with more intensive therapy to maintain a target Hct level <45%) or the high-Hct group (n=183; with less intensive therapy to maintain a target Hct level of 45%-50%). Baseline characteristics were balanced between the groups. Approximately 50% of patients had received an initial diagnosis of PV within 2 years prior to randomization; 67.1% of patients (n=245) were at high risk because of age ≥65 years or previous thrombosis. The composite primary endpoint was the time until cardiovascular death or major thrombosis.[1]

CYTO-PV=Cytoreductive Therapy in Polycythemia Vera; MF=myelofibrosis; MPN=myeloproliferative neoplasm.

References: 1. Marchioli R, Finazzi G, Specchia G, et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med.* 2013;368:22-33. **2.** Emanuel RM, Dueck AC, Geyer HL, et al. *J Clin Oncol.* 2012;30(33):4098-4103.

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

$10,386,824

Waste

$13,837,001

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

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

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TARGETING BREAST CANCER

A possible paradigm shift in HER2 therapy, new role of TKIs, clinical updates, integrating the ASCO/NCODA Patient-Centered Standards and archery as therapy

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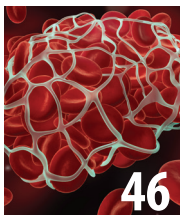
REGULAR SECTIONS

FEATURED ARTICLES



Oncolytics Today

PUBLISHED BY THE
NATIONAL COMMUNITY ONCOLOGY
DISPENSING ASSOCIATION, INC.

FALL 2022 | VOLUME 4, NO. 2

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

NCODA SPECIAL EDITION: TARGETING BREAST CANCER FOCUSES ON THE LATEST THERAPIES

Welcome to the Fall 2022 issue of *Oncolytics Today*, your source for the latest news on oral oncolytic approvals, indications, clinical studies and patient success stories, as well as updates on NCODA's new and existing initiatives.

In this issue, we take a special look at a variety of new treatments that are impacting breast cancer:

▲ **Jessica Warner**, PharmD, reports on fam-trastuzumab deruxtecan-nxki (ENHERTU®) and its potential to facilitate a paradigm shift in the treatment of HER2-low expressing breast cancer.

Randy Erickson

▲ **Ashleigh Cheikelard**, PharmD, and **Kaetlyn Parker**, PharmD, discuss the role of tyrosine kinase inhibitors (TKIs) in HER2-positive breast cancer, including treatment recommendations and management of TKI side effects.

▲ **Colleen Bohnenkamp**, PharmD, BCPS, BCOP, provides an update on (neo)adjuvant treatments for non-metastatic breast cancer.

▲ A new Canadian study showcases the impact of the **ASCO/NCODA Patient-Centered Standards for Medically Integrated Dispensing** on cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) treatment use in women treated for advanced breast cancer.

▲ And, finally, **Alejandro Arango Rueda** talks about Pink Archers, an archery program created at Infanta Leonor University Hospital in Madrid, Spain, which provides therapeutic relief from lymphedema for women who have undergone mastectomies.

Coverage on our special section, **Targeting Breast Cancer**, begins on **Page 51**.

ALSO IN THIS ISSUE

As always, *Oncolytics Today* also features coverage on a wide variety of other NCODA news and cancer-related topics.

▲ The annual **NCODA Oncology Institute** turned out to be an enormous success, with more than 250 industry professionals attending this year's event Aug. 16-17 in Indianapolis.

The institute covered a wide range of topics, including tips on how industry partners can collaborate with practice leaders, proposals for addressing disparities in the oncology landscape, a look at how the Inflation Reduction Act of 2022 is likely to have a negative impact on both practices and patients, and extensive discussion about the negative impact that pharmacy benefit managers (PBMs) have on patients.

A recap of the 2022 NCODA Oncology Institute begins on **Page 7**.

▲ Disparity in healthcare, particularly cancer care, has been a long-overlooked issue, and one that NCODA strives to spotlight.

Porscha Johnson, PharmD, CPGx, takes a look at racial exclusion in cancer clinical trials, and how the populations most in need of treatment are being left behind.

An article identifying the barriers to clinical trial inclusion and methods to overcome them begins on **Page 23**.

▲ A pilot program designed to increase access to cancer support services is showing promise at a Southern California hospital.

Inadequate referrals to the facility's cancer center were causing many patients to "fall through the cracks." A new pathology-based referral system that focuses on early referrals has dramatically improved patient access.

Dallas Lawry, DNP, FNP-C, OCN, highlights both the program and its potential impact on cancer care on **Page 18**.

▲ TKIs targeting the BCR-ABL protein have significantly improved survival for adult patients with acute lymphoblastic leukemia (ALL), a rare cancer with an increasingly poor outcome for the elderly. Coupled with corticosteroids, they offer a potential chemotherapy-free treatment for patients that do not tolerate intensive chemotherapy well.

Emily Dworkin, PharmD, BCOP, and **Jessie Signorelli**, PharmD, BCOP, provide an overview of treatments utilizing dasatinib and ponatinib on **Page 38**.

▲ Although the basic treatment of cutaneous melanoma (CM) has not changed significantly over the past few years, new treatment options and strategies continue to be developed.

Dane Fritzsche, PharmD, BCOP, **Andrew Ruplin**, PharmD, and **Stephanie Pang**, PharmD, provide an extensive report on current therapies and new combinations involving medications and/or immunotherapy for CM as well as uveal melanoma starting on **Page 87**.

We hope you will find this issue of *Oncolytics Today* insightful as well as inspirational.

It's just one of the many tools NCODA offers to fulfill our promise to provide educational resources that positively impact healthcare professionals and the patients they serve.

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

More than 250 industry professionals from over 70 companies attended the 2022 NCODA Oncology Institute from August 16 to August 17 in Indianapolis.

MORE THAN 250 PROFESSIONALS ATTEND 4TH ANNUAL NCODA ONCOLOGY INSTITUTE

Representatives from more than 70 different companies turned out for NCODA's fourth annual Oncology Institute, "Understanding the Challenges Oncology Patients and Practices Face Today: Engaging Partners in Shaping Our Future Together."

The Institute, from August 16 to August 17 in Indianapolis, featured a full day of presentations led by administrators, physicians, nurses, pharmacists and other professionals affiliated with NCODA. Topics discussed included:

- How Industry Partners Can Collaborate with Practice Leaders;
- Innovation in Pharma;
- Addressing Disparities in the Oncology Landscape; and
- Other sessions designed to better integrate the partnership between the pharmaceutical industry and healthcare providers.

The leadoff session, "Oncology 301: Business of Oncology and Treatment Education," was hosted by **Ray Bailey**, BPharm, RPh | Florida Cancer Specialists, **Meg Butler**, PharmD | Clearview Cancer Center and **Kelli Heathman** | BeiGene.

The panel kicked off the presentation with a discussion of how copay accumulators and maximizer programs implemented by pharmacy benefit managers (PBMs) are affecting patient benefits, drug prices and practice effectiveness.

Kelli Heathman

"We've seen copays for patients go from $100 or $200 to over $1,300 because the PBMs and the plans have figured out a way to really optimize our support programs to benefit them and not the patient," Heathman said.

"With the accumulators, since the patients can't afford the copay, then adherence becomes a problem. Patients drop off, they fall off their medication ... if adherence becomes a problem, then patients are probably going to end up progressing. And then they end up no longer taking their medication."

Drug discontinuation, in turn, has cut into the PBM revenue stream, Heathman explained, prompting the industry to create maximizer programs that force patients into specialty pharmacies "to avoid exorbitant out-of-network fees that they really shouldn't have in the first place."

One key difference between the two programs is that copay accumulators (now banned in 14 states) base patient deductibles and maximum out-of-pockets on list price, while maximizers base their prices on the maximum amount of the manufacturer copay card.

Bailey noted that NCODA sees federal and state legislation as a key deterrent to

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ONCOLOGY INSTITUTE

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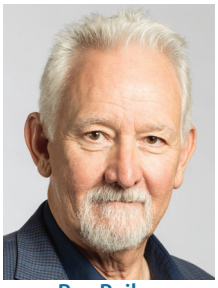
current and future PBM abuse.

"There are now groups going to large employers and selling plans where you don't have specialty drug coverage unless you fail to get free drug coverage through the pharma program," Bailey said. "Free drug programs should be a last resort. That is very troubling to me."


Ray Bailey

The panel also provided a summary of Medicare's new Enhancing Oncology Model, a discussion on the challenges of value-based contracts and an overview of total cost of care.

COLLABORATING WITH INDUSTRY

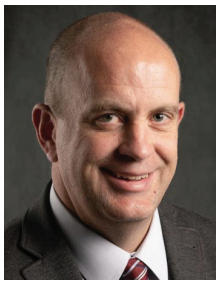
Sonya Taylor, MBA | GSK led a discussion on how industry partners can collaborate with practice leaders with **Marie Garcia**, RN | Virginia Cancer Specialists, **Kyle Kitchen**, PharmD | Utah Cancer Specialists and **Barry Russo**, MBA | The Center for Cancer and Blood Disorders.

Garcia talked about the "Great Resignation" and the challenge of finding, hiring and training new, mostly inexperienced, oncology staff. By working with company representatives, she was able to schedule non-branded oncology education opportunities en masse to new nurses, pharmacists and technicians.


Marie Garcia

"We polled our staff about what their needs were and they wanted more structured education," Garcia said. "They wanted to be pulled out of staffing for the day, and know that we were investing in their education."

Kitchen echoed Garcia's comments on staff turnover in the post-COVID era, noting that hiring and staff retention has now surpassed payer issues as his practice's greatest challenge.


Kyle Kitchen

"There certainly is a lot of opportunity and need for oncology education," Kitchen said. "There's a great opportunity for industry partners to get involved ... there will be a need for speakers."

Staff burnout is another closely related issue.

"We need to help staff stay interested in their jobs, reinvent themselves, have educational opportunities and just feel appreciated," Kitchen said. "I've seen industry participate in nursing appreciation weeks. They'll do special things for the nurses to help them feel appreciated. I haven't seen as much of that in pharmacy, so there's an opportunity ... a chance to show us a little love."

Russo noted that it is essential for practices to understand a new drug's impact on total cost of care.


Barry Russo

"I can't emphasize that enough," Russo said. "If you have a new drug, a new indication ... does your drug reduce in-patient utilization? Do you have data that shows that? Does you drug reduce the overall cost of care, and do you have data to show that? Because we're taking a risk financially to use your drug."

HEALTHCARE DISPARITIES

Disparities in healthcare was another hot button topic at the Institute.

According to the American Association of Cancer Research (AACR), 34% of all cancer deaths could be prevented if socioeconomic disparities were eliminated.

By the AACR's reckoning, eliminating healthcare disparities for racial and ethinic minorities would have saved $230 billion in direct healthcare costs and more than $1 trillion in premature deaths and illnesses between 2003 and 2006.


Kashyap Patel

"Every year we lose about 230,000 Americans to something that can be prevented," said presenter **Kashyap Patel**, MD | Carolina Blood and Cancer Care Associates. "So by the time we are done with this conference, 800 or 900

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MORE THAN 70 COMPANIES REPRESENTED AT FOURTH ANNUAL ONCOLOGY INSTITUTE

The NCODA Oncology Institute was created to help establish a more collaborative relationship between medically integrated oncology practices, their industry partners and NCDOA.

More than 250 industry professional from over 70 companies attended this year's Oncology Institute. Companies represented included:

AbbVie, Acentrus Specialty, Acrotech, Adaptive Biotechnologies, ADC, AmerisourceBergen, Amgen Oncology, Apellis Pharmaceuticals, AstraZeneca, Aveo Oncology,

Bayer, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Carolina Blood and Cancer Care Associates, Clearview Cancer Institute, Daiichi Sankyo, Eisai, EMD Serono, Epizyme, etectRx, Exelixis, Florida Cancer Specialists & Research Institute, Fresenius Kabi,

G1 Therapeutics, Genentech, Gilead, GSK, Helsinn, Incyte, Ipsen Biopharmaceuticals, Jazz Pharmaceuticals, Karyopharm Therapeutics, Kyowa Kirin, Lilly Oncology, MacroGenics, MEI Pharma, Merck & Co., Mirati Therapeutics, Myovant, New Mexico Cancer Center, Norton Cancer Institute, Novartis,

OSF HealthCare, Palm Beach Atlantic University Gregory School of Pharmacy, PatientPoint, Pfizer, Pharmacosmos, Pharmacyclics, PharmaEssentia, Pontchartrain Cancer Center, Puma Biotechnology, Rigel, Sanofi Genzyme, Servier, SpringWorks Therapeutics,

Stemline Therapeutics, Taiho Oncology, Takeda Oncology, Tennessee Cancer Specialists, Texas Oncology, The Center For Cancer And Blood Disorders, University of Minnesota College of Pharmacy, Utah Cancer Specialists and Virginia Cancer Specialists.

ONCOLOGY INSTITUTE

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Americans will not be alive that otherwise would."

"This is what's keeping me awake as a care supporter, as a public health worker, as a published health expert and as someone with compassion," Patel said.

The economic argument to end healthcare disparity is equally strong, he noted. "The $230 billion that could have been saved in 2003-2006 could be three or four times as much now with the newer treatments."

For cancer-related illnesses, rates of incident and mortality among Blacks exceed that of Whites in nearly all categories. Social Determinants of Health (SDOH) — where you were born, work, etc. — are a major factor in these disparities, as are lack of research in non-White Next Generation Sequence (NGS) and other research, lack of screening and lack of trial access, as well as financial toxicity and payer-related issues.

Patel detailed strategies in his efforts to obtain effective, affordable healthcare for minority cancer patients. These included providing screening for 400 patients who lacked the option, raising $2.3 million to help cover out-of-pocket costs or obtain free drugs, supporting a pilot to identify gaps in germline testing and participating in three large studies with expanded NGS testing.

LEGISLATIVE CONCERNS

Barbara McAneny, MD | New Mexico Cancer Center, discussed the potential impact of the Inflation Reduction Act of 2022 during an update presentation on current bills and legislation affecting healthcare and oncology.

Barbara McAneny

Under the new law, Medicare will be able to negotiate prices for Part B and Part D drugs. A total of 100 single-source drugs that have been on the market for at least nine years will be targeted between 2026 to 2031. Manufacturers will be penalized if prices rise faster than inflation. Part D out-of-pocket will be capped at $2,000 in 2025. Catastrophic cost sharing will be reduced to zero in 2024.

While the legislation may sound great to the voters, its consequences on medical practices will be severe, McAneny said. According to an analysis by a healthcare consulting company Avalere Health, practices can expect to see a 39.8% reduction in Medicare add-on payments for Part B drugs. Oncology practices can expect a reduction of 42.9%.

"This is going to be a significant impact, and there are some unintended consequences," McAneny said. "There's going to come a day when I buy a drug and a pay manufacturer's price ... and the next day the drug board is going to decide to pay me significantly less, that their Maximum Fair Price is going to be lower than what I would have paid for the drug."

"So, who's hurt in that scenario? The practice is. Does it hurt the manufacturer? No, they got paid. So, unless I'm crazy, I'm not going to be buying that drug when I'm going to lose $1,000 a dose. So, when I stop buying that drug, particularly in a small market like New Mexico, the person who is most going to be hurt is going to be the patient who needs that drug."

"So, we need to work together to let Congress know that this may be a mistake," she noted, and that it should instead focus on "low-hanging fruit" such as PBM regulation.

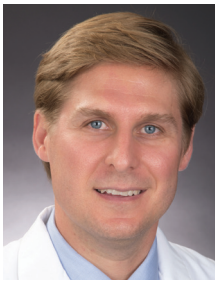
ATTENDEE REACTION

Industry participation in the Oncology Institute has grown steadily, with attendance at this year's conference increasing by nearly a third over last year's event.

Michelle Taymuree

"NCODA's Oncology Institute (OI) is such a unique conference as it is tailored to teach the pharmaceutical industry how best to partner with oncology professionals, said **Michelle Taymuree**, PharmD, MBA | Epizyme, an Ipsen Company. "The call for real-world evidence and diversity in clinical trials were some of the highlights of the conference, in my opinion. The OI proved once again to be an incredibly valuable experience both personally and professionally."

Stephen Schleicher, MD, MBA | Tennessee Oncology, was equally enthused about the program.



Stephen Schleicher

"This was my first OI experience and I was blown away!" Schleicher said. "The topics discussed and experts in the room — ranging from physicians, pharmacists, practice leaders, and pharmaceutical representatives — created a wonderful chance for us to all learn from each other. I'm looking forward to the next one!"

Finally, **Sonya Taylor**, MBA | GSK and NCODA 2022 Oncology Institute Co-Chair, lauded the 1.5-day event for providing both educational and networking opportunities.

Sonya Taylor

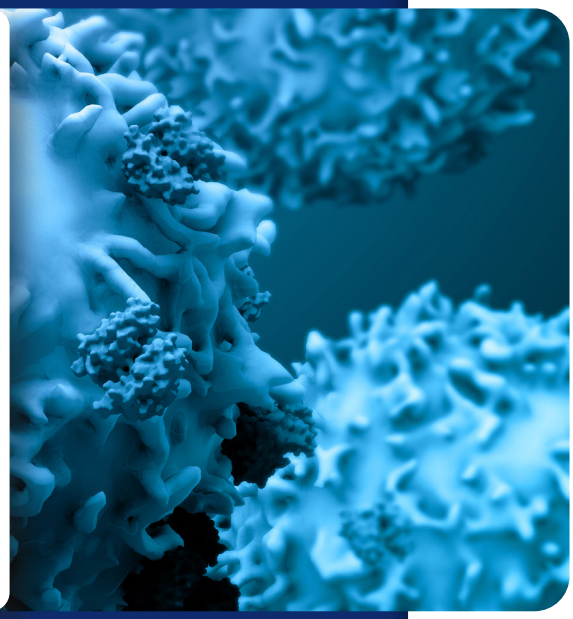
"I really enjoyed the networking reception, where industry attendees can meet new people or reconnect with old colleagues, and the panel discussions, where industry can engage with practice leaders on everything from patient care to healthcare policy," Taylor said.

"Attending the Oncology Institute is a must for all industry partners in oncology who want to stay up to date on healthcare trends, and learn more about how to collaborate with leaders who are transforming patient care and the patient experience."

Brukinsa®
80 mg
zanubrutinib capsules

ZANUBRUTINIB (BRUKINSA®) IS INCLUDED AS A CATEGORY 1 PREFERRED TREATMENT OPTION

for front-line and previously treated Waldenström macroglobulinemia (WM) in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*†



BRUKINSA is a treatment option with demonstrated efficacy and safety benefits for patients with WM

To learn more about the Bruton tyrosine kinase (BTK) inhibitor BRUKINSA and all its indications, visit BRUKINSA.com

*As primary therapy or therapy for previously treated patients.
†Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma V.3.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 2, 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.**

INDICATION

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

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.

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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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 7% 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 coadministration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

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

SPECIFIC POPULATIONS

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

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

BeiGene MARKET ACCESS

Brukinsa® zanubrutinib 80mg capsules

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^{WMUT}*) 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 infestation	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
	Rash‖	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.
‖ 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 Higher %
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

[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)]*.

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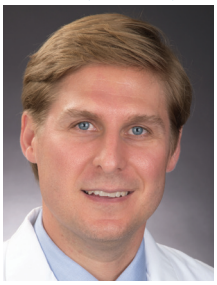
STATE-LEVEL LEGISLATION AGAINST PBM REFORM: AN EXAMPLE FROM TENNESSEE

By Carolyn Kelsey, Stephen Schleicher, MD, MBA, & Mahsa Talbott, PharmD

As a large percentage of novel cancer treatments have shifted from intravenous to oral administration, patients have become increasingly impacted by the role of pharmacy benefit mangers (PBMs) in their care.

Carolyn Kelsey



Stephen Schleicher

Mahsa Talbott

One common burden for patients is steerage, whereby they may be required to use a PBM-selected (and often PBM-owned) mail-order pharmacy, causing additional burdens and gaps in patient care.

At Tennessee Oncology, a large community practice spanning 35 clinics across Tennessee and North Georgia, patients can receive their oral cancer medications from Park Pharmacy, Tennessee Oncology's medically integrated pharmacy (MIP) specializing in cancer care.

The Park Pharmacy team consists of pharmacists, technicians, nurses and advocates that have access to the patient's electronic medical record (EMR). This allows the pharmacist to follow the patient from their cancer diagnosis and throughout the course of treatment.

The team at Park Pharmacy provides comprehensive and coordinated cancer care by evaluating pertinent patient-specific labs, reviewing current medication list, completing prior authorizations, obtaining copay assistance, providing initial patient education and completing monthly adherence calls.

Pharmacists also have real-time access to the clinical record to monitor any changes in clinical status, such as changes in weight, labs, and active medications. As part of the unified patient care team, pharmacists document patient education, adherence/nonadherence updates, side effect management, and outcomes and interventions within the EMR.

This collaborative and open relationship between Park Pharmacy and physicians allows continuous dialogue to optimize patient care. Park Pharmacy's oral adherence metric rate is 95.2%, and the average turnaround time from script receipt to medication fill is less than two days.

Park Pharmacy is fully accredited in Specialty Pharmacy by the Utilization Review Accreditation Commission (URAC) and the Accreditation Commission for Healthcare (ACHC), and has a 30-member team dedicated to Tennessee Oncology patients.

RESISTANCE FROM PBMs

Yet PBMs continue to block Park Pharmacy and other pharmacies from participating in their networks, and instead often require patients to use their affiliated pharmacies.

The following examples demonstrate the patient and provider frustrations, as well as illustrate why new laws are needed.

▲ Following completion of chemotherapy, a 50-year-old patient with Stage III rectal cancer was seen by his Tennessee Oncology physician. The patient was scheduled to begin curative radiation concomitantly with an oral radio-sensitizing therapy the following week. The order was entered, the prescription was presented to Park Pharmacy the same day. The patient was contacted, and the prior authorization was completed within 24 hours.

When the claim was submitted to the PBM, however, Park Pharmacy had to inform the patient that, due to insurance mandate, his prescription would have to be transferred to the pharmacy required by the PBM. Even with the prior authorization already in place, there was a delay in the external pharmacy contacting the patient, coordinating payments and shipments. When the patient finally received his medication two weeks later, he had already completed five radiation treatments without it.

▲ A 49-year-old patient with metastatic breast cancer was prescribed a CDK4/6 inhibitor, while waiting on a clinical trial to open. Upon receipt of the prescription, Park Pharmacy's patient advocate team began the process of obtaining a prior authorization, which according to their insurance would take at least 10 days. The technicians at Park Pharmacy proactively activated a manufacturer free trial, and the patient was able to begin her first cycle therapy the next day while waiting for the prior authorization to be approved.

Yet once the prior authorization was approved, the patient was forced by their PBM to use an outside pharmacy. Park Pharmacy transferred her prescription with approved prior authorization in place to the mandated specialty pharmacy for her second cycle. The patient did not receive her medication from the PBM specialty pharmacy in time to begin her second cycle therapy. This patient progressed and was later prescribed another medication, which also had to

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LEGISLATION

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be filled at the same outside specialty pharmacy. She became so frustrated with the process of trying to receive this prescription that she opted to pay the out-of-network price and fill at Park Pharmacy.

▲ A 44-year-old patient with stage IV non-small cell lung cancer (NSCLC) harboring an anaplastic lymphoma kinase (ALK) rearrangement was prescribed an oral ALK inhibitor to treat her cancer. Park Pharmacy received the prescription and processed the prior authorization. The patient was forced to use an PBM-affiliated pharmacy. Park Pharmacy transferred the prescription to the PBM pharmacy, with the approved prior authorization and an activated manufacturer copay card to reduce patient's copay. The patient did not receive her medication until four weeks later, delaying initiation of therapy.

REGULATION & TRANSPARENCY LEGISLATION

Sen. Shane Reeves of Tennessee — who is also a pharmacist — witnessed "firsthand the negative impact on patients cause by modern PBMs."[1] In an effort to increase transparency and regulate PBMs and their unfair practices, the Tennessee State Legislature along with other states across the country have introduced and passed legislation to regulate and increase transparency for PBMs.[2]

With assistance from the Tennessee Oncology Practice Society (TOPS), the Tennessee Pharmacist Association, Reeves, physicians, patients and advocates across the state of Tennessee, a law was passed in 2021 to alleviate the amount of power the PBMs have over pharmacies and patients. Mitigating patient steerage was a primary pillar of this law.

Tennessee Oncology, along with other institutions and pharmacies in the state, began submitting cases to the Tennessee Department of Commerce and Insurance (TDCI) every time a PBM violated the new law, especially cases of forced patient steerage away from Park Pharmacy to PBM-owned pharmacies. Unfortunately, every case was challenged by a PBM. In the end, the law was unable to influence PBM behavior.

Two primary reasons for the law's lack of impact were its lack of specification on plans subject to the law — specifically, self-funded plans falling under the Employee Retirement Income Security Act of 1974 (ERISA) and a lack of enforcement power by TDCI.

Once again, Tennessee Legislators and advocates acted. The result was an amended bill that clearly defined covered plans (including those under ERISA) and added language to give authority to TDCI to regulate and penalize PBMs. This bill amendment overwhelmingly passed and was signed into law in May 2022 to take full effect Jan. 1, 2023.

Tennessee Oncology's pursuit of PBM reform is just one example. Similar anti-steerage efforts have occurred in Texas[3] and elsewhere.

For more information about NCODA's **Oncology Legislation Tracker**, scan the QR code above.

NCODA has created an Oncology Legislation Tracker to allow healthcare professionals to understand legislative efforts and challenges across different states so that we can all learn from each other.

In the end, a concerted effort by physicians, pharmacists and legislators is necessary to regulate PBMs and reduce the burden on our patients.

▲ **Carolyn Kelsey** is Program Director of Pharmacy Regulatory and Accreditation at Tennessee Oncology's Park Pharmacy in Nashville, Tennessee. **Stephen Schleicher**, MD, MBA, is Chief Medical Officer at Tennessee Oncology in Nashville, Tennessee, and an active member of the Tennessee Oncology Practice Society. **Mahsa Talbott**, PharmD, is the Senior Vice President of Pharmacy Services at Park Pharmacy.

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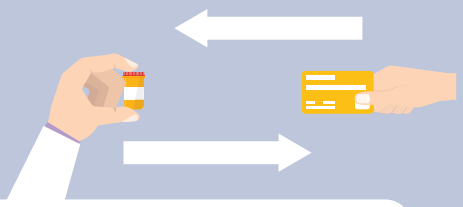
A concerted effort by physicians, pharmacists and legislators is necessary to regulate PBMs and reduce the burden on our patients.

COPAY ACCUMULATORS: WHAT TO KNOW

WHAT'S THE DIFFERENCE?

WITHOUT ACCUMULATOR PROGRAMS

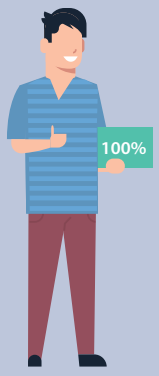


Patients with certain types of insurance can use manufacturer coupon cards to cover copays

0% 100%

Your Deductible

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



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

RECEIPT

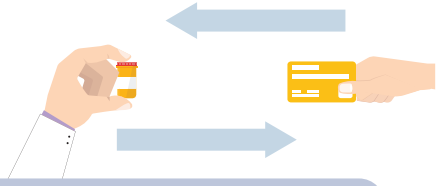
Prescription Drug Cost	$2,000.00
Manufacturer Coupon Value	-$1,995.00
Your Total at the Counter	$5.00

$2,000.00
Annual Deductible

$0.00
Remaining Deductible After Coupon*

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

WITH ACCUMULATOR PROGRAMS



Patients can still use their coupon cards but ...

0% 100%

Your Deductible

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

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

RECEIPT

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

$2,000.00
Annual Deductible

$1,995.00
Remaining Deductible After Coupon*

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

VS.

An example of what happens at the pharmacy counter

NCODA

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

LEGISLATIVE & POLICY ADVISORY COMMITTEE: EDUCATION ON CRITICAL ONCOLOGY LEGISLATION

By Nancy Egerton, PharmD, BCOP

In the summer of 2020, NCODA began exploring strategies to increase its legislative presence, including educating membership on issues that impact patients, physicians, pharmacists, nurses and anyone involved with the oncology community.

In order to achieve optimal success, NCODA was determined to form a committee of highly dedicated practice leaders who always put patients first and believed that legislative reform would positively impact the oncology landscape of the future.

Nancy Egerton

The NCODA Legislative & Policy Advisory Committee (LPAC) was founded in January 2021. LPAC began with eight members and has now grown to 12. LPAC members include:

- **Nancy Egerton** (Chair), PharmD, BCOP | New York Oncology Hematology
- **Holly Books**, BSN, RN, OCN | Texas Oncology
- **Barry Brooks**, MD | Texas Oncology
- **Eric Dallara**, RPH | Amerisource Bergen Specialty Group, Inc.
- **Ben Jones** | McKesson Specialty Health
- **Barbara McAneny**, MD | New Mexico Cancer Center
- **Jessica Nagro**, MPA | PhRMA
- **Wayne Ormsby**, MD | Utah Cancer Specialists
- **Debra Patt**, MD | Texas Oncology
- **Joy Pratt**, PharmD | Tennessee Cancer Specialists
- **Stephen Schleicher**, MD | Tennessee Oncology
- **Kevin Scorsone** | NCODA

The Legislative & Policy Advisory Committee's mission is to become the primary educational resource in the legislative oncology space.

The committee's mission is to become the primary educational resource in the legislative oncology space.

The LPAC is a non-partisan organization; at present it does not lobby for change. Its purpose is to keep NCODA members aware of the challenges, successes and progress encountered by state legislatures throughout the United States.

It strives to provide content to the NCODA membership that is both informative and purposeful, while raising awareness of critical legislation.

Content from the LPAC has become some of the most well-consumed information on the NCODA social media platforms and website.

At the time this article was written, the legislative affairs department of NCODA has released more 40 statements related to legislative activity. It plans to release approximately 50 statements by early 2023.

LPAC's Roundtable Webinar Series, which was launched in 2021, has provided NCODA members with easy access to legislative discussions.

The committee hosted its first onsite discussion at the 2021 Fall Summit, featuring a representative of the Arkansas Attorney General's Office who spoke on Pharmacy Benefit Manager (PBM) reform.

A similar event was held at the 2022 Spring Forum, with a panel discussion on PBM reform featuring John Driscoll, a former state representative from Washington.

LPAC's most ambitious project to date is the Comprehensive State Legislation Tracker. The tracker, which debuted in early 2022, provides:

- Detailed summaries of every legislative bill focusing on oncology and patient care in all 50 states;
- A detailed "why it matters" section to inform users as to how this impacts all parties involved; and
- A keyword section that defines basic and complex legislative terminology.

Additional improvements designed to give users a more impactful and comprehensive experience are planned for the coming months.

NCODA members can access the tracker on the NCODA website. Non-members can gain access by contacting Kevin Scorsone, NCODA Legislative & Policy Liaison, at kevin.scorsone@ncoda.org.

The LPAC efforts in 2022 are far from over. The legislative staff is continually speaking with student and professional organizations about NCODA legislative initiatives. More discussions and webinars will be available through the end of the year.

The committee hopes to continue the Legislative Interview Series that debuted this year on Apple and Spotify as a special edition of the PQI Podcast.

As always, feedback from NCODA members is vital to our mission. The committee wants to hear what matters to you, how it can positively impact your efforts and how legislative reform can improve patient care.

Nancy Egerton, PharmD, BCOP, is Director of Pharmacy at New York Oncology Hematology in Albany, New York.

REDESIGNING REFERRALS

INCREASING ACCESS TO CANCER SUPPORT SERVICES THROUGH UPSTREAM REFERRALS DIRECTLY FROM PATHOLOGY

By Dallas Lawry, DNP, FNP-C, OCN

Because cancer remains a leading cause of morbidity and mortality, oncology patients need supportive services throughout treatment and into survivorship.[1,2] Supportive services specific to cancer care include nurse navigation, social work consultation, psychosocial/socioeconomic support, nutrition, palliative care, and hospice.

Unfortunately, current literature and the COVID-19 pandemic revealed multiple barriers to accessing these types of supportive care.[3-5] Furthermore, the consequences of delayed access, or no access to supportive care, negatively impact healthcare outcomes for cancer patients and United States healthcare costs.[5-9]

Dallas Lawry

A needs assessment at a Southern California hospital revealed inadequate referrals to its cancer center via 19 different referral pathways. This long-standing unstandardized referral process has been inefficient and poses another "access-to-care barrier" in patients' abilities to receive cancer support services (Lawry, 2019).

Most notably, a majority of cancer center referrals came from patients themselves through walk-in-hours. The COVID-19 pandemic placed another novel barrier to accessing care with nationwide shutdowns of medical offices and social distancing regulations. With a majority of these patients historically referring themselves to the cancer center, COVID-19 had the potential to further delay or deprive patients of vital support services.

PROJECT PURPOSE

The primary barrier of this pilot project was simple: some cancer patients were not receiving these vital cancer support services by way of not being referred to the cancer center.

In 2017, the nurse navigator at this facility only saw 51% of the newly diagnosed cancer patients — exhibiting significant shortcomings in the referral process.[10]

Inadequate referrals to this cancer resource center were causing patients to "fall through the cracks" of the cancer care continuum, with future possibilities of poorer patient outcomes, decreased quality of life and increased healthcare costs.

This project aimed to redesign the referral program, attempting to ensure that every newly diagnosed cancer patient within the healthcare system was referred to the cancer center, guaranteeing access to vital supportive care. The primary intervention was implementing upstream referrals from pathology directly to the cancer resource center.

Participants included all newly diagnosed or cancer-recurrent adult oncology patients from the hospital's pathology lab. At the time of this publication, this is the first known report of referring patients to supportive care directly from pathology.

THE IMPORTANCE OF EARLY ACCESS

Because cancer centers often serve as the gateway to many of these services, delayed access to cancer centers can have a negative impact on patient outcomes.

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No literature was found directly evaluating the impact of not being referred to cancer center services as a whole. Instead, delayed referrals to each of these support services (i.e., hospice, palliative care, nutrition) were evaluated individually and are described in detail below.

Consequences of Delayed Treatment: In cancer care, time is of the essence. Late diagnostic and treatment referrals have proven to be detrimental.[11] One study reported that 45% of Stage 1 lung cancer patients that were presumed to be lower risk and in less dire need of a fast workup suffered a doubling in tumor size during the "watch and wait" period from diagnosis to referral to radiation therapy mapping. Data on late-stage presentation for initial cancer diagnoses is still being collected.[11]

Consequences of Delayed Nutrition Consults: Cancer patients have difficulty maintaining weight or adequate nutritional status during treatment. This can be further complicated by preexisting comorbidities or types of cancer that directly affect eating, such as head and neck cancer patients with dysphagia or pancreatic cancer patients with early satiety and malabsorption pathologies.

In addition, timely screening for cancer anorexia or cachexia that generates a nutrition referral is rare.[12] Malnutrition is associated with poor quality of life and worse clinical outcomes.[12] The placement of nutrition consults is recommended at the time of diagnosis,[13] and screening patients during "pre-cachexia" can address malnutrition while there is still time to intervene.[12]

Consequences of Delayed Palliative and Hospice Care: The literature makes a consistent and unanimous argument that palliative care consults occur too late and too close to death.[7,14] Late palliative care consults translate to aggressive treatment near the end of life in the form of increased emergency department visits, intensive care unit admissions and detrimental chemotherapy within weeks of death.[3,7,15] These result in an increased risk of dying in the hospital instead of at home.[3,5]

There is a scholarly consensus that early palliative and hospice services result in less burdensome medical interventions at the end of life, increase the quality of life at the end of life, and decrease the likelihood of dying within a hospital.[3,5] Improvements in the length of life and quality of life are both possible with earlier palliative care referrals.[5,7-9] Cancer centers help patients navigate end-of-life decision-making via advanced directives, and can refer to palliative care and hospice when appropriate.

Consequential Costs of Care Delays: Delaying or failing to refer oncology patients to cancer support services is contributing to morbidity and mortality nationwide and contributes to the national cost of medical care, especially in the form of increased costs from burdensome medical interventions at the end of life.[14,15]

As much as 12% of all United States healthcare dollars are spent on care at the end of life, with a quarter of the Medicare budget spent on beneficiaries' last year of life.[13] Common themes within the literature strongly suggest considerable cost savings with referring patients to services early, primarily to hospice and palliative care.[8,14,15] One study showed a nearly 50% decrease in the average cost and length of stay for patients receiving an early palliative referral.[8]

The current literature provides a robust argument for the importance of providing cancer support services to oncology patients and an even stronger argument for providing them early. Decreased healthcare costs, increased quality of life, improved treatment outcomes and ethical end-of-life decision-making are all benefits of referral to cancer support services.

PROJECT PURPOSE

The purpose of this project was to pair existing research on the benefit of early referrals to cancer support services with evidence-based interventions that improve referrals.

Automated referrals (i.e., flagging charts, electronic pop-ups that trigger providers to follow best practice guidelines) are described throughout the literature as a method of improving referrals.[16-26] The intervention of automatic, upstream pathology referrals presented in this project may be the first publication of its kind.

Ethical Considerations: This Doctor of Nursing Practice (DNP) scholarly project was deemed IRB exempt by two separate International Review Boards and was approved by the Quality Improvement Chair at the participating hospital. Patients were allowed to decline referrals to the cancer center. This project posed no more risk than that which occurs in everyday life.

PATHOLOGY REFERRALS AS A NOVEL REFERRAL PATHWAY

The pathology lab took on an innovative process of generating referrals from the lab bench, creating the most "upstream" referral route available. No studies exist that measure the feasibility or efficacy of initiating referrals to cancer support services directly from pathology. However, one study mentioned it as a possible way to improve referrals.[15]

INTERVENTION WORKFLOW

- A biopsy is performed and the pathologist makes a diagnosis of cancer;
- Pathology reports positive for malignancy now include a referral to the cancer center;
- Pathology generates a list of all pathology referrals and send it to the cancer center; and
- The cancer center's nurse navigator and social worker call these patients to establish care and offer supportive services.

Though pathology referrals are

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immediate, a lag time was in place to decrease patient anxiety and the potential of the nurse navigator reaching out to a patient before they have received news of cancer.

The goal was to establish telephone contact with patients about four to eight weeks after diagnosis, allowing time for appointments and an official diagnosis by a physician to take place.

PRE-PROJECT DATA

The most frequented service at this cancer center is the oncology nurse navigator, responsible for 32.2% of all points of contact at the cancer center in 2017.[10]

However, during this same year, the nurse navigator only saw or had phone conferences with 378 "new patients" out of the 741 "newly diagnosed" patients — roughly 51% of new cancer patients at this hospital.[10]

This means that the remaining half of newly diagnosed patients were not offered nurse navigation services. Newly diagnosed patients have no history with the cancer center, and therefore it is unlikely that they know it exists.

In past years, as many as 38% of patients were referring themselves to the cancer center annually, mainly by way of walk-in hours after chemotherapy infusions or radiation treatments.

With self-referrals being the highest frequency pathway, COVID-19 restrictions and the elimination of walk-ins had the potential to devastate referrals and the resultant patient care altogether. Referrals from pathology alleviated this novel stressor.

The project phase was six months in total, or two calendar year quarters of data (quarter four: 10/1/2020-12/31/2020, and quarter one: 1/1/2021-3/1/2021).

During these six months, California experienced its COVID-19 surge from December 2020 through January 2021. For the greatest possible accuracy and generalizability, quarters one and four were averaged and analyzed against the quarters that fell within this project's implementation phase.

METRICS DEFINED

Frequency distributions were conducted for all project measures. The metrics used to capture project success were:

- **Pathology referral compliance:** the percentage/number of cancer-containing pathology reports that now contain a formal referral to the cancer center out of all malignant (cancer-positive) pathology reports generated from the pathology lab.
- **Cancer center compliance:** the percentage/number of patients that receive a callback from the cancer center out of all referrals from pathology.
- **Nurse navigator statistics:** nurse navigator "points of contact" and how many referrals now come from pathology. This metric was the data available at the start of the project and includes the 19 referral pathways originally identified.

RESULTS

Pathology referral compliance improved from 3% (October 2020) to 68% (March 2021), with an average of 39.5% for the entire project phase. In total, over the six-month project period, 248 patients were referred to the cancer center and its resources through this DNP project and its novel pathology referral program.

Cancer center compliance: The monthly average for pathology referrals (patients) that received a callback from cancer center staff was 88% of eligible patients. This translates to 137 newly diagnosed or newly recurrent cancer patients offered supportive cancer services.

The discrepancy between the 248 referrals and 137 patient callbacks is justified by two factors: the built-in lag time, which accounted for patients pending callbacks, and patients that met exclusion criteria (children, current hospital admissions, previously established with the cancer center or passed away during the callback time frame).

Nurse navigator statistics: From 2017 to 2020 the average number of patients reaching the nurse navigator during quarter one (January- March) was 163, less than the 176 patients assisted or seen during the project phase quarter one.

This comparison from previous years to the final quarter of project data displays an overall increase in number of patients seen, also displaying an overall increase in the number of patients gaining access to cancer support services.

Lastly, where initially 0% of patients were referred to the nurse navigator by way of pathology because the process did not yet exist, as of March 2021, 39.6% of all referrals to the cancer center's nurse navigator came directly from pathology. This is clinically significant because in past years, as many as 38% of patients annually and 44% of patients quarterly referred themselves to the cancer center by way of walk-in hours.

As a result of this project, still in its infancy, at least 39.6% of patients are being referred from pathology, nearly matching the past statistic of self-referrals during a time when this historical leading pathway ceased to exist during the COVID-19 pandemic.

At six months, pathology referrals have become the leading pathway of referrals to the cancer center and have increased access to care for at least 137 cancer patients, with that number growing monthly.

IMPLICATIONS

COVID-19 restrictions, social distancing and the transition of services to a virtual platform made for very timely implementation of this project's digital referral system.

Pathology referrals circumvented the elimination of walk-in hours, and optimized callbacks via telehealth to serve the needs of patients at a time when face-to-face was prohibited by law.

Telehealth adjuncts, such as Zoom support groups and appointments,

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relieved any transportation stressors that patients may have experienced in the past.

The global pandemic strengthened this DNP project because pathology referrals prevailed through the shutdown, allowing patients continued access to vital cancer resources.

Upstream pathology referrals may eventually eliminate the need for all other forms of referral.

Other implications include:

Increased Access to Care: In six months, more than 200 patients gained access to cancer supportive services after being directly referred from pathology. By project completion, the nurse navigator was seeing more patients per quarter than the quarterly average from previous years, illustrating an overall increase in "patients seen."

Equity and Inclusion: As a result of this project, the cancer center began to see more patients diagnosed with head and neck cancer, prostate cancer, melanomas and gynecological malignancies. The sicker, perhaps more vulnerable patients, who did not historically refer themselves, were now automatically referred from pathology.

Patients who are health-literate, involved in the community, have relatives within the healthcare system, or have had a previous cancer diagnosis may have had increased access to the cancer center's resources simply by knowing of its existence. Pathology referrals provide equal opportunity to all patients referred, regardless of primary language, cancer type, cancer stage, insurance or other accessibility factors. It is unlikely that a newly diagnosed patient would have any knowledge of the cancer center, and this pathology referral program alleviated this inequity.

A Novel Referral Pathway: Starting as upstream as pathology in the cancer care continuum allows patients to receive care before problems occur during treatment or end-of-life decision-making. Pathology referrals are safe, feasible, cost-effective, and impactful. Referring patients to cancer centers directly from pathology has the potential to become a new best practice standard.

This project is the beginning of a larger conversation:

- **What is the impact of early access to cancer supportive services?**
- **Are there cost savings for early referrals to cancer centers in the form of decreased hospital admissions, decreased lengths of stay, or decreased burdensome treatment at the end of life in oncology patients?**
- **Do certain services, such as nutrition or palliative care, have high-yield positive outcomes when patients are referred earlier, perhaps as early as the moment of diagnosis from pathology?**
- **What are the quality-of-life implications?**

CONCLUSION

Because the "cure to *all* cancers" does not yet exist, patients living with and surviving cancer need cancer support services.

The adverse consequences of a late referral or underutilization of these services are many: malnutrition, increased healthcare costs, late-stage diagnosis or sub-optimal treatment, increased burden of medical management in hospitals towards the end of life and undermanaged side effects, resulting in inferior quality of life.

It is crucial that cancer patients receive these specialty services to decrease morbidity and mortality, and increase quality of life.

With the COVID-19 barrier of patients being unable to refer themselves, pathology referrals proved to be a feasible way to get patients to the cancer center, and furthermore, to cancer supportive services.

This project is closing the gap. If current trends continue, significantly fewer patients will fall through the cracks. Redesigning this referral process increased access to cancer support services and has the potential to set a new standard of offering services early in the cancer care trajectory: during the diagnostic phase.

In the future, this exemplary model of accessing early supportive care for oncology patients may prove vital in preventing oncologic complications that would necessitate hospitalization.

Though these findings are not displayed in terms of a cost-benefit analysis, this project has shed light on the risks of ignoring these needs, with a return on investment being the positive outcomes cancer support services have when patients are referred sooner.

This project is the beginning of a larger conversation: What is the impact of early access to cancer supportive services? Are there cost savings for early referrals to cancer centers in the form of decreased hospital admissions, decreased lengths of stay, or decreased burdensome treatment at the end of life in oncology patients? Do certain services, such as nutrition or palliative care, have high-yield positive outcomes when patients are referred earlier, perhaps as early as the moment of diagnosis from pathology? What are the quality-of-life implications?

The pathology referral program also has the potential for translation into other specialties that originate in pathology, like nephrology, rheumatology, and infectious disease.

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Limitations: This project occurred over a short time frame of six months, within one hospital system and one electronic medical record (EMR). It is important to note the COVID-19 impact on this data: fewer patients sought care, clinics closed, and biopsies were delayed. The outcomes of this project may be even more potent than they appear because of the COVID-19 variable.

Disclaimer/Disclosure: The opinion and conclusions presented herein are those of the author and do not necessarily represent the views of Loyola University New Orleans School of Nursing or Community Memorial Health System.

▲ **Dallas Lawry**, DNP, FNP-C, OCN, is an Oncology Nurse Practitioner at the University of California San Diego. She has dedicated this project to all pancreatic cancer patients, especially her late father, Scott Richard Lawry.

MORE INFORMATION ONLINE

To access the appendix to this project, including detailed charts and data, scan the QR code at right.

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THE UNDERLYING BIAS OF

PHARMACOGENOMICS

RACIAL EXCLUSION IN CANCER CLINICAL TRIALS HAS LEFT BEHIND THE POPULATIONS MOST IN NEED OF TREATMENT

Porscha Johnson

By Porscha Johnson, PharmD, CPGx

While research has led to profound advancements in cancer treatments — including antibody-drug conjugates and immunotherapy, as well as the utilization of pharmacogenomics to aim for precision medicine through gene-drug matched targeted therapy — there is a lack of representation in clinical trials for drug development for the very populations that need it most.

According to the American Cancer Society, Black people are projected to have approximately 224,080 new cancer cases and 73,680 cancer deaths in 2022. In contrast to their counterparts of any other racial/ethnic group within the United States, Black people are disproportionately subjected to the highest

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death rate and shortest survival for most cancers.[1]

Additionally, in certain situations, there is a double minority disadvantage: Black women are estimated to be 41% more likely to die from breast cancer, despite a lower incidence rate of this disease compared to White women.[1]

While the Black population undoubtedly has received the proverbial short end of the prevention, treatment and survivorship stick, it should be noted that Hispanics, Asian Americans and American Indians/Alaska natives often suffer a similar fate due to social determinants and racial disparities in clinical trials, as well as undeniable genetic variations.[2]

Clinical trial participation is vital for the expansion of scientific knowledge, as well as the improvement of patient outcomes as they ultimately determine safety and efficacy. However, it has been noted that very few adults enroll in cancer clinical trials.

Recent meta-analysis studies show that within the entire U.S. system, only an estimated 6.3% participated in these trials. Such enrollment was highest at NCI-designated comprehensive cancer centers (18.9%), while the treatment trial rates for community cancer programs (CCPs) and comprehensive CCPs were 4.4% and 3.6%, respectively.[3]

Strikingly, enrollment numbers are even lower for minorities. While less than 10% of those diagnosed with cancer participate in a clinical trial, almost three-fourths of those participants are White men.[3]

Clinical trials fail to inclusively represent the entire cancer treatment population, thereby forcing providers to unjustly extrapolate the provided data based on a majority White male population in attempt to fit those they serve.

Biologically, we simply are not made equally — whether it be men versus women or compounded with the variations throughout races. Therefore, an in-depth understanding and application of pharmacogenomics through increased minority genetic testing and clinical trial participation is fundamental for an all-inclusive treatment advancement approach towards true precision medicine.

BARRIERS

Ethically, we should all be striving to seek a change for the sake of our patients. However, to search for a solution, we must first understand the problem.

Inevitably, there is deep-rooted hurt and trauma resulting in the mistrust of the healthcare system by people of color. This hyperpigmented blemish derives from years of repetitive historical injustices of minorities and people of color, including:

- The North Carolina state government-funded eugenics program that sterilized Black females for population control;
- The misappropriation of Henrietta Lacks' now-infamous HeLa cells exploited in cancer-focused research amongst other medical discoveries without the consent of her surviving family members;
- The lead-poisoned water crisis that ravaged the majority Black-populated town of Flint, Michigan; and
- The global coronavirus pandemic that highlighted the disproportionate allocation of treatment and medical services for minorities resulting in a higher death toll.

Most notably, this year marks the 50th anniversary of the unveiling horrific details of the four-decade-long Tuskegee Syphilis Study led by the U.S. Public Health Service and the ongoing repercussions that followed for future medical encounters.[4]

OTHER FACTORS

While we must never make light of the horrid medical treatment history which has tainted the views of people of color, we should also be mindful of additional underlying contributors to racial/ethnic disparities and barriers to genomics inclusion in cancer clinical trials.

While Blacks and other minorities suffer an unbalanced share of cancer mortality, patients are holistically much more than their disease. Cancer disparities reveal the multifaceted connections between many factors which have an overpowering effect on cancer risk and patient outcomes — including social determinants of health, behavior, human biology and genetics.[5]

Certain individuals are more predisposed to cancer disparities due to their increased likelihood of encountering healthcare obstacles. Such potential impediments include financial limitations due to low incomes and limited paid medical leave, health literacy gaps, language barriers, restricted access to equitable healthcare, extensive travel distances to screening sites, unreliable transportation, exposure to harmful cancer-causing

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environmental conditions or food deserts due to historic redlining, clinical trial-excluding comorbidities, structural racism and health system wariness.[1,6]

As a result of residential segregation, majority Black and Hispanic areas are more likely to have restricted access to quality care. Therefore, people of color are often forced to heavily rely on community health centers, emergency room/outpatient care and community-based providers due to the lack of available primary care providers in a given geographic area.[7]

While traveling outside of the immediate geographic area to access healthcare may be an option for some people, this can prove to be a challenge for others due to lack of access to transportation for those with limited incomes or for those living in rural areas.[7]

The lack of Medicaid expansion in key states, health disparities and healthcare provider shortages make it incredibly hard to comprehensively address the healthcare needs of disadvantaged Americans.[7]

These populations are less likely to receive recommended cancer screening tests; and when paired with delayed seeking of medical attention due to mistrust in the medical community, they are more likely to be diagnosed with advanced-stage cancer compared to those who do not encounter these obstacles.

In addition, social issues such as dependence on others for childcare, caregiving and transportation for timed medical visits, labs and scans may create a higher probability for clinical trial protocol violations for enrolled patients.

Furthermore, inherited factors including germline mutations or somatic tumor aberrations suggest that there are differences in the genetics, tumor biology, and immune environment of individuals which may profoundly contribute to inequalities in incidence, aggressiveness, and response to treatment of certain cancers.[6]

While immunotherapy and other targeted therapies have undoubtedly revolutionized cancer care, we must encourage minority participation in biomarker testing for better informed treatment selection and increased enrollment in applicable clinical trials.

Oftentimes, being the only person of color serving as the cultural liaison for my patients is a glaring reminder that the healthcare profession has a long road to trudge in ensuring that patients can see glimpses of themselves from whom they seek care.

METHODS TO OVERCOME

Uncoiling the web of barriers begins with fostering cultural competency and eliminating both conscious and unconscious bias. Healthcare providers must employ empathy while recognizing that inherently, we all are not intrinsically engineered the same.

A team-based effort to incorporate diversity, equity and inclusion into training for healthcare professional students, residents, preceptors and providers is critical for attempting to level the playing field for those who are struggling to navigate our healthcare system.

When identifying strategic priorities moving forward, the recruitment process for clinical trials must be at the forefront, involving implementing methods to combat the hesitancy or limitations to participation.

One of the greatest contributing factors to disparities is the shortage of minority healthcare providers in these greatly affected communities.[7]

Oftentimes, being the only person of color serving as the cultural liaison for my patients is a glaring reminder that the healthcare profession has a long road to trudge in ensuring that patients can see glimpses of themselves from whom they seek care.

Minority healthcare providers tend to alleviate anxiety and instill assurance for people of color by offering a familiar and trusted face to speak with patients reluctant to pursue treatment, enroll in clinical trials or seek genetic testing. Ultimately, it is beneficial to have confidence that your healthcare provider can see your humanity and offer you the adequate treatment you deserve.

Organizations such as the American Society of Clinical Oncology (ASCO), in conjunction with the Association of Community Cancer Centers (ACCC), provide online assessment tools to assist research teams with identifying potential opportunities to increase diversity, equity, and inclusion in clinical trials by facilitating an internal review of existing policies, programs and procedures.[8]

The assessment results provide sites with strategies for improvement such as diversifying the workforce, developing sustainable community partnerships, implicit bias training, and routinely collecting screening and enrollment data to assess and address disparities. [8]

Additionally, the corresponding ASCO-ACCC Just ASK™ Training Program is an online implicit bias training program focused on increasing diversity in cancer clinical research.[8]

Reducing or eliminating cancer disparities in the pursuit of health equity will require healthcare policy changes and reform to overcome systemic social, racial, and/or institutional inequalities.[5,9]

In an attempt to prioritize minorities — especially in research — sponsoring pharmaceutical companies have begun to specifically inquire about the signing institution's minority programs/strategies

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as part of initial feasibility surveys for new clinical trials participation.

In order to overcome the enrollment hurdle in some minorities, reevaluation of clinical trial eligibility criteria is necessary to account for the number and gravity of coexisting health conditions, as well as lessening detriment to their families, employment and finances.

State Medicaid plans were among the last major forms of insurance in the United States that did not cover routine clinical trial expenses, discouraging many Medicaid enrollees from participation. The American Cancer Society Cancer Action Network (ACS CAN) has successfully led and advocated for state and federal legislation reform to ensure countrywide Medicaid coverage of these associated costs.[1]

ACS CAN is also urging the passage of the DIVERSE Trials Act, which would facilitate an increase in racial, socioeconomic and geographic diversity in clinical trials, as well as ease the financial burden of participants by granting trial sponsors permission to reimburse patients for ancillary costs, such as travel or lodging.[1]

These changes, along with state-driven expansion of Medicare reimbursement for pharmacogenomics, are the catalysts for proactive evaluation of polygenic risk scores, carrier status of certain enzyme deficiencies, and increased knowledge about the influences of polymorphic variations on treatment response to select oncolytics.

CONCLUSION

To truly practice at the height of their license, a provider must be an advocate, rather than part of the problem. It can be challenging to attract and enroll those who are traditionally underrepresented by ethnicity, race, socioeconomic status, genetic variations, especially those who are underserved in rural areas.

However, eliminating disparities in cancer by diversifying clinical trial participation should be an overarching goal for all healthcare practices for everyone to have a fair and just opportunity to live a longer, healthier life regardless of their inevitable differences. Such systemic metamorphosis requires extensive staff education.

Since social determinants truly do affect their outcome, it is critical for us to forgo preconceived assumptions while listening intently to seek understanding in determining the 'why not' when exploring clinical trials as a treatment option.

We as providers must comprehensively assess the home needs of each patient throughout their entire cancer continuum, including proximity to quality care, transportation, lodging, nutritional meals, childcare and family support/assistance.[10]

Since social determinants truly do affect their outcome, it is critical for us to forgo preconceived assumptions while listening intently to seek understanding in determining the "why not" when exploring clinical trials as a treatment option.[6]

Clinical utility of pharmacogenomics is the foundational key to health equity. Studies have proven that distinct ethnicity-related variations in genes and allele frequencies can influence the pharmacokinetics, efficacy, and safety of particular medications,[2] thus providers must account for these genomics implications during treatment selection.

Ultimately, the decision to seek identification of these genetic variants and act upon them has the potential to dramatically alter a patient's equitable access to clinical trials and overall treatment outcomes.

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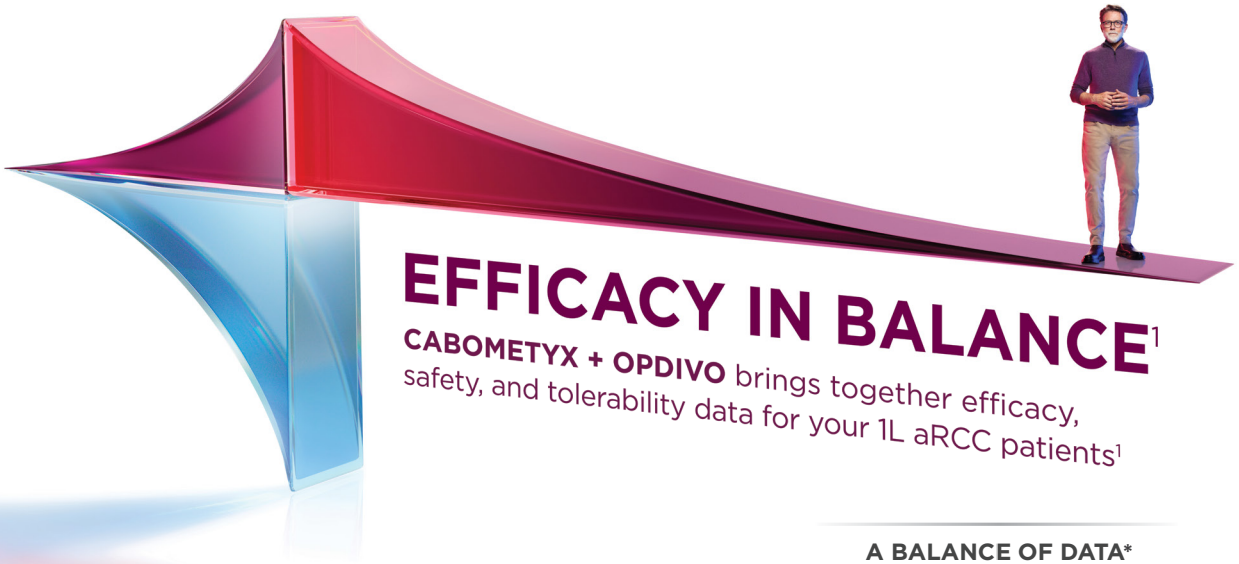
1L aRCC

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



EFFICACY IN BALANCE[1]

CABOMETYX + OPDIVO brings together efficacy, safety, and tolerability data for your 1L aRCC patients[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=objective 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 throughout and Brief Summary of the Prescribing Information for CABOMETYX on following pages.

Superior PFS and ORR results in the ITT population in the primary analysis[1]

Median follow-up time of 18.1 months; range: 10.6-30.6 months[2]

Primary endpoint

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)

Secondary endpoint

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.

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.

Early and sustained separation of OS curves in the primary analysis[1]

Secondary endpoint

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. An updated efficacy analysis was conducted when 271 events were observed based on the pre-specified number of events for the pre-planned final analysis of OS.

Final analysis of OS (median follow-up: 32.9 months; range: 25.4-45.4 months): Median OS was 37.7 months for CABOMETYX + OPDIVO (95% CI: 35.5-NR; n=323) compared with 34.3 months for sunitinib (95% CI: 29.0-NR; n=328); HR=0.70 (95% CI: 0.55-0.90).[1,6-7]

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; 2022. **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. **6.** Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(7):888-898. **7.** Data on file. Exelixis, Inc.

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

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CABOMETYX® (cabozantinib) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

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

1 INDICATIONS AND USAGE

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

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

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

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Renal Cell Carcinoma

METEOR

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

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

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

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

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

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

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

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

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

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

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

CABOSUN

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

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

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

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

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

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

CHECKMATE-9ER

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

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

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

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

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

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

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

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

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

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

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

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

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

[h] Includes primary hypothyroidism.

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

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis

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

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

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

Hepatocellular Carcinoma

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

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

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

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

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

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

[2] NCI CTCAE Version 4.0

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

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

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

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

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

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

Differentiated Thyroid Cancer

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

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

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

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

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

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

[2] NCI CTCAE Version 5.0

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

[4] Includes the following terms: fatigue, asthenia

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

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

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

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

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

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

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CABOMETYX

Strong CYP3A4 Inhibitors

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

Strong CYP3A Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

Infertility

Females and Males

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

8.4 Pediatric Use

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

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

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 07/2022

Distributed by Exelixis, Inc. Alameda, CA 94502

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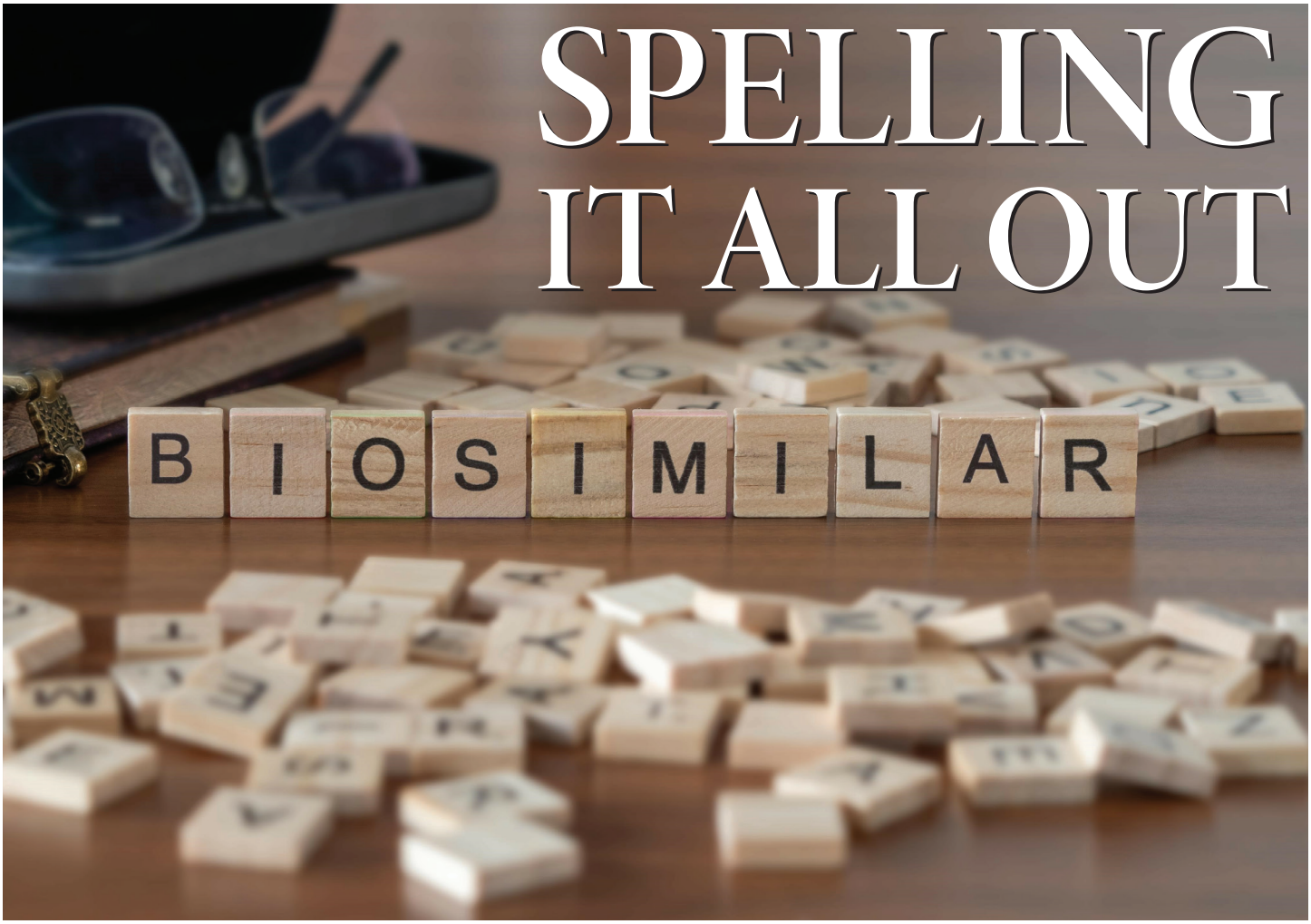
Printed in USA 07/2022 CA-1121-5



BIOSIMILAR INTERCHANGEABILITY IN THE U.S. & PRACTICAL CONSIDERATIONS

By Melody Chang, RPh, MBA, BCOP

Biological products are the fastest-growing class of medications in the United States and now account for 43% of total medicine spending in the United States.[1]

Since the passage of the Biologics Price Competition and Innovation Act (BPCIA) of 2009, biosimilars have created an abbreviated approval pathway to provide patients with greater access to safe, effective, and more affordable biologics.[2,3]


Melody Chang

The introduction and uptake of biosimilars will reduce biologic spending by more than $40 billion through 2026.

The largest impact is projected to occur in 2023, when top-selling prescription drug adalimumab (Humira), which generated $20 billion in sales in 2021, begins facing competition from its biosimilars.[4]

To date, there have been 37 biosimilars and three interchangeable approvals in the U.S. biosimilar market.[5]

This article will discuss what interchangeability is from a regulatory standpoint, and will look at the implication and practical consideration of biosimilar interchangeability.

WHAT IS INTERCHANGEABILITY?

The term interchangeable or interchangeability, in reference to a biological product that is shown to meet the standards described in section 351(K)(4) of the Public Health Service (PHS) Act, means that "the biological product

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INTERCHANGEABILITY

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may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product."[6]

This is called pharmacy-level substitution, such as generic drugs commonly substituted for brand-name drugs at a retail pharmacy, depending on state pharmacy laws. An interchangeable biologic must be a biosimilar, but not all biosimilars are interchangeable products.

Manufacturers seeking approval for an interchangeable product designation need to provide additional data to the U.S. Food & Drug Administration (FDA) in their application.

The interchangeability status will be granted if the FDA determines that the information is sufficient to show that the biological product is:

▲ Biosimilar to the reference product;

▲ Can be expected to produce the same clinical result as the reference product in any given patient; and that

▲ For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.[6,7]

The extent of additional data needed to support interchangeability will depend on a variety of factors, such as the complexity of the product or the products specific immunogenicity risk.

The FDA may assess data from a "switching study" in which subjects alternate between the reference product and the interchangeable product multiple times over a specific period. The switching arm is generally expected to incorporate at least two separate exposure periods (switch intervals) to each of the two products (i.e., at least three switches with each switch crossing over to the alternate product). The results must show no decrease in effectiveness or increase in safety risk associated with switching.[6,7]

The general rule is one reference product per application, and the first interchangeable biosimilar product will have the benefit of having one-year marketing exclusivity, meaning the FDA will not make a determination that the second or subsequent biosimilar is interchangeable for any condition of use until one year after the first commercial marketing of the first interchangeable biosimilar.[6]

PRACTICAL CONSIDERATIONS

To date, three interchangeable biosimilars have been approved by the FDA.

It is critical to provide retail pharmacists — who ultimately will be the key agents driving interchangeable biosimilar adoption as we approach 2023 — with tools and resources needed to effectively support the patient journey with biosimilars.

The first is Cyltezo®. Cyltezo® (adalimumab-adbm, Boehringer Ingelheim) was originally approved in August 2017. It is scheduled to go on the market on July 1, 2023, based on an agreement the company has with AbbVie, the producer of the originator product, HUMIRA®.[8,9]

The second is SEMGLEE®. SEMGLEE® (insulin glargine-yfgn, Mylan) was approved by the FDA in July 2021 and has been available on the market since then. It is both biosimilar to — and interchangeable with — its reference product Lantus® (insulin glargine, Sanofi-Aventis).[10]

The third is CIMERLI™. CIMERLI™ was approved August 2, 2022. It is a biosimilar to the reference product LUCENTIS®, an anti-VEGF used in opthamology.[11]

The interchangeability is more relevant for products dispensed in a retail pharmacy setting where automatic substitution is completed by pharmacists at the point of sale, without a prescriber's consent.[12]

The interchangeable designation will be more applicable to those products that are administered subcutaneously by patients themselves (i.e., adalimumab and insulin), dispensed from a retail pharmacy, and fall under pharmacy benefit.

Manufacturers have less interest seeking interchangeable status for oncology therapeutic products that are dispensed at the clinic where the prescriber is usually on-site or accessible, when the

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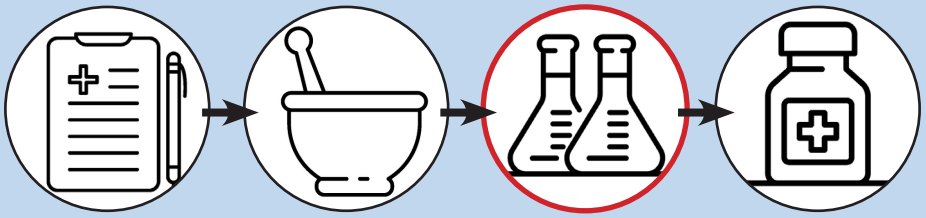
PHARMACY-LEVEL SUBSTITUTION OF INTERCHANGEABLE BIOSIMILARS



Source: The U.S. Food & Drug Administration

INTERCHANGEABILITY

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product is administered by a healthcare professional as an IV infusion, and when the product is reimbursed under the medical benefit.

STATE LAWS AND INTERCHANGEABILITY

The role of substituting drugs within the pharmacy is governed by state pharmacy laws which typically include features such as:

▲ How does the state define "interchangeable"?

▲ Does the prescriber have the option to opt out and to prevent substitution?

▲ Is the pharmacist required to notify the prescriber of substitution?

▲ Will the patient be notified that a substitution has been made?

▲ Will the pharmacy or the prescriber retain record of substitution? And for how long?

▲ Will the substitution only occur if the substituted product results in a lower cost to the patient?

Currently, all 50 states and the District of Columbia have laws pertaining to interchangeability. However, pharmacy laws and practices vary from state to state, including requirements related to provider notification/permission, patient communication, and documentation practices.[13]

SOLELY A REGULATORY DESIGNATION

Interchangeability is a regulatory designation, not a clinical designation.

Interchangeable status does not signify clinical superiority of a product.

Not all biosimilars are interchangeable products, but an interchangeable biologic must be biosimilar.

Just because the interchangeable product is required to have an additional switching study doesn't mean that it is safer or more effective than a biosimilar without interchangeable status.

Rather, interchangeability gives additional assessment toward regulating auto-substitution at the pharmacy level. It is unrelated to the biosimilar product's quality, safety and efficacy, which have already been established during biosimilar evaluation.[14,15]

In fact, according to updated FDA guidance, a comparative clinical immunogenicity study (i.e., switching study) may be unnecessary to support the demonstration of biosimilarity or interchangeability for biologic products such as insulin.[16]

Interchangeability is unique to the United States. The European Medicines Agency (EMA), which has been ahead of the FDA in terms of biosimilar approvals, does not make a distinction between biosimilars and interchangeable products. Rather, it has given decision-making authority regarding interchangeability or substitution to each national agency in its member states.[17]

Other major markets such as India, South Korea and China have developed their own regulations regarding biosimilars in recent years, but the interchangeability has not yet been addressed in their regulatory framework. In Japan, there are no regulations on interchangeability for biosimilars.[14,18]

SUMMARY

The year 2015 marked a milestone for the U.S biosimilar market when the FDA approved the first biosimilar, Sandoz's ZARXIO®.[19]

In 2021, the market moved into a new phase with three biosimilar products receiving interchangeability designation.

Interchangeability is a regulatory designation but not a clinical designation. The additional stamp of approval may help take the edge off the concerns from pharmacists working in the retail setting when auto substitution happens without a prescriber's consent.

The extent of the impact of interchangeability will still depend on payer coverage. However, it is critical to provide retail pharmacists — who ultimately will be the key agents driving interchangeable biosimilar adoption as we approach 2023 — with tools and resources needed to effectively support the patient journey with biosimilars.[20]

As for the physician's office, healthcare providers and patients can be confident in the safety and effectiveness of both biosimilar and interchangeable products, just as they are for reference products.

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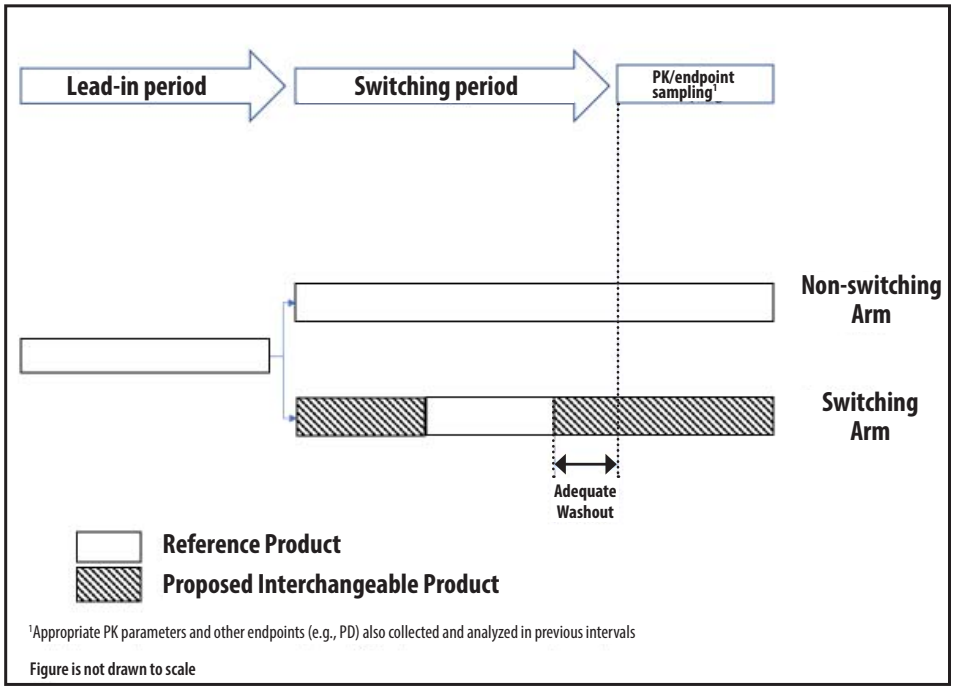
AN EXAMPLE OF A SWITCHING STUDY DESIGN



INTERCHANGEABILITY

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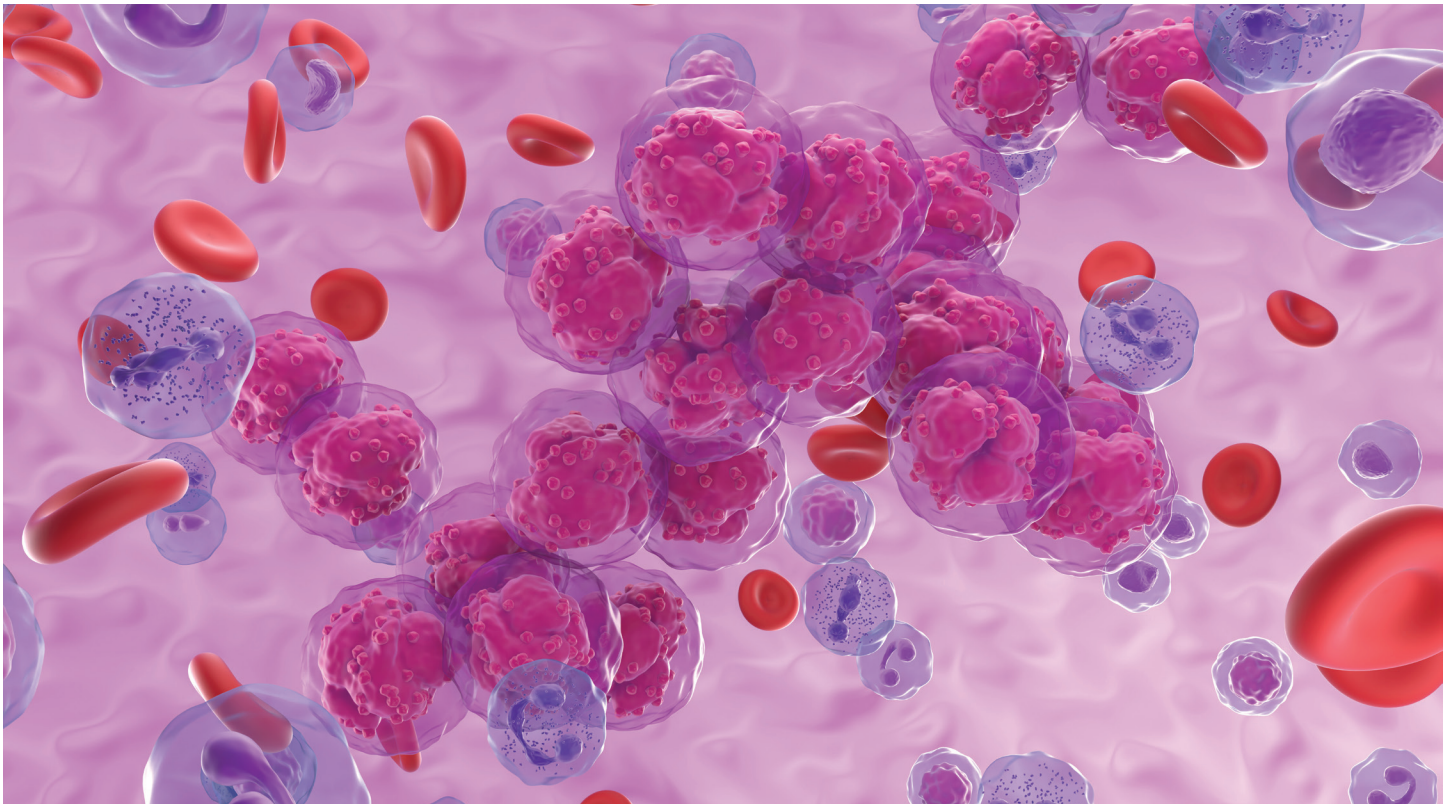

An isometric 3D illustration of acute lymphoblastic leukemia (ALL) cancer cell clusters in the blood.

A POSSIBLE CHEMOTHERAPY-FREE ERA FOR ACUTE LYMPHOBLASTIC LEUKEMIA?

By Emily Dworkin, PharmD, BCOP & Jessie Signorelli, PharmD, BCOP

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic malignancy that is defined by the unrestricted proliferation of lymphoblasts in the bone marrow and peripheral blood.[1]

It makes up approximately 0.3% of all new cancers and 0.3% of all cancer deaths in the United States, with an estimated 5,690 patients being diagnosed with ALL in 2021.[2]

The overall survival for patients with ALL drastically decreases by age, with five-year overall survival (OS) of 90%, 63%, 40%, 26% and 10% for patients < 15 years, ages 15-39 years, ages 40-64 years, ages 65-74 years and 75 years and older respectively.[2]

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Extramedullary disease is not infrequent in ALL with common reservoir sites including lymph nodes, testes and the central nervous system (CNS). In fact, more than 50% of patients will experience a CNS relapse if not given CNS directed therapy regardless of CNS disease status at diagnosis.[1]

The Philadelphia chromosome is found in approximately 5% of pediatric ALL patients and 25% of adult ALL patients (Ph+ ALL).[1] The Philadelphia chromosome is formed from the translocation of the Abelson (ABL) gene on chromosome 9 to the breakpoint cluster region (BCR) gene on chromosome 22. This changed chromosome 22 constitutes the Philadelphia chromosome and results in the BCR-ABL fusion gene.

The BCR-ABL gene codes for a tyrosine kinase signaling protein that is continually activated, signaling a cascade that leads to uncontrolled cell division.[3] Two distinct transcript sizes of the BCR-ABL have been defined: the p190 and p210 isoforms. In chronic myeloid leukemia (CML), a disease driven by the Philadelphia chromosome and BCR-ABL protein, the p210 isoform is most commonly seen, whereas the p190 is more commonly seen in Ph+ ALL.[1,4]

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Imatinib was the first approved tyrosine kinase that inhibits the BCR-ABL protein by competitively blocking the kinase domain site and blocking phosphorylation of downstream substrates and halting cell signaling for proliferation.[5,6]

Since the approval of imatinib, several other BCR-ABL tyrosine kinase inhibitors have been approved: dasatinib, nilotinib, bosutinib and ponatinib.[5] These agents first revolutionized the treatment of CML and have continued to alter the landscape of treatment for Ph+ ALL.

Prior to the TKI era, five-year OS for adult patients with Ph+ ALL treated with chemotherapy alone was reported at 19%.[7] The use of allogeneic stem cell transplant (allo-HCT) in first complete remission (CR) increases the five-year OS to 36-44%.[7] The incorporation of TKIs with chemotherapy, advancements in minimal residual disease (MRD) testing and use of allo-HCT in first remission have continued to significantly improve survival for Ph+ ALL adult patients.[8-10]

Given the significant improvement in survival with TKIs added to chemotherapy, the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) examined the use of therapy with only imatinib and a corticosteroid in elderly patients as a chemotherapy sparing treatment in a population that does not tolerate intensive chemotherapy well.

In this single-arm study, they reported a complete hematologic response (CHR) of 100% without using chemotherapy and thus beginning the journey toward a chemotherapy-free era in the treatment of Ph+ALL.[11]

DASATINIB AND CORTICOSTEROID INDUCTION

The demonstration of high complete hematologic response (CHR) rates in older patients with Ph+ ALL treated with systemic chemotherapy-free induction led the GIMEMA cooperative group to design a phase II trial expanding this approach to any adult patient aged 18 years or older. The second-generation TKI dasatinib was utilized in this trial given its higher potency against BCR-ABL and ability to overcome imatinib resistant BCR-ABL mutations. Patients with CNS disease were excluded from this study.

TABLE 1: OVERVIEW OF DASATINIB AND PONATINIB[20-23]

	DASATINIB	PONATINIB
Dose in Ph+ ALL	140 mg by mouth once daily	45 mg by mouth once daily
Administration	With or without food	With or without food
Drug interactions	Major CYP3A4 substrate Dose reductions required with strong CYP3A4 inhibitors Gastric acid-suppressing agents Separate from antacids by 2 hours before and after dosing	Major CYP3A4 substrate, but also metabolized by BCRP/ABCG2, CYP2C9 (minor), CYP2D6 (minor) and P-glycoprotein Gastric acid-suppressing agents have minimal effect on absorption
Warnings/ precautions	Bone marrow suppression, cardiovascular events, dermatologic toxicity, fluid retention, hemorrhage, PAH, QTc prolongation	Arrhythmias, arterial occlusion, bone marrow suppression, fluid retention, GI perforation, heart failure, hemorrhage, hepatotoxicity, neuropathy, ocular toxicity, pancreatitis, posterior reversible leukoencephalopathy, venous thromboembolism
Adverse events (>20%)	Headache, fluid retention, diarrhea, nausea, thrombocytopenia, neutropenia, anemia, musculoskeletal pain, pleural effusion, dyspnea	Cardiac arrhythmia, edema, hypertension, arterial occlusive disease, skin rash, xeroderma, endocrine and metabolic effects, abdominal pain, constipation, decreased appetite, diarrhea, increase lipase, nausea/vomiting, pancreatitis, anemia, hemorrhage, neutropenia, thrombocytopenia, hepatotoxicity, increased LFTs, fatigue, headache, neuropathy, arthralgia, asthenia, myalgia, ocular toxicity, increase serum creatinine
Monitoring	CBC with differential weekly for first two months, then as clinically indicated Liver function tests (LFTs), electrolytes, and EKG as clinically indicated Routine blood pressure monitoring. Perform chest X-ray for symptoms suggestive of pleural effusion	CBC with differential every two weeks for three months, then as clinically indicated LFTs monthly, lipase every two weeks for two months then monthly Perform routine blood pressure monitoring. Ocular exam at baseline then periodically

Treatment consisted of a seven-day steroid prephase of oral prednisone at increasing doses of 10-60 mg/m^2/day. Induction therapy consisted of dasatinib 70 mg by mouth twice daily for 84 days with prednisone 60 mg/m^2 (capped at 120 mg/day) on days 1-24 followed by a taper and discontinuation at day 32. CNS prophylaxis with intrathecal methotrexate was administered on days 22 and 43.

The primary endpoint was CHR after dasatinib induction and secondary endpoints included safety, immunophenotypic response rate, molecular response rate, disease-free survival (DFS), relapse rate and OS.

Fifty-five patients were enrolled on the trial and 53 were included in the analysis (one patient refused treatment and one patient discontinued therapy after 14 days due to gastrointestinal toxicity which subsequently resolved).

Of the 53 evaluable patients, the median age was 53.6 years (range 23.8-76.5 years) and 53% were female. The median white blood cell count (WBC) at diagnosis was 18.8 x10^9/L (range 2.2-132.9x10^9/L); 62% of patients had the p190 isoform, 25% had p210 and 13% had both.

The protocol did not include any planned treatment after day 84. Post-protocol treatment included no further treatment (n=2), TKI alone (n=19), TKI

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plus chemotherapy (n=10), auto-HCT (n=4) and allo-HCT (n=18).

All 53 patients (100%) achieved a CHR, with a median time to CHR of 23 days. At a median follow-up of 24.8 months, the median DFS and OS was 21.5 months and 30.8 months respectively. The 20-month DFS and OS rates were 51.1% (95% CI, 44.4%-58.7%) and 69.2% (95% CI, 60.7-79%) respectively.

No relapses occurred during the 84 days of dasatinib induction. At the last follow-up, a total of 23 relapses occurred with a median time to relapse from first CHR of 5.9 months (range 18-655 days).

Relapses occurred in 33.3% of the p190 patients, 77% of the p210 patients and 29% of the p190/p210 patients. Relapses occurred in both patients who received no further treatment post-induction, in 74% of patients that received TKI only, in 35% of patients who received TKI plus chemotherapy or auto-HCT and in 11% of patients who received allo-HCT. Mutations were frequently detected at relapse with the T315I mutation reported in 12 of 17 patients analyzed.

BCR-ABL transcript levels decreased rapidly during dasatinib induction with p190 patients having more rapid molecular responses compared to p210 patients. Molecular response was predictive for DFS. Patients who achieved BCR-ABL levels $<10^{-3}$ by day 22 had significantly improved DFS compared to those who never achieved BCR-ABL levels $<10^{-3}$(p=0.0381). Immunophenotype and therapeutic response were not correlated and immunophenotypic response (<0.1% of leukemic cells in the bone marrow) was associated with DFS only at day 85 (p=0.0397). In a univariate analysis the WBC count at diagnosis correlated with DFS and in a multivariate model only BCR-ABL reduction correlated with DFS.

Four patients discontinued treatment after day 64 of induction (one for weight gain, fever of unknown origin, grade 1/2 pleural effusion, and grade 2 superficial edema; one for grade 2 fever of unknown origin and grade 3 nausea and vomiting; one for grade 3 proteinuria; one for a personal decision and grade 4 transaminitis). Eleven patients temporarily discontinued therapy for a median of four days for mild increase of liver function tests (n=3), gastrointestinal toxicity (n=2), clinical decision (n=2), infection (n=2), mood alteration (n=1) and hyperkalemia (n=1). All 11 patients resumed therapy at full dose.

Of the patients who did not discontinue treatment, only two reported serious adverse events related to dasatinib: one moderate pleural effusion and one mild fever of unknown origin. No deaths occurred during dasatinib therapy. A total of 19 patients died after completing the 84-day induction phase, 16 due to relapse and two due to complications of allo-HCT.

This trial demonstrated the efficacy and safety of a systemic chemotherapy-free induction with dasatinib plus prednisone in adult patients with newly diagnosed Ph+ALL. Despite 100% of patients achieving a CHR with this approach, more than half of the patients experienced a relapse. This trial did not include post-induction therapy and was not powered to evaluate differences in the post-induction approaches, leaving the question of optimal post-induction therapy unanswered.

It should also be noted that patients with CNS disease were excluded from this trial, and post-induction CNS directed therapy as well as occurrence of CNS relapse was not reported.

Although post-induction therapy was not evaluated in this trial, information that may help guide treatment decisions after induction was presented. The importance of MRD monitoring of BCR-ABL transcripts was highlighted in this study as a predictor of DFS. Patients who achieved undetectable levels ($<10^{-3}$) at day 22 had significantly higher DFS than those who did not achieve MRD negativity at any time point.

In the multivariate analysis, MRD negativity at day 85 was also correlated with DFS. This data suggests that patients who have delayed molecular responses or who do not achieve deeper molecular responses are likely at higher risk of relapse. In addition, the occurrence of the T3151 mutation was found to be the major driver of dasatinib resistance and indicates a need to tailor therapy based on BCR-ABL mutations.[12]

CALGB-10701 STUDY

The Cancer and Leukemia Group B (CALGB) attempted to answer the question of optimal post-induction therapy with the phase II, non-randomized, CALGB-10701 study. The primary endpoint was three-year OS and DFS.

Patients age 18 years or older with untreated Ph+ ALL received therapy starting with course I (induction) with dasatinib 140 mg by mouth once daily and dexamethasone 10 mg/m^2 on days one through seven. Course II consisted of continued dasatinib plus an additional seven days of dexamethasone if ≤ 20% lymphoblasts in the day 15 bone marrow, and if >20% lymphoblasts patients also received vincristine and daunorubicin.

A course III (second induction) was given to patients who did not achieve a complete response or complete response with incomplete count recovery (CRi) and included dasatinib, cyclophosphamide, vincristine, daunorubicin and dexamethasone.

A course IV was given for CNS prophylaxis which included dasatinib, vincristine, and intravenous, oral and intrathecal methotrexate.

For course V, patients received either an allo-HCT, autologous stem cell transplant (auto-HCT) or chemotherapy, followed by course VI dasatinib maintenance.

The initial report included 65 evaluable patients and final report 64 evaluable patients with a median age of 60 years (age 22-87). The BCR-ABL p190 and p210 isoform were found in 59% and 17% of patients respectively. CR/CRi occurred in 48% of patients by day 15 and in 95% of patients overall.

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Fifty-five patients completed course IV and a total of 20 patients went on to receive an allo-HCT, 7 auto-HCT and 9 chemotherapy. Greater than 50% of planned dasatinib maintenance doses were administered in 72%, 80% and 80% of patients on the allo-HCT, auto-HCT and chemotherapy arms.

At a median follow-up of 48 months the three-year OS and DFS were 55% and 43% respectively. The three-year OS for patients undergoing allo-HCT, auto-HCT and chemotherapy were 75%, 71% and 55% respectively and DFS was 55%, 43% and 46% respectively. The p210 isoform was associated with shorter mean OS and DFS. Relapsed occurred in 23 patients with 25% of allo-HCT, 43% of auto-HCT and 37% of chemotherapy patients experiencing a relapse. The T315I mutated was found in six of eight marrow relapses. A total of five CNS relapsed occurred.

This trial again demonstrated tolerability and high CR rates with a chemotherapy-free induction. The authors concluded that three-year OS rates using a chemotherapy-free induction followed by allo-HCT, auto-HCT or chemotherapy were comparable to intensive induction chemotherapy.[13,14]

DASATINIB & CORTICOSTEROID INDUCTION FOLLOWED BY BLINATUMOMAB

With the knowledge of an excellent response to glucocorticoids plus dasatinib induction and knowing a profound decrease in minimal residual disease increases chance of cure, the GIMEMA cooperative trial group evaluated patients newly diagnosed with Ph+ ALL with glucocorticoids plus dasatinib followed by two cycles of blinatumomab.

Patients included were age 18 years or older (no upper age limit) with newly diagnosed B-precursor Ph+ ALL. Exclusion criteria included neurology disorders (epilepsy, dementia, etc.), impaired cardiac function and impairment in gastrointestinal function

With a median follow-up of 18 months (1-25 months), OS was 95% and disease-free survival was 88%. Disease-free survival was increased in those who achieved molecular remission at the end of induction to 100% versus 85% in patients who did not achieve a molecular remission.

such as ulcerative diseases. The primary endpoint included molecular response with secondary endpoints of DFS, OS, relapse and safety profile.

Prior to starting dasatinib, patients were started on a steroid pre-phase of prednisone (or intravenous methylprednisolone equivalent) of 20 mg/m^2 on day 6 and escalating the dose by 10 mg/m^2/day up to day 4. Once the full dose of prednisone 60 mg/m^2 was reached on day 3, this dose was continued until day 24. Starting on day 25 the prednisone dose was decreased by 20 mg/m^2 every two days (days 25-26: 40 mg/m^2, days 27-28: 20 mg/m^2, days 29-30: 10 mg/m^2, day 31: 5 mg/m^2). Dasatinib was dosed at 140 mg by mouth daily, days 1 through 85.

Consolidation included blinatumomab was administered as a continuous infusion at a dose of 28mcg per day for four weeks, followed by a two-week break, for a cycle length of six weeks. Patients received at least two cycles of blinatumomab. Dasatinib was administered continuously throughout consolidation with blinatumomab.

Patients were hospitalized for the first three days of cycle one and the first two days for subsequent cycles. Dexamethasone 20 mg intravenously was administered one hour prior to each blinatumomab cycle for cytokine release syndrome prophylaxis and levetiracetam 500 mg by mouth twice daily was used as seizure prophylaxis. From the end of induction to the start of blinatumomab, the median number of days was 10 (range 7-41).

Central nervous system prophylaxis with intrathecal (IT) chemotherapy was administered on diagnosis, and on days 14, 22, 43, 57, 85, and at the end of each blinatumomab cycle for a total of 12 doses. IT chemotherapy consisted of methotrexate 15 mg and methylprednisolone 20 mg. Post-consolidation treatment was guided by individual investigators.

There were 63 patients enrolled between May 9, 2017, to January 9, 2019. Median age at diagnosis was 54 years old (range 24-82) with half the patients being women. The p190 and p210 fusion proteins were detected in 41 (65%) and 17 (27%) of patients, respectively. Five patients had both the p190 and p210 fusion proteins detected.

Induction was completed by 61 patients, with two patients withdrawing from the trial, one of which had a complete hematologic response. A complete hematologic response was achieved in 98% of the patients at the end of induction and 29% (17 of 59) had a molecular response.

The number of patients who received one cycle, two cycles, three cycles, four cycles and five cycles of blinatumomab were 58, 56, 45, 27 and 29, respectively. A molecular response was achieved in 60% of patients by the end of the second cycle of blinatumomab.

With each cycle of blinatumomab, the number of molecular responses increased to 70% (28 of 40 patients), 81% (29 of 36 patients) and 72% (21 of 29 patients) after the third, fourth and fifth cycles of blinatumomab, respectively.

With a median follow-up of 18 months (1-25 months), OS was 95% (95% confidence interval [CI], 90 to 100) and disease-free survival was 88% (95% CI, 80 to 97). Disease-free survival was increased in those who achieved molecular remission at the end of induction to 100% versus 85% in patients who did not

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achieve a molecular remission.

Patients with an increase in minimal residual disease during induction (15) or over relapse (1) had an ABL1 mutational analysis conducted. Mutations were detected in seven of the 15 patients with an increase in MRD (6 with T315I and 1 with E255K).

These mutations developed at the end of induction (between day 57 and 85), with the exception of one mutation occurring earlier than day 57. All mutations were cleared by blinatumomab.

Twenty-four patients received an allogeneic HCT, with 23 patients receiving HCT during the first complete hematologic response and one during a second complete hematologic response.

Out of the six relapses that occurred, five had a T315I mutation. Two relapses were isolated to the CNS. There were four deaths, with only one death during induction due to progression of pneumonia. Two deaths occurred after HCT, one from relapse and one from veno-occlusive disease.

The regimen was well-tolerated, with only two patients experiencing pleural effusions, only one of which was grade 3. Other grade 3 toxicities included cytomegalovirus (CMV) reactivation or infection (six patients), neutropenia (four patients), pyrexia (two patients), pulmonary hypertension (one patient) and neurotoxicity (one patient).[15]

PONATINIB AND BLINATUMOMAB

The efficacy of ponatinib in combination with blinatumomab was evaluated in a single-arm phase 2 study. Inclusion criteria included adults with newly diagnosed or relapsed/refractory (R/R) Ph+ ALL.

Treatment included blinatumomab for up to five cycles at standard doses in combination with ponatinib 30 mg by mouth daily. Once a patient was within a complete molecular remission (CMR), ponatinib was decreased to 15 mg by mouth daily. Ponatinib was continued after blinatumomab was completed for at least five years. Prophylactic intrathecal chemotherapy was administered for a total of 12 doses.

The primary endpoint was CMR rate and overall response rate (ORR) for newly diagnosed and relapsed refractory patients, respectively; ORR was defined as a composite complete remission (CCR) of CR, or CR with CRi.

Forty-three patients were treated between February 2018 and July 2021. This included 24 patients with newly diagnosed Ph+ ALL, 14 with relapsed refractory, and five with chronic myeloid leukemia in lymphoid blast phase (CML-LBP).

The newly diagnosed group had a median age of 60 years (range, 34-83 years), while the R/R Ph+ ALL group median age was 38 years (range, 24-61 years). This was second-salvage therapy for 43% of patients in the R/R group.

There were 32 patients evaluable for morphologic remission of which all patients, but one, responded (97%). The one non-responding patient received ponatinib as an earlier salvage therapy.

The CCR was 100% in the newly diagnosed and CML-LBP patients and 91% in the R/R patients. CMR was achieved in 84% of patients with 91%, 91% and 40% achievement of CMR in the newly diagnosed, R/R and CML-LBP cohorts, respectively. After cycle 1, the CMR rates were 64%, 82% and 20%, in the three groups, respectively.

With a median follow-up of nine months (range, 1-38 months), 24 of the patients in the newly diagnosed cohort had ongoing response with a median duration of CR of eight months (range, 1-36 months). These patients did not undergo HCT. One patient in the newly diagnosed group died in CR.

The two-year EFS and OS for the newly diagnosed group was 95%, while the EFS and OS were 53% and 39% in the R/R group, respectively. The R/R group included one patient who did not respond, two patients who were too early to evaluate for response, four who underwent HCT, and one patient who died in CR.

Of the six patients in the R/R group who did not go to HCT, two relapsed and four had ongoing response. Out of the five patients who responded in the CML-LBP group, two patients relapsed and three had ongoing response without HCT.

Most adverse events observed were grade 1-2 and consistent with previous toxicity profiles of the two agents. Ponatinib was discontinued in two patients for thrombotic events (one due to stroke and one due to DVT).

The authors concluded this regimen may serve as an effective chemotherapy-free, transplant-free treatment approach for patients ND or R/R Ph+ ALL or patients with CML-LBP.[16,17]

PRACTICAL CONSIDERATIONS OF USING TKI PLUS STEROIDS

TKI resistance is an ongoing challenge in the treatment of Ph+ ALL.

The development of kinase mutations has been associated with more aggressive and advanced disease, likely due to proliferation rate and clonal instability.[18,19] Although kinase mutations can be detected in subclones at diagnosis, these generally die out with initiation of TKI therapy.[19]

The T315I mutation is of significant concern as it is a driver of TKI treatment failure and relapse, and confers resistance to all TKIs with the exception of ponatinib.[1] In patients who developed this mutation the median time from TKI initiation to detection of T315I is approximately 9.1 months for patients with Ph+ ALL.[18]

Mutation testing is recommended for patients who are refractory to initial TKI therapy or at time of relapse.[1] Prompt recognition of treatment failure or relapse, and initiation of ponatinib if appropriate, is crucial in obtaining disease control and improving outcomes.

While ponatinib is the only currently available TKI that can overcome the T315I

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mutation, it is associated with significant toxicities. Ponatinib has four U.S. black box warnings: arterial occlusive events, heart failure, hepatotoxicity and venous thromboembolism. These warnings should not be taken lightly, as incidences up to 31%, 13%, 32% and 6% have been reported, respectively.[4,20]

Vascular events associated with ponatinib include strokes, myocardial infarctions and tissue ischemia.[1] The risk of arterial occlusive events and cardiovascular events is highest in patients with underlying cardiovascular disease, however arterial occlusive events have been reported in patients without risk factors and under the age of 50.[4,20] If no contraindication, the use of low-dose aspirin is recommended for prophylaxis.[4]

Myelosuppression can occur with both ponatinib and dasatinib, typically occurring early on in treatment, within the first one to two months, and is more common in aggressive disease such as Ph+ ALL or CML in blast phase.[20,21]

Fluid retention, such as peripheral edema, may occur with both agents, however dasatinib is associated with a higher incidence of pleural and pericardial effusions.[4] Patients with a history of cardiac disease, hypertension or administration of twice daily dosing may increase the risk of dasatinib induced pleural effusions.[4] Pulmonary arterial hypertension (PAH) is a rare but serious side effect that can occur at any time point while on dasatinib therapy.[4]

Dasatinib and ponatinib have off-target effects on platelet-derived growth factor receptors and therefore have an increased risk of hemorrhage.[20,22]

Ponatinib also inhibits the vascular endothelial growth factor receptor resulting in a risk of delayed wound healing and hypertension.[20]

Additional information on dasatinib and ponatinib can be found in the prescribing information.[20-23]

Multiple reports indicate that dasatinib at a dose of 140 mg crosses the blood brain barrier and has activity in CNS.[13,14,24-26] Limited data on the extent of penetration of ponatinib into the CNS is available and any clinical significance is not yet known.[27-28] Regardless of TKI therapy, CNS directed therapy with intrathecal chemotherapy is necessary in a systemic chemotherapy-free era to prevent CNS relapse.[1]

Corticosteroids are a backbone of induction therapy for ALL given their cytotoxicity against lymphoblasts. Even in a systemic-chemotherapy-free induction of high-dose bursts of corticosteroids, usually dexamethasone or prednisone, are utilized.

Adverse events are frequent and can be serious if not managed appropriately. Fluid retention, blood sugar dysregulation, hypertension, insomnia, mood alterations/psychiatric effects, infections and sepsis can occur early in therapy.

Patients with underlying heart failure may be at risk of exacerbation from sodium retention and resultant fluid retention, and patients with diabetes are especially prone to hyperglycemia.

Myopathies, acne-like rashes, and gastrointestinal toxicities may occur during therapy. Longer-term therapy has been associated with cushingoid features, opportunistic infections, bone fractures, osteonecrosis and adrenal insufficiency.[29-31]

DISCUSSION

The National Comprehensive Cancer Network (NCCN) recommends a clinical trial first line for all patients with newly diagnosed ALL. In the case where clinical trials are not available, NCCN recommends a multitherapy approach of chemotherapy or corticosteroids in combination with a TKI for newly diagnosed Ph+ ALL.

For patients > 65 years old, induction therapy is guided by performance status and presence of comorbidities.[1] Where exactly this chemotherapy-free approach of induction with corticosteroids and TKI should be used upfront over traditional chemotherapy and TKI remains to be determined.

Survival rates at five years for children and AYA patients estimate at 89 and 61%, respectively, while survival for adults is lower ranging from 20-40%.[32-34]

Although survival rates may in part be from differences in chromosomal and molecular abnormalities in adults versus children, differences in chemotherapy regimens may contribute to differences in survival.

In general, the tolerability of myelosuppressive therapy decreases with age. Compared to pediatric protocols, adult protocols include decreased doses of myelosuppressive chemotherapy, less intrathecal chemotherapy, and are more likely to include allogenic HCT.[35]

Despite decreased intensity in regimens for adults compared to children, induction-related death due to infection remains prevalent.[1] For patients that complete chemotherapy for the treatment of ALL, long-term adverse events from extended durations of chemotherapy may persist.[36]

The option of a chemotherapy-free induction offers an approach with potentially decreased risk of death during induction compared to other multiagent approaches.

This was demonstrated in the phase II with dasatinib plus prednisone induction and the phase III of dasatinib and prednisone followed by blinatumomab, where there were no deaths during induction in the phase II and only one death during induction in the phase III. This demonstrated the safety of a TKI and corticosteroid induction strategy.[12,15]

Other benefits of corticosteroid plus TKI induction include less toxicity and fewer long-term adverse events from traditional chemotherapy.

Traditional chemotherapy regimens for ALL often include a backbone of vincristine, anthracyclines and corticosteroids. Weekly vincristine can lead to long-lasting peripheral neuropathy, while higher

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lifetime anthracycline exposure can lead to cardiotoxicity and risk of heart failure over time. By omitting some of these conventional chemotherapy agents, the risk of long-term toxicities is decreased.[36]

In the first study by Foa and colleagues examining induction therapy with dasatinib plus corticosteroid, 12 of 17 patients developed a T315I mutation.[12] A similar pattern was examined in the dasatinib plus corticosteroid induction followed by blinatumomab.

However, the addition of blinatumomab cleared all T315I mutations.[15] This finding could be the reason there were so few relapses in this trial.[37] Additionally, utilizing ponatinib plus blinatumomab upfront would also circumvent T315I-related relapses.[20]

Traditional chemotherapy approaches for ALL include high-dose systemic therapies, such as high-dose cytarabine and methotrexate for CNS prophylaxis in addition to intrathecal therapy.

Although dasatinib penetrates the CNS, blinatumomab is less effective in CNS disease.[38] Two of the six relapses with the use of dasatinib plus corticosteroids followed by blinatumomab call into question if dasatinib and intrathecal chemotherapy are adequate CNS prophylaxis compared to the same combination with high dose systemic chemotherapy.[15,38,39]

Ongoing clinical trials include an open-label, randomized, phase III study in adults newly diagnosed Ph+ ALL receiving induction chemotherapy with ponatinib followed by a minimum of two cycles of blinatumomab versus conventional chemotherapy in addition to imatinib.

Ponatinib will be dosed at 45 mg per day for patients aged 18-65 years old for the first 22 days followed by a dose reduction to 30 mg daily based on response. Patients older than 65 years old will receive a decreased starting dose of ponatinib at 30 mg per day. Ponatinib will be continued up to day 70, followed by a minimum of two cycles of blinatumomab.

The addition of blinatumomab cleared all T315I mutations. This finding could be the reason there were so few relapses in this trial. Utilizing ponatinib plus blinatumomab upfront would also circumvent T315I-related relapses.

This study will start the conversation of whether these chemotherapy-free regimens compare to our conventional chemotherapy regimens in combination with TKIs in terms of long-term survival. The study (NCT04722848) is projected to complete in September 2027. The regimen of decreasing ponatinib to 30 mg after achieving remission has showed sustained response rates and decreased cardiovascular events.[4,40-42] Whether this will be the same in ALL remains to be answered.

Another question that remains unanswered: as we utilize these therapies that were traditionally used in the relapsed/refractory setting, how will these patients be treated if they relapse? It remains to be answered whether the long-term data shows sustained responses that outweigh decreasing options for relapse later.

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CHEMOTHERAPY-FREE

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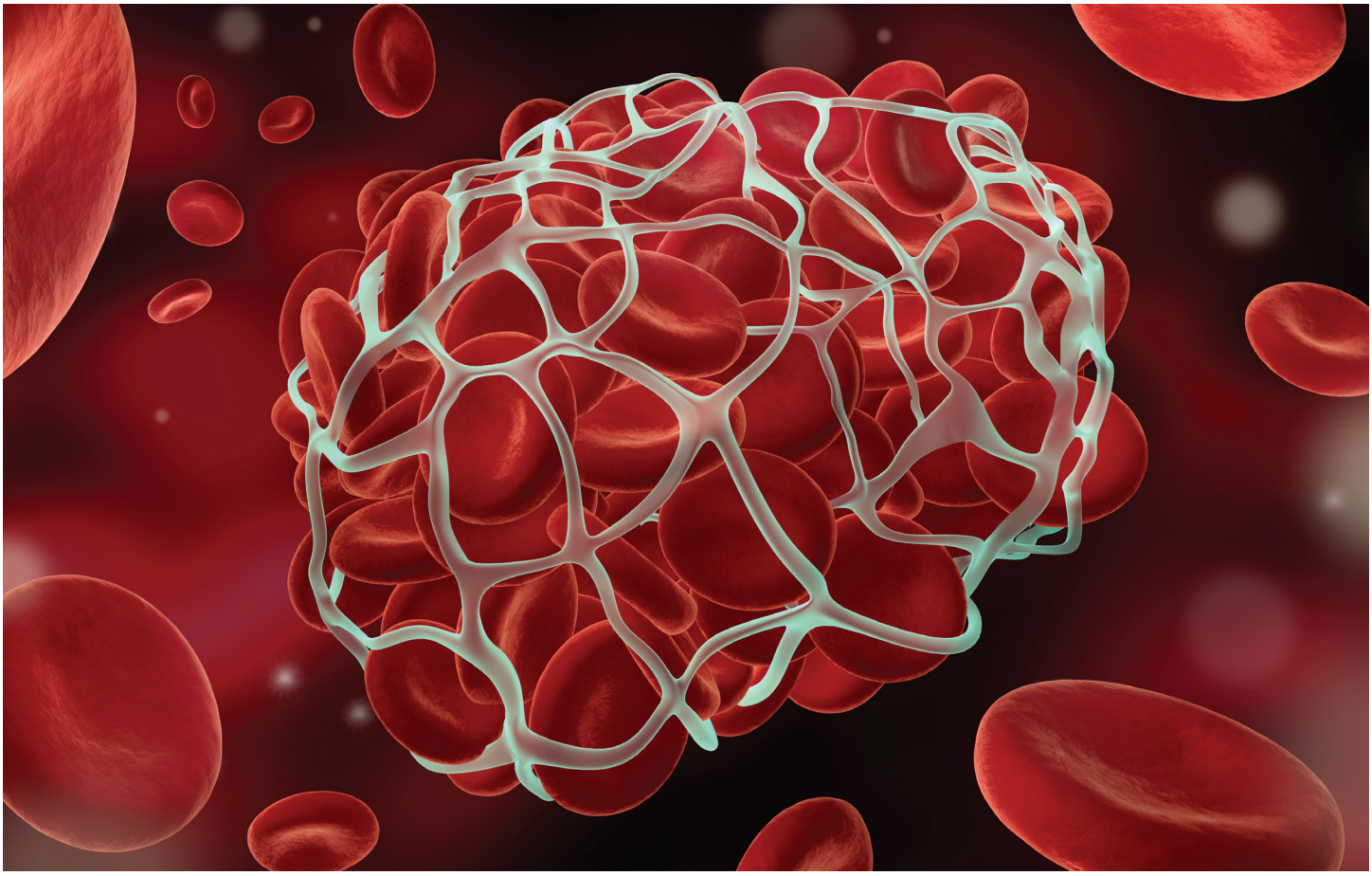
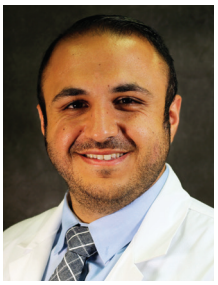


ORAL ANTICOAGULATION THERAPY

MAKING APPROPRIATE CHOICES IN CLINICAL PRACTICE

By Aamir Hussain, MD, Andrew Iskandar, MD, Hema Vankayala, MD, & Bijoy Telivala, MD

Aamir Hussain



Andrew Iskandar

Hema Vankayala

Bijoy Telivala

For decades, the vitamin K antagonist (VKA) warfarin has been the standard of care for outpatient treatment of acute venous thromboembolic disease (VTE). In the past 10 years, however, several direct oral anticoagulants (DOAC) have been approved by the United States Food and Drug Administration (FDA).

Initially, dabigatran gained approval for atrial fibrillation based on the RE-LY trial, followed by the approval for rivaroxaban and apixaban for this purpose based on the ROCKET-AF and ARISTOTLE trials respectively. VTE approvals for rivaroxaban, apixaban and endoxaban were based on EINSTEIN, AMPLIFY and the Hokusai-VTE trials respectively.

The DOACs have a broad therapeutic window, allowing for fixed dosing and no requirement for routine and frequent laboratory monitoring like the international normalized ratio (INR). However, choosing between VKA or DOACs is not always easy considering different clinical and non-clinical variables.

Prescribing dilemmas in hematology clinics include:

- Physician's comfort level;

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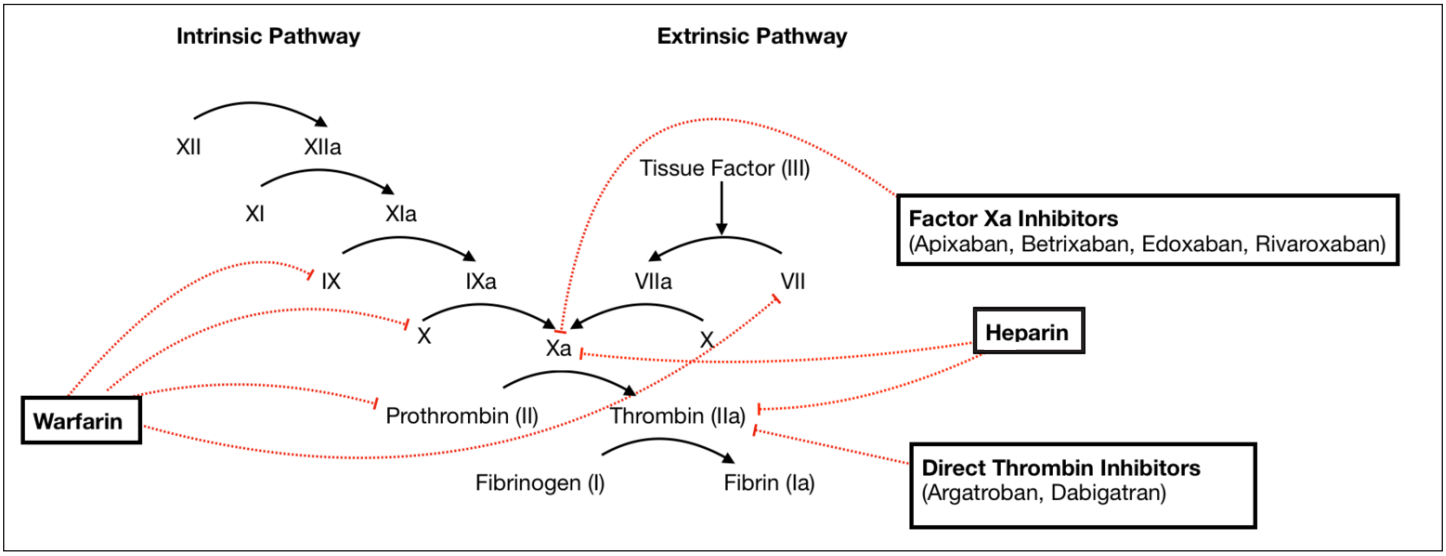
PATHWAYS FOR ANTICOAGULATION THERAPY[9]



ORAL ANTICOAGULATION

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- Patient's preference;
- Adherence to regimen;
- Special considerations;
- Extended therapy; and
- Cost.

PHYSICIAN'S COMFORT LEVEL

Wheelock et al, reported a study using prescriber-level annual national Medicare provider utilization and payment data from 2013 through 2018. In this study, most clinicians continued to use warfarin as their predominant or only anticoagulant instead of DOACs, including one in five general medicine practitioners exclusively using warfarin in 2018. Despite an increase in DOAC prescribing, those prescribing only warfarin in 2013 had lower proportionate DOAC use throughout the study than 2013 DOAC prescribers.[1]

PATIENT'S PREFERENCE

Palacio et al, reported that patients who may be exposed to an anticoagulation decision prefer to actively participate in the decision-making process and have individual values for making a decision that cannot be predicted or assumed by anyone in the healthcare system. Having an antidote was the most cited reason to prefer one anticoagulant over the other.

The second most commonly cited attribute of importance was the "medication that gives the best quality of life."[2]

Elewa et al, found that dietary freedom was the major incentive of over half of patients to switch from VKAs to DOACs and according to several studies INR monitoring is the key difficulty for patients taking VKAs.[3]

Some prefer medicines which have no major dietary restrictions and no routine monitoring while others feel more confident having a lab value to guide their care.

Another big issue is cost. The average cost of warfarin is around $10 a month, while that of DOAC is around $300 a month.

ADHERENCE TO REGIMEN

Vaanholt et al, reported that the most cited factors negatively impacting adherence included:

- Lack of knowledge;
- Poor patient-doctor relationship;
- Distraction due to employment or social environment;
- Prior bleeding event(s) or the fear of bleeding; and
- Changes in routine.

An important barrier to adherence was patients' inadequate understanding of the need to take their medication in terms of risks/benefits, and conflicting instructions they receive from various providers.

A prime example in this study was that patients were unaware of the fact that there are reversal strategies available to reverse the anticoagulant effect in emergencies (accidents, urgent surgery), for various anticoagulants.

The similar adherence to DOACs versus warfarin was demonstrated in a meta-analysis of randomized trials that evaluated drug discontinuation rates in patients with VTE or atrial fibrillation (AF), who were treated for more than 12 weeks with a DOAC or a pharmacologically active comparator.[4]

SPECIAL CONSIDERATIONS

Active Cancer: Based on ASH 2021 Guidelines for Prevention and Treatment of Venous Thromboembolism in Patients with Cancer, for patients with active cancer, DOACs or LMWH is recommended for initial treatment of VTE. DOACs are preferred over LMWH or VKA for short term (three to six months) treatment. DOACs or LMWH is recommended for long term secondary prophylaxis.[5]

Chronic Kidney Disease: All the DOACs are excreted by the kidney to some degree, which has led to some concern about use and dose adjustments in individuals with chronic kidney disease. Despite these concerns, use of DOACs

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AVAILABLE ORAL ANTICOAGULANTS

	WARFARIN	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
Mechanism	Vitamin K antagonist	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Indications	• VTE treatment • VTE prevention in patients with mechanical heart valve • Stroke prevention in patients with valvular A-fib	• VTE treatment • VTE prophylaxis • VTE prevention in post-operative patients • Stroke prevention in patients with non-valvular A-fib	• VTE treatment • VTE prophylaxis • VTE prevention in post-operative patients • Stroke prevention in patients with non-valvular A-fib	• VTE treatment • VTE prophylaxis • VTE prevention in post-operative patients • Stroke prevention in patients with non-valvular A-fib	• VTE treatment • VTE prophylaxis • Stroke prevention in patients with non-valvular A-fib
Dosing Frequency	Variable	Twice daily	Once or twice daily, taken with food	Twice daily	Once daily
Crushable?	Yes	No	Yes; can't be administered through J-tube	Yes	Yes
Half Life	20-60 hours	12-17 hours	5-9 hours	12 hours	10-14 hours
Renal Dosing	Not necessary	• CrCl >30: No adjustment • CrCl 15-30: 75 mg twice daily • CrCl <15: Avoid use	• CrCl >50: No adjustment • CrCl <50: Dosage adjustment may be necessary based on indication for use	• No dosage adjustment necessary if indication is VTE treatment • Atrial fibrillation prophylactic dosing may require dose adjustment based on other parameters	• Avoid use in patients with CrCl >95 or <15 • CrCl 50-95: No adjustment • CrCl 15-50: 30 mg daily
Drug Interactions	**Drugs that ↑ INR:** Amiodarone, macrolides, ciprofloxacin, sulfonamides, azoles, acetaminophen, cimetidine & levothyroxine **Drugs that ↓ INR:** Rifampin, barbiturates, carbamazepine, phenytoin & cholestyramine	• CYP3A4 inducers & inhibitors (i.e., ketoconazole, dronedarone)	• CYP3A4 inducers & inhibitors • Avoid use with itraconazole, ketoconazole, lopinavir/ritonavir, indinavir and conivaptan	• CYP3A4 inducers & inhibitors • Avoid use with ketoconazole, itraconazole, ritonavir, clarithromycin, rifampin, carbamazepine and phenytoin	• CYP3A4 inducers & inhibitors • Avoid use with rifampin

ORAL ANTICOAGULATION

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in individuals with chronic kidney disease (CKD) appears to be safe and effective, especially in individuals with mild-to-moderate CKD.

A 2020 systematic review that included nine studies (two of which were randomized trials) of individuals with atrial fibrillation or VTE who had CKD or were receiving dialysis found similar efficacy with DOACs versus warfarin and similar bleeding risks with apixaban versus warfarin. Renal clearance of apixaban is about 25% which is least among DOACs.[6]

Mechanical Prosthetic Heart Valves: DOACs are not used in patients with mechanical prosthetic heart valves, due to greater risk of valve thrombosis, which may be fatal. The RE-ALIGN trial was terminated prematurely because of an excess of thromboembolic and bleeding events

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ORAL ANTICOAGULATION

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among patients in the dabigatran group.[7]

Pregnancy: DOACs are not used during pregnancy, due to lack of clinical experience in this setting. LMW heparin is preferred in most pregnant women who require an anticoagulant. If a patient taking one of the DOACs becomes pregnant, she should be switched to LMW heparin immediately.

Antiphospholipid Syndrome: In patients with the antiphospholipid syndrome (APS) who require anticoagulation, heparin followed by warfarin is the preferred therapy, especially for those with a history of arterial thrombosis or other high-risk features. TRAPS and PROBE studies for rivaroxaban and apixaban respectively, were stopped prematurely due to increase thrombosis in DOACs arms.

Colon/Terminal Ileus Resection: Apixaban should be avoided in patients with resection of ascending colon and terminal ileus as almost 60% absorptions happen in this area of GI tract

HIV: HIV patients on protease inhibitors should not be treatment with apixaban or rivaroxaban. Dabigatran should be fine in this situation.

EXTENDED THERAPY

Patients who are at high risk of recurrence and in whom the bleeding risk is not high, are typically administered extended/indefinite anticoagulant therapy rather than discontinuing therapy.

The EINSTEIN-EXT Study was the first to compare a DOAC (rivaroxaban) to placebo for extended VTE therapy. Standard dose rivaroxaban 20 mg daily was compared to placebo for a median duration of 265 days.

Rivaroxaban was superior to placebo for reducing the primary efficacy outcome of recurrent VTE events. Major bleeding was the primary safety outcome which occurred only in patients on rivaroxaban and all events were non-fatal.

The AMPLIFY-EXT trial showed that low dose and standard dose apixaban reduce the risk of recurrent VTE in high-risk patients, without an increased risk of major bleeding; however, it was not powered to directly compare the two doses of apixaban to each other.

The 2016 Chest guidelines suggests use of DOACs for treatment of acute VTE and continuation of the same anticoagulant for prolonged therapy.

Extended anticoagulation treatment beyond one year was in real-life settings associated with a lower risk of recurrent VTE and all-cause mortality among VTE patients with an intermediate risk of recurrence.[8]

SUMMARY

Choosing oral anticoagulant therapy (OAT) is a complex decision in hematology clinics and should involve detailed discussion between patients and physicians.

Patient preferences should be considered as they can vary significantly. One patient could prefer VKA due to assurance by regular INR monitoring, while another could prefer DOACs for better quality of life without routine monitoring.

Lack of knowledge is one of the main barriers to adherence and patients should have detailed understanding of indication of OAT, risks, benefits and reversal plan in case of bleeding.

Certain clinical factors like renal disease, pregnancy and active cancer should be considered when choosing an anticoagulant. Patients with intermediate risk of recurrence should be offered extended therapy if they are not high risk for bleeding.

Beginning in 2022, CVS Caremark (part of CVS Health) has excluded ELIQUIS® (apixaban) from the CVS Caremark Preferred Drug List. CVS Caremark's decision to exclude apixaban means that patients who are filling their prescriptions through network will need to transition to rivaroxaban or be willing to pay 100% of the cost of apixaban.

There were extensive complaints, and many medical and pharmacy groups opposed this unilateral decision by CVS. In the summer of 2022 this decision was reversed, and apixaban was placed back on the formulary.

▲ **Aamir Hussain**, MD, and **Andrew Iskandar**, MD, are fellow physicians at HCA – Florida Orange Park Hospital in Orange Park, Florida. **Hema Vankayala**, MD, is a fellowship program director of hematology/oncology for HCA – Florida Orange Park Hospital, as well as a partner physician at Cancer Specialists of North Florida in Fleming Island, Florida. **Bijoy Telivala**, MD, is a partner physician at Cancer Specialists of North Florida in Jacksonville, Florida.

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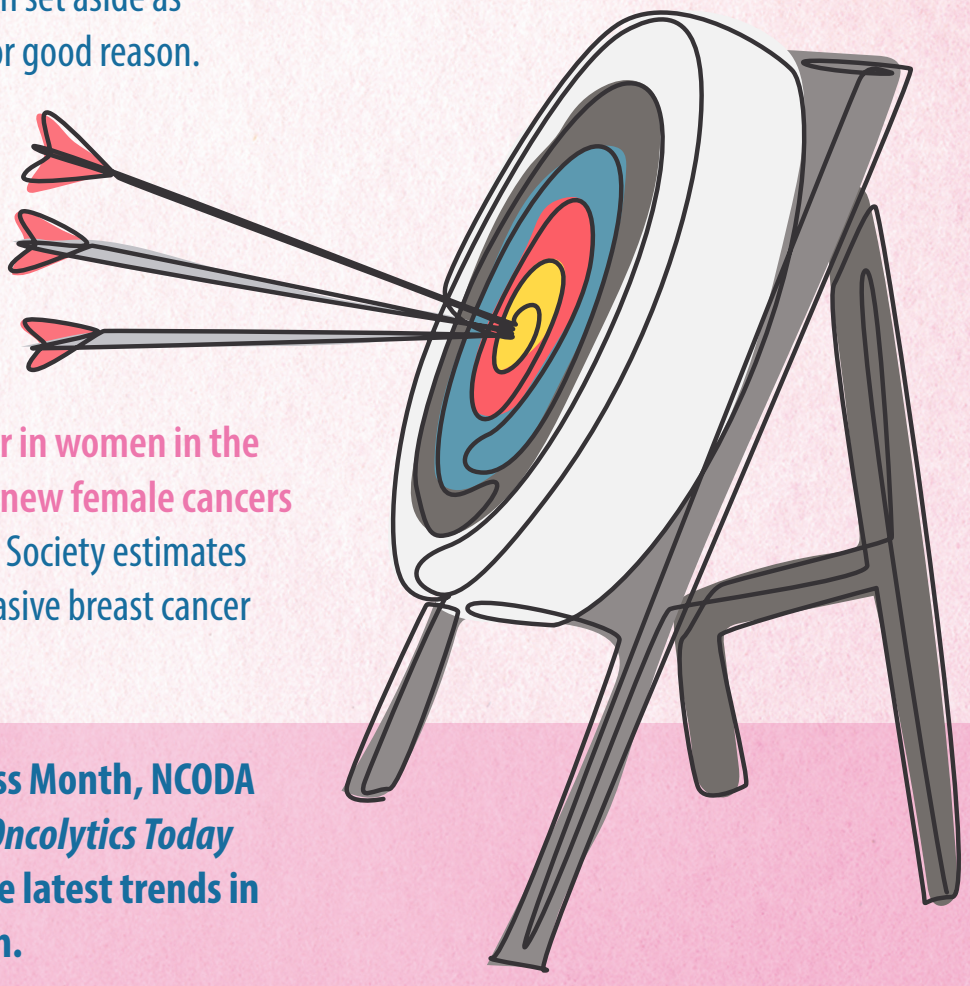
9. Image: "Coagulation Cascade and Major Classes of Anticoagulants." by SteveKong3. CC BY-SA 4.0.

TARGETING BREAST CANCER

Since 1985, the month of October has been set aside as Breast Cancer Awareness Month. And for good reason. Overall, the average risk of a woman in the United States developing breast cancer sometime in her life is about 13%. This means there is a one in eight chance she will develop breast cancer.



Breast cancer is the most common cancer in women in the United States, accounting for 30% of all new female cancers each year. This year, the American Cancer Society estimates approximately 287,850 new cases of invasive breast cancer will be diagnosed in women.

In support of Breast Cancer Awareness Month, NCODA has dedicated the Fall 2022 issue of *Oncolytics Today* to a series of articles that focus on the latest trends in breast cancer treatment and research.

HER2-DIRECTED THERAPY

A PARADIGM SHIFT IN THE TREATMENT OF HER2-LOW EXPRESSING BREAST CANCER?

By Jessica Warner, PharmD

Breast cancer, the second leading cause of cancer death in the United States and the most common malignancy diagnosed in women, is expected to affect close to 300,000 Americans in the year 2022.[1]

While treatment modalities for breast cancers are stratified, nuanced, and varied, oncolytic decisions are guided in part by hormone receptor and HER2-amplification status.

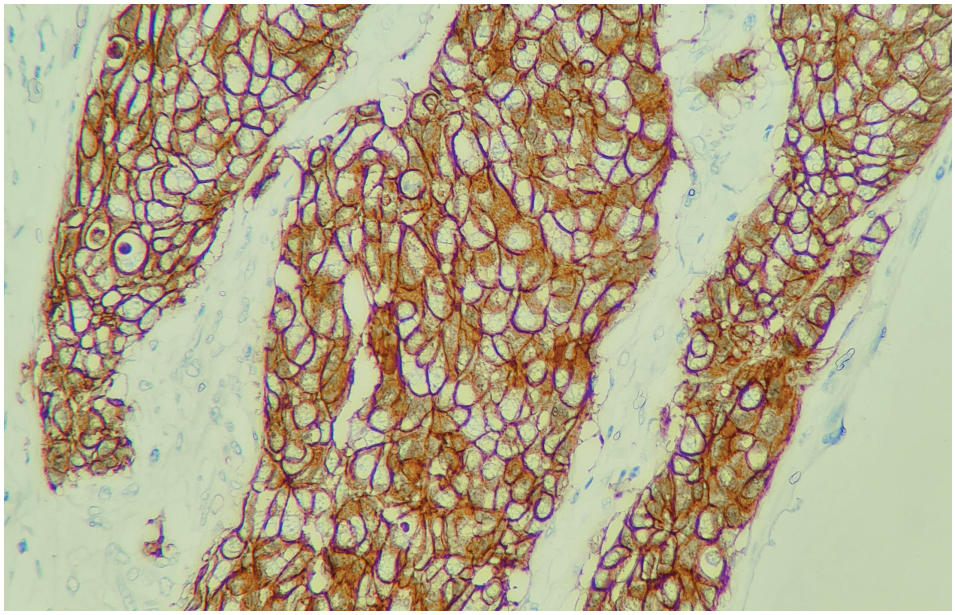
HER2 (human epidermal growth factor 2) status is usually classified as positive/amplified via testing with a validated immunohistochemistry assay resulting in an immunohistochemistry (IHC) result of 3+, equivocal if the result is IHC 2+, or negative with an IHC result of 0 or 1+.[1]

Jessica Warner

HER2-amplification status, in particular, holds prognostic significance in invasive breast cancers and HER2-directed therapies are a mainstay for HER2-positive breast cancers.

Up until recently, HER2-directed therapies have not been utilized for breast cancers classified as HER2-low or HER2-equivocal.

However, the results of the DESTINY-Breast04 trial — which looked at HER2-targeted therapy for HER2-low metastatic breast cancer with fam-trastuzumab deruxtecan-nxki (ENHERTU®) — may point to a forthcoming paradigm shift for these specific breast cancers, especially with the development and availability of new antibody drug conjugates.



This magnification of a microscopic photo of breast cancer shows positive result of a HER2 stain.

DESTINY-BREAST04 RESULTS

The phase 3 results of DESTINY-Breast04, a randomized clinical trial published in *The New England Journal of Medicine*, found that patients with HER2-low, identified as IHC 1+ or 2+/ISH negative, metastatic breast cancer treated with fam-trastuzumab deruxtecan-nxki at a dose of 5.4 mg/kg given intravenously every three weeks, experienced clinically significant longer progression-free survival as well as overall survival compared to physician's choice chemotherapy.[2]

Trastuzumab deruxtecan-nxki improved median progression-free survival by 4.8 months and median overall survival by 6.6 months.[2] Median follow up exhibited a 50% reduction in risk of disease progression or death.[2]

The implications of these results are notable because approximately two-thirds of HER2-negative metastatic breast cancers express low levels of HER2.[2] This is a large proportion of patients who may now have access to a treatment modality that was previously deemed ineffective for such a patient population.

It is worth noting that the classification of HER2 expression in this study was determined through an investigational IHC assay and its comparability to available pathologic testing is unknown.[2]

While these results open a treatment pathway for these patients, they also support the reclassification of HER2-low as a subcategory of metastatic breast cancer patients who may benefit from HER2-targeted therapy.[3]

FAM-TRASTUZUMAB DERUXTECAN-NXKI

Fam-trastuzumab deruxtecan-nxki, marketed and sold as ENHERTU®, is an antibody drug conjugate consisting of trastuzumab, a HER2-directed antibody, covalently linked to deruxtecan, which is a topoisomerase inhibitor.[4]

Antibody drug conjugates like ENHERTU® do not exclusively rely on oncogenic blockade of HER2 signaling activity; the antibody drug conjugate

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HER2

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only needs the HER2 receptor to guide delivery of the cytotoxic deruxtecan component.[3]

There are approximately eight molecules of deruxtecan attached to each antibody molecule, compared to ado-trastuzumab emtansine, another HER2-directed antibody drug conjugate marketed and sold as KADCYLA®, whose drug-to-antibody ratio is only 3.5:1 in comparison.[4,5] The cytotoxic off-target effects of such a high drug-to-antibody ratio conjugate are notable both in toxicities and its exceptional payload as well.[4]

The most notable toxicities for fam-trastuzumab deruxtecan-nxki include life-threatening interstitial lung disease or pneumonitis, neutropenia including febrile neutropenia, and, as with any anti-HER2 therapy, left ventricular dysfunction as well.[4] A differential diagnosis for lung-related complications should be nuanced and prioritized, particularly in the setting of the COVID pandemic.

Risk-assessment must be undertaken with all therapies, but the double-edged nature cannot be overstated for antibody drug conjugates in particular whose effect often comes hand in hand with significant adverse reactions.

OTHER HER2-LOW BREAST CANCER STUDIES

There are currently several ongoing studies evaluating the use of HER2-targeted therapies. Some of these clinical trials include novel investigational antibody drug conjugates including ARX788, RC48-ADC and vic trastuzumab duocarmazine (SYD985) in patients with low HER2-expressing breast cancers, both in the adjuvant and neoadjuvant setting.[6]

It will be interesting to see if the results of such studies corroborate the potentially practice-changing results that came of DESTINY-Breast04 and how many ADCs make it through the pipeline.[6]

It is very likely that the treatment landscape for these cancers will broaden in the future.

The success that fam-trastuzumab deruxtecan-nxki exhibited in this patient population is a welcomed and hopeful sign of greater possibilities.

ANTIBODY DRUG CONJUGATES

It can be argued that there is now added impetus for the development of antibody drug conjugates, not just in breast cancers, but in other oncologic malignancies as well.

Antibody-drug conjugates are a fast-growing group of anticancer drugs and are highly effective at targeting an antigen expressed on a cancer cell and delivering cytotoxic agents in a way that reduces systemic exposure and toxicity.[7]

Sacituzumab-govitecan, for example, is an antibody drug conjugate that has expanded the narrow catalog of treatment options for triple-negative breast cancer for the better.[8]

It would not be unreasonable to expect several antibody-drug conjugates to hit the market in the next decade, and management of their toxicities will be of paramount importance, particularly for oncology pharmacists.

CONCLUSION

The option to take advantage of HER2 homing for patients with low and equivocal expression of HER2 opens the possibility of successful treatment options for close to 60% of patients who previously did not have that opportunity.

The success that fam-trastuzumab deruxtecan-nxki exhibited in this patient population is a welcomed and hopeful sign of greater possibilities.

ENHERTU® was approved by the U.S. Food & Drug Administration (FDA) as the first targeted therapy for HER2-low breast cancers on Aug. 5, 2022.[9]

HER2-low patients are considered eligible to receive treatment with fam-trastuzumab deruxtecan-nxki if they were previously treated with chemotherapy in the metastatic setting or experienced recurrence during or within six months of completion of adjuvant chemotherapy.[9]

Clinicians should be looking to pursue this avenue in appropriate and eligible patients.

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THE ROLE OF TYROSINE KINASE INHIBITORS (TKIs) IN HER2-POSITIVE BREAST CANCER

By Ashleigh Cheikelard, PharmD, & Kaetlyn Parker, PharmD

Breast cancer remains the most prevalent cancer diagnosis among women globally. The average age-adjusted incidence rate between 2014-2018 in the United States was 129 per 100,000 women annually. It is estimated that more than 287,000 women in the U.S. will be diagnosed with breast cancer in 2022. Of these diagnoses, approximately 15% to 20% are HER2-positive.[1,2]

Human epidermal growth factor 2, also known as HER2, is a member of the epidermal growth factor receptor (EGFR)/HER1 family, which also includes proteins HER3 and HER4. Activation of HER2 occurs with hetero- and homodimerization. These dimers drive the phosphorylation of cytoplasmic tyrosine kinases which facilitate the interaction between the proteins and the cell to activate the phosphatidylinositol triphosphate kinase (PI3K) and mitogen-activated protein kinase (MAPK) signaling pathways. Subsequently, HER2 is an oncoprotein that controls cell cycle progression, cellular growth and survival, as well as metastasis of tumor cells (see illustration).[3,4]

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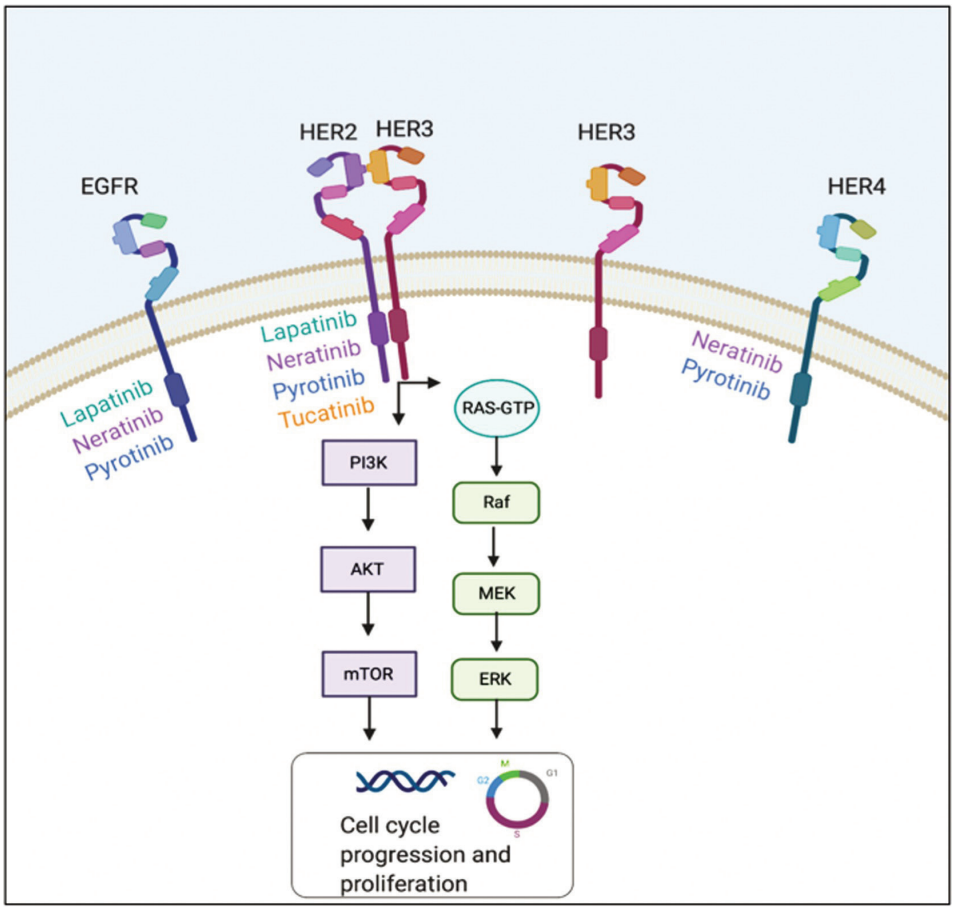
HER2-positive breast cancer is characterized by the overexpression of the HER2 protein, typically associated with amplification of the ERBB2 gene. HER2-positive breast cancers are known to be aggressive and poorly respond to standard therapies contributing to the nearly one-third of patients that develop metastatic disease.[3,5,6] As such, HER2 represents a viable therapeutic target and has resulted in the production of multiple novel drug products over the last few decades.[4]



EGFR/HER1, HER2, HER3, and HER4 are activated by hetero- and homodimerization, further activating a signaling cascade which controls cell cycle progression and proliferation, leading to the growth and migration of cancer cells. These proteins demonstrate vulnerability to various HER2-targeting therapies.

TARGETED THERAPIES

In the last 25 years, targeted therapies have evolved to form the foundation for HER2-positive breast cancer treatment. Anti-HER2 treatment modalities, including monoclonal antibodies, antibody drug conjugates and small-molecule tyrosine kinase inhibitors (TKIs), have significantly improved outcomes for patients diagnosed with HER2-positive breast cancer.

In 1998, trastuzumab became the first HER2-targeted therapy approved by the FDA. Since this approval, pertuzumab, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan and small molecule TKIs (lapatinib, neratinib, and tucatinib) also have been brought to market providing additional options to target HER2-positive breast cancer.[3]

Monoclonal antibodies — trastuzumab

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and pertuzumab — act by binding to the extracellular domain of HER2, inhibiting further signaling and indirectly invoking antibody-dependent cellular toxicity by the hosts' immune system.[7,8]

Unfortunately, the use of monoclonal antibodies opens the door to the development of resistance pathways. The initiation of TKIs has shown to overcome this resistance and further work to control the cell cycle progression of the tumor-producing cells, making TKIs a viable third- or fourth-line treatment option.[3]

TREATMENT RECOMMENDATIONS

Treatment recommendations in the metastatic setting currently call for trastuzumab and pertuzumab coupled with chemotherapy based on the CLEOPATRA trial.[9]

In the second-line setting, the DESTINY-Breast03 trial suggests treatment with an antibody drug conjugate, fam-trastuzumab deruxtecan.[10]

Third-line treatment recommendations include capecitabine and tucatinib with trastuzumab.[27]

After further progression, TKIs typically form the basis of therapy.[5,6]

While the advent of trastuzumab provided hope and an improved prognosis for a subset of patients facing a very aggressive form of breast cancer, the development of resistance quickly led to the need for additional HER2-targeted therapies.

Roughly 10% of patients diagnosed with HER2-positive breast cancer will progress to develop metastases in the central nervous system (CNS). Older treatment modalities lack the freedom to easily access the tumor cells in the CNS. Newer treatments such as fam-trastuzumab deruxtecan and tucantinib show greater CNS response than their predecessors.[10,11]

DEVELOPMENT OF TKIs

Small-molecule TKIs such as lapatinib, neratinib and tucatinib have earned FDA approval as oral treatment options for trastuzumab-exposed and progressive HER2-positive breast cancer. HER2-targeted TKIs have shown benefit in their ability to circumvent and even reverse trastuzumab resistance, while also containing qualities more suitable for penetration of the blood brain barrier providing better access to tumor cells that have metastasized to the CNS.[11]

Lapatinib was the first HER2-targeted TKI approved in 2007 to be used in combination with capecitabine for advanced or metastatic HER2-positive breast cancer previously treated with an anthracycline, trastuzumab and a taxane.[11,12] Lapatinib is a reversible inhibitor of both HER1/EGFR and HER2, further inhibiting the subsequent signaling cascade and preventing the progression of the tumor cell cycle.[6]

In 2013, lapatinib gained an additional indication when used in combination with trastuzumab for hormone receptor (HR)-negative, HER2-positive advanced breast cancer after previous treatment with trastuzumab and chemotherapy. Letrozole was added to this regimen in postmenopausal women diagnosed with triple-positive (HR and HER2-positive) breast cancer.

Second to the market, neratinib joined the list of HER2-targeted TKIs in 2017. This irreversible TKI targets HER1/EGFR, HER2, and HER4, exhibiting antiproliferative effects on cancer cells.[11,13] It was approved for adjuvant treatment of early HER2-positive breast cancer previously treated with one year of trastuzumab.

In 2020, neratinib gained a second indication for treatment of advanced or metastatic HER2-positive breast cancer following two or more previous lines of anti-HER2 therapy in combination with capecitabine.[6]

The most recent TKI to be brought to market is tucatinib. Tucatinib earned FDA approval in 2020 for the treatment of metastatic HER2-positive breast cancer in combination with trastuzumab and capecitabine.[6,14] Tucatinib, a reversible TKI, demonstrates high selectivity for HER2 over other HER proteins, producing fewer side effects than its predecessors.[11]

TKI SIDE EFFECTS

Selection of a HER2-targeted TKI depends on tumor cell and patient characteristics. While each TKI plays a vital role in the treatment of HER2-positive breast cancers, the distinct binding characteristics of each may influence treatment selection.

For example, neratinib's high potency demonstrates increased efficacy against HER2-positive cancer cells. With this potency and the pan-HER action, neratinib also poses an increased risk of toxicity and treatment interruption.[6]

While TKIs can significantly improve the overall prognosis and survival of patients diagnosed with HER2-positive breast cancer, they come with a unique set of off-target effects and resulting toxicities, especially when combined with capecitabine and trastuzumab. Managing these toxicities appropriately can prolong duration of treatment, patient tolerability and quality of life, and further prolong survival.

Diarrhea is a commonly reported side effect (>30%) of capecitabine and TKIs.[15] While less common (10-29%), it is also a reported side effect of trastuzumab.[16]

Not only can diarrhea significantly impair quality of life, it can also lead to many other side effects, including but not limited to dehydration, fatigue and malnutrition. Diarrhea can be dose-limiting and may require treatment breaks or drug discontinuation, potentially impacting the efficacy of the treatment regimen.

There are several measures that can be used to prevent, lessen or treat diarrhea. Patients should be encouraged to stay hydrated, drinking eight to 10 glasses of water or fluid each day (unless on fluid restriction noted by their doctor).[17] Smaller, more frequent meals that focus on bland, low-fiber foods are recommended. Patients should be encouraged to avoid high-fiber foods, lactose-containing foods, and spicy, fried or greasy foods.

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It is helpful for the patient to establish a baseline number of bowel movements per day. If that number increases by four or more in a single day, the patient should contact their provider. If the patient was unable to establish a baseline, more than four to six episodes in a 24-hour period can serve as a general guide as to when to contact their doctor. In addition, regardless of the number of episodes, the patient should contact their doctor if they feel dizzy or light-headed, or if they have black or bloody stools.

In addition to these supportive care recommendations, there are prescription and over-the-counter medications that can help prevent or treat diarrhea.

Loperamide is an over-the-counter anti-diarrheal that works in the intestinal tract as an opioid receptor agonist, reducing motility and lessening fluid and electrolyte loss.[18] Loperamide may be used prophylactically, as recommended with neratinib,[13] or on an as-needed basis.

If loperamide is ineffective or otherwise contraindicated for a patient, diphenoxylate-atropine is a prescription anti-diarrheal option. Diphenoxylate-atropine acts on gastrointestinal muscles to inhibit excessive gastrointestinal motility and slow gastrointestinal excess propulsion.[19]

Another prescription option is opium tincture. Opium tincture reduces gastrointestinal motility by enhancing gastrointestinal muscle tone thereby reducing gastrointestinal propulsion.[20]

Palmar-plantar erythrodysesthesia, also known as **hand-foot syndrome**, is a commonly reported side effect of capecitabine (54-60%),[21] lapatinib (53% with capecitabine)[22] and tucatinib (63%).[23]

Hand-foot syndrome is caused when chemotherapy leaks from the capillaries in the palms of the hands and soles of the feet, causing damage to the surrounding tissues.[24] This damage may present as redness, discomfort, or dry, peeling skin. The discomfort is commonly reported as numbness or tingling.

Hand-foot syndrome can cause significant discomfort that can reduce quality of life and impair patients' ability to complete their activities of daily living.

Like diarrhea, hand-foot syndrome may require dose reductions and/or treatment breaks, potentially creating a negative impact on treatment efficacy.

There are several supportive care recommendations to reduce symptoms of hand-foot syndrome:

- **Avoid exposing the hands and feet to heat and friction:**[24] Heat and friction can increase the amount of drug in the capillaries as well as the amount of drug leakage from the capillaries. This may require a change to the patient's daily routines, such as minimizing long, hot showers or baths, avoiding tight-fitting shoes, socks, or gloves, and minimizing long periods of pressure or friction on the palms of the hands or soles of the feet, such as while taking long walks.
- **Patients should be encouraged to keep the palms of the hands and soles of the feet moisturized:** Keeping the skin moisturized can relieve and prevent dry, peeling skin. Urea cream can be beneficial in this setting. Urea softens skin experiencing hyperkeratosis via dissolution of the intracellular matrix.[25] The use of a cream with at least 10% urea has been shown to decrease the extent of hand-foot syndrome and prolong its time to onset.[26] Patients may experience short-term relief of discomfort with cooling contact such as an ice pack.
- **Some patients may benefit from taking Vitamin B6 (pyridoxine).** However, its effectiveness has not been clinically proven.

Patients should be instructed to call their provider at the first sign of hand-foot syndrome.

NCODA PATIENT RESOURCES

NCODA provides many resources to help patients succeed on these therapies, including Treatment Support Kits (TSKs) for capecitabine and neratinib.

The capecitabine TSK contains loperamide for diarrhea, and Flexitol Heel Balm and Very Dry Skin Cream for hand-foot syndrome. Each of the Flexitol products contains urea, aloe, shea butter, and lanolin, all of which work to keep the skin moisturized.

In addition to these products, the capecitabine TSK contains Flexitol Lip Balm, sunscreen, a digital thermometer, a weekly a.m./p.m. pill container, a treatment calendar and educational materials.

The neratinib TSK contains a voucher for various anti-diarrheal medications, a treatment calendar and educational materials.

Oral Chemotherapy Education (OCE) sheets are another NCODA resource.

These drug-specific documents highlight key information to support patients' success with therapy. They contain information on administration, missed dose instructions, storage and handling, drug and food interactions, side effects with management tips, handling of body fluids and waste, and guidance regarding pregnancy and sexual activity.

The OCE sheets also contain web addresses where patients can search for additional information. These education sheets are free, accessible and written in an easy-to-read format for patient understanding.

This information can be critical to a patient's success with staying on therapy.

For example, as noted, loperamide is recommended for prophylactic use in patients starting neratinib, given the high incidence of diarrhea (95%).[13] The recommended dosing schedule for loperamide for diarrhea prophylaxis is clearly outlined in the NCODA oral chemotherapy education sheet for neratinib.

The OCE sheets also provide patients with guidance on when to contact their providers if a side effect presents, enhancing patient safety.

NCODA PROVIDER RESOURCES

NCODA also has resources for healthcare providers.

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Positive Quality Interventions (PQI) are complimentary and accessible resources that cover a range of topics related to oncology.

There is a PQI available for tucatinib, which covers many key and helpful points for providers, including guidance on dose reductions if necessary.

There is also a PQI specific to neratinib-induced diarrhea, including the recommended dose escalation of neratinib, dose adjustment guidance if necessary, and recommended lab draw schedule.

In addition to drug-specific PQIs, PQIs that cover specific symptoms also are available, including:

- **Oncolytic-induced diarrhea**, identifying common offending medications, counseling points and treatment medication options; and
- **Palmar-plantar erythrodysesthesia,** which provides counseling points and a comprehensive list of offending medications.

In summary, HER2-positive breast cancer is a prevalent and aggressive condition with a variety of effective treatment options. Many HER2-positive breast cancer patients will undergo treatment with an oral TKI and may experience unique side effects to the new treatment.

With appropriate counseling and side effect management, utilizing the many available resources, pharmacists can help to set patients and their caregivers up for success in their treatment journey, and by doing so help the patients achieve the best possible outcomes.

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UPDATES TO (NEO)ADJUVANT TREATMENT OF NON-METASTATIC BREAST CANCER

By Colleen Bohnenkamp, PharmD, BCPS, BCOP

There have been several practice-changing advancements to the treatment of non-metastatic breast cancer in the past several years, including incorporation of immunotherapy to neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) and the use of oral targeted medications for adjuvant treatment in high-risk, early breast cancer.

Colleen Bohnenkamp

Breast cancer is the most diagnosed cancer among women and the second leading cause of cancer death in the United States.[1]

The treatment of breast cancer is complex and continually evolving. Treatment of non-metastatic breast cancer typically consists of local therapy, with surgery and/or radiation, and systemic therapy with chemotherapy, endocrine therapy, biologics or combinations thereof.[2] The choice of treatment depends on tumor histology, tumor molecular markers, tumor size and lymph node status, estimated risk of recurrence and patient-specific factors.[1,2]

The treatment of breast cancer is complex and continually evolving ... Choice of treatment depends on tumor histology, tumor molecular markers, tumor size and lymph node status, estimated risk of recurrence and patient-specific factors.

RxPONDER[3]

Multigene prognostic assays, such as the Oncotype DX, are widely used to estimate the risk of recurrence among women with hormone-receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative early breast cancer. The Oncotype DX assay determines a recurrence score, ranging from 0-100, with a higher score indicating a worse prognosis.

Based on the results of the TAILORx trial[4] which was conducted among women with recurrence scores between 11 to 25 with HR+, HER2-negative, axillary lymph-node-negative breast cancer, no benefit to adjuvant chemotherapy was noted among women who were >50 years old.

The RxPONDER trial sought to determine the benefit of adjuvant chemotherapy in addition to standard endocrine therapy (ET) among women with one to three positive axillary lymph nodes.

Women who had HR+, HER2-negative, nodal stage N1, and recurrence scores of 0 to 25 were randomized 1:1 to receive adjuvant chemoendocrine therapy or ET alone. The primary endpoint was invasive disease-free survival (IDFS).

In the overall trial population (N=5,083), the IDFS at five years was 92.2% among women in the chemoendocrine group versus 91% in the ET only group (p=0.10). However, when adjusted for menopausal status, based on a prespecified analysis, IDFS at five years was significantly greater in premenopausal women that received chemoendocrine therapy (93.9%) as compared to those who received ET only (89%), (hazard ratio, 0.6; 95% CI, 0.43 to 0.83; p=0.002).

The authors concluded that among premenopausal women with one to three positive lymph nodes and a recurrence score of <25, chemoendocrine therapy resulted in a longer IDFS and distant relapse-free survival than ET alone. These results were not consistent among the postmenopausal participants. Further, the relative chemotherapy benefit based upon an increasing recurrence score was not supported in either population.

monarchE[5]

The majority of breast cancer is diagnosed as early-stage disease and is predominantly the HR+, HER2-negative subtype.[6]

The monarchE trial was an open-label phase III trial conducted to determine if the addition of abemaciclib, an oral cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, to standard ET would result in improved IDFS among women with high-risk early breast cancer.

Patients with HR+, HER2-negative, node-positive, high-risk, early breast cancer who had surgery +/- radiotherapy and/or adjuvant/neoadjuvant chemotherapy were randomized 1:1 to receive abemaciclib 150 mg orally twice per day plus standard ET or ET alone. Patients received abemaciclib for up to two years. ET was continued to complete a total of five to 10 years. High-risk disease was defined as >4 positive pathologic axillary lymph nodes or one to three positive axillary lymph nodes and at least one of the following: tumor size > 5 cm, histologic grade 3 or Ki-67 > 20%.

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The primary endpoint was IDFS and was performed on the intent to treat population (abemaciclib + ET N=2,808; ET alone N=2,829).

At the preplanned interim analysis, after a median follow-up time of 15.5 months, there was a statistically significant improvement in two-year IDFS, 92.2% in the abemaciclib + ET arm versus 88.7% in the ET alone arm (p=0.01; HR, 0.75; 95% CI, 0.60 to 0.93). The treatment effect was observed in all prespecified subgroups. Overall survival data were immature and will be reported in the final analysis.

Grade ≥ 3 adverse events occurred in 45.9% of patients in the abemaciclib arm and 12.9% of patients in the control arm. The most frequent adverse events of any grade were diarrhea (82.2%), neutropenia (44.6%) and fatigue (38.4%) in the abemaciclib arm, and arthralgia (31.3%), hot flush (21%) and fatigue (15.5%) in the control arm.

The authors concluded that the addition of abemaciclib to standard ET resulted in a 25% reduction in the risk of developing an IDFS event relative to ET alone and an absolute improvement of 3.5% in two-year IDFS rate among women and men with HR+, HER2-negative, node-positive, high-risk, early breast cancer.

On Oct. 12, 2021, the U.S. Food and Drug Administration (FDA) approved abemaciclib in combination with ET for adjuvant treatment of adult patients with HR+, HER2-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%.[7] However, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO)[2,8] have updated their guidelines to state that among patients with HR+, HER2-negative, high-risk, early breast cancer, two years of abemaciclib + ET can be considered, irrespective of Ki-67 score.

KEYNOTE-522[9]

Neoadjuvant chemotherapy is a preferred treatment strategy for high-risk, early, triple-negative breast cancer (TNBC), as TNBC is associated with a high mortality rate and risk of recurrence.[2,9] Pathologic complete response (pCR) after neoadjuvant therapy is associated with longer event-free and overall survival rates.[9-13] The CREATE-X trial, demonstrated that the addition of adjuvant capecitabine resulted in improved DFS and overall survival as compared to placebo in patients that did not achieve a pCR to neoadjuvant therapy.[14]

The KEYNOTE-522 trial was a randomized, double-blind, phase III trial conducted to evaluate the safety and efficacy of the addition of pembrolizumab, an immune checkpoint inhibitor, to neoadjuvant chemotherapy followed by adjuvant pembrolizumab or placebo.

Patients with newly diagnosed, non-metastatic (tumor stage T1c, nodal stage N1-2, or tumor stage T2-4, nodal stage N0-2), untreated, and confirmed TNBC were randomized 2:1 to receive pembrolizumab + chemotherapy followed by surgery then adjuvant pembrolizumab (N=784) or placebo + chemotherapy followed by surgery then adjuvant placebo (N=390).

KEYNOTE-522 TREATMENT PROTOCOL

Neoadjuvant phase 1: paclitaxel weekly + carboplatin (AUC 5 every three weeks or AUC 1.5 weekly) + pembrolizumab/placebo every 21 days x four cycles

Neoadjuvant phase 2: doxorubicin/epirubicin + cyclophosphamide + pembrolizumab/placebo every 21 days x four cycles

Adjuvant phase: pembrolizumab/placebo every 21 days x nine cycles

The first neoadjuvant phase consisted of four cycles of pembrolizumab (200 mg) or placebo once every three weeks plus paclitaxel (80 mg/m^2) weekly for 12 weeks plus carboplatin (AUC 5 every three weeks or AUC 1.5 once weekly for 12 weeks). The second neoadjuvant phase consisted of pembrolizumab (200 mg) or placebo plus doxorubicin (60 mg/m^2) or epirubicin (90 mg/m^2) plus cyclophosphamide (600 mg/m^2) once every three weeks for four cycles.

Patients then completed definitive surgery (lumpectomy or mastectomy with lymph node evaluation or dissection). Adjuvant therapy began after surgery and consisted of pembrolizumab (200 mg) or placebo every three weeks for up to nine cycles, and radiation therapy if indicated. Adjuvant capecitabine was not allowed per protocol. Most patients in the study were PD-L1 positive (83.7% in the pembrolizumab-chemotherapy group compared to 81.3% in the placebo-chemotherapy group).

The co-primary endpoints were pCR, defined as ypT0/Tis ypN0, and event-free survival, in the intent-to-treat population. At the preplanned interim analysis, the pCR in the pembrolizumab-chemotherapy group (N= 401) was 64.8% versus 51.2% in the placebo-chemotherapy group (N= 201) (estimated treatment difference, 13.6%; 95% CI, 5.4 to 21.8; p<0.001). Kaplan-Meier estimates of 36-month event-free survival favored the pembrolizumab-chemotherapy group at 84.5%% (95% CI, 81.7 to 86.9) versus 76.8% (95% CI, 72.2 to 80.7) in the placebo-chemotherapy group (HR for event or death, 0.63; 95% CI, 0.48 to 0.82; p<0.001).[15]

Grade ≥ 3 treatment-related adverse events occurred in 76.8% of the pembrolizumab-chemotherapy arm and 72.2% in the placebo-chemotherapy arm. The most frequent adverse events of any grade in both groups were nausea, alopecia, anemia, neutropenia and fatigue. Adverse events of interest occurring more frequently in the pembrolizumab-chemotherapy arm included infusion reaction (16.9% vs 11.1%), hypothyroidism (13.7% vs 3.3%), hyperthyroidism (4.6% vs 1%), severe skin reaction (4.4% vs 1%) and adrenal insufficiency (2.3% vs 0).

The authors concluded that among patients with high-risk early TNBC, the combination of pembrolizumab and chemotherapy resulted in significantly higher pCR rates than patients receiving chemotherapy alone.

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BREAST CANCER

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The NCCN guidelines have been updated to recommend the KEYNOTE-522 regimen for patients with high-risk stage II-III TNBC.[2]

OlympiA[16]

Poly ADP-ribose polymerase (PARP) Inhibitors are approved for use in advanced germline BRCA1 (gBRCA1) and BRCA2 (gBRCA2)-mutated breast cancer.[17,18] The OlympiA trial was conducted to determine if adjuvant olaparib would provide benefit among patients with high-risk, gBRCA1 or gBRCA2-mutated breast cancer.

Patients with HER2-negative, high-risk, early breast cancer harboring a gBRCA1 or gBRCA2 mutation, were randomized 1:1 to receive olaparib 300 mg orally twice per day (N=921) or placebo (N=915) for one year, after the completion of local therapy and adjuvant or neoadjuvant chemotherapy. Patients were excluded if they had a pCR after neoadjuvant chemotherapy. Adjuvant chemotherapy was not allowed in patients that received neoadjuvant chemotherapy.

The primary endpoint was IDFS. At the interim analysis, the median follow-up was 2.5 years in the ITT population and 3.5 years in the mature cohort. The three-year IDFS was 85.9% in the olaparib group and 77.1% in the placebo group (HR for invasive disease or death, 0.58; 99.5% CI, 0.41 to 0.823; p<0.001).

The most frequent grade ≥ 3 adverse events occurring in the olaparib group were anemia (8.7%), decreased neutrophil count (4.8%), decreased white blood cell count (3%), and fatigue (1.8%). No grade ≥ 3 adverse events occurred in over 1% of the placebo group.

The authors concluded that adjuvant olaparib was associated with a significantly longer survival free of invasive disease or distant disease as compared to placebo among patients with high-risk, HER2-negative, gBRCA-mutated, early breast cancer.

The NCCN guidelines state one year of olaparib can be given to patients with a gBRCA1 or gBRCA2 mutation after the completion of chemotherapy and radiation.[2] Olaparib can be given concurrently with endocrine therapy, if appropriate.

▲ **Colleen Bohnenkamp**, PharmD, BCPS, BCOP, is an Oncology Clinical Pharmacist at The University of Kansas Cancer Center.

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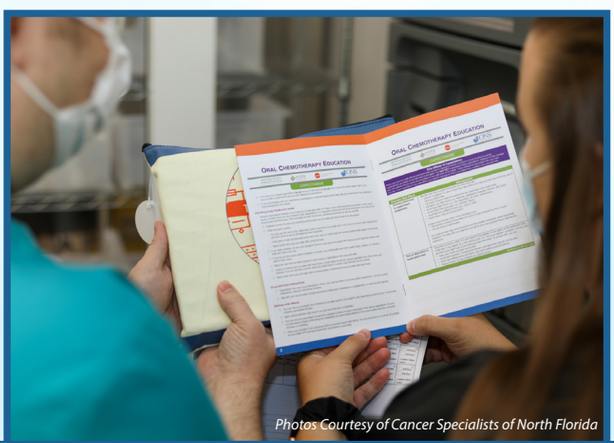

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CYCLIN-DEPENDENT KINASE 4/6 INHIBITOR TREATMENT USE IN WOMEN TREATED FOR ADVANCED BREAST CANCER

INTEGRATING ASCO/NCODA PATIENT-CENTERED STANDARDS IN A COMMUNITY PHARMACY

A recent real-world study published in the *Journal of Oncology Pharmacy Practice* focused on the impact of the ASCO/NCODA Patient-Centered Standards for Medically Integrated Dispensing (MID) on cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) treatment use in women treated for advanced breast cancer (ABC).[1]

Researchers studied a cohort of 65 women ages 39 to 94 with confirmed hormone receptor-positive/human epidermal growth factor 2 negative locally advanced or metastatic breast cancer treated with either palbociclib or abemaciclib combined with letrozole or fulvestrant.

The study's primary objective was to document the type and frequency of pharmacists' clinical and administrative activities performed in a practice setting, using the ASCO/NCODA Patient-Centered Standards for benchmarking.

Secondary objectives were aimed at describing clinical outcomes, including:

- Treatment adherence rate as measured by the modified medication possession ratio (MPRm) and the proportion of days covered (PDC);
- Relative dose intensity (RDI) and duration of treatment/time-to-treatment discontinuation (TTD); and
- Time-to-treatment initiation (TTI).

The study was conducted by pharmacists Alexandre Marineau, MSc, PharmD, Catherine St-Pierre, BPharm, MSc, Directrice des Affaires Externes et Corporatives, Roxanne Lessard-Hurtubise, and Marie-Ève David of Larivière and Massicotte Pharmacy in Montréal, Quebec (Canada); Jean-Philippe Adam, BPharm, MSc, BCPS, BCOP, of the Department of Pharmacy, Centre hospitalier de l'Université de Montréal, and CHUM Research Center, CHUM, Montréal, Canada; and Isabelle Chabot, BPharm, MSc, PhD, Faculty of Pharmacy of Université de Montréal, Montréal, Canada.

Larivière and Massicotte Pharmacy (LMP) was the site of the study. LMP is an independent pharmacy that has been dedicated to the dispensing of specialty drugs for more than 14 years. It has a practice model which integrates most of the recommendations found in the ASCO/NCODA MID Standards.

Published in December 2019, the ASCO/NCODA Standards focus on improving patient outcomes by minimizing administrative delays in patient treatment, promoting treatment adherence, preventing and managing adverse events, and empowering patients to become a partner in their own care.[2]

NCODA defines Medically Integrated Dispensing Pharmacy as a dispensing pharmacy within an oncology center of excellence that promotes a patient-centered, multidisciplinary team approach.[3]

The ASCO/NCODA Standards provide an outcome-based collaborative and comprehensive model that involves healthcare professionals and other stakeholders who focus on the continuity of coordinated quality care and therapies for cancer patients.[3]

For the CDK4/6i study, the ASCO/NCODA Standards translated into an average of seven clinical and administrative activities for each 28-day CDK4/6i treatment cycle.

Direct communication with patients was the most common of these activities. This included systematic initial teaching, seven-day follow-up calls after treatment initiation, and monthly adherence calls.

Other communication activities included follow-ups related to adherence, adverse events, adjustment of antiemetic medication, planning of next refill and/or laboratory test recommendations.

One key finding in the study was the importance of minimizing TTI for advanced breast cancer patients.

"Delaying the initiation of treatment for ABC can negatively impact the treatment outcomes and is a major source of anxiety and distress for patients," the authors stated. They determined that standardized follow-up could help

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This study was published in the May 31, 2022, issue of the *Journal of Oncology Pharmacy Practice*. To view the article, scan the QR code above.

ASCO/NCODA STANDARDS

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decrease delays before initiating treatment. Insurance delays were cited as a major factor. Nonetheless, once reimbursement was granted (mean 14.5 days), patients were able to initiate treatment within four calendar days on average, representing a minimal delay.

Comparatively, an earlier Canadian study showed that initiation of first-line treatment for CDK4/6i following metastatic diagnosis averaged 1.4 months.

The researchers also found that adherence rates also benefited from the ASCO/NCODA model. Participants reported adherence of more than 90% throughout the study period, compared to a previous CDK4/6i study that reported an average 81% adherence for patients using specialized pharmacies.

The ASCO/NCODA model's flexibility in dealing with dose modifications also was noted.

The study concluded that a "structured patient-centered pharmacy practice model integrating the ASCO/NCODA Patient-Centered Standards and ongoing communication with patients and healthcare providers ensure timely refills, close monitoring, and allows patients to achieve high adherence and persistence rates comparable to those reported in clinical trials."

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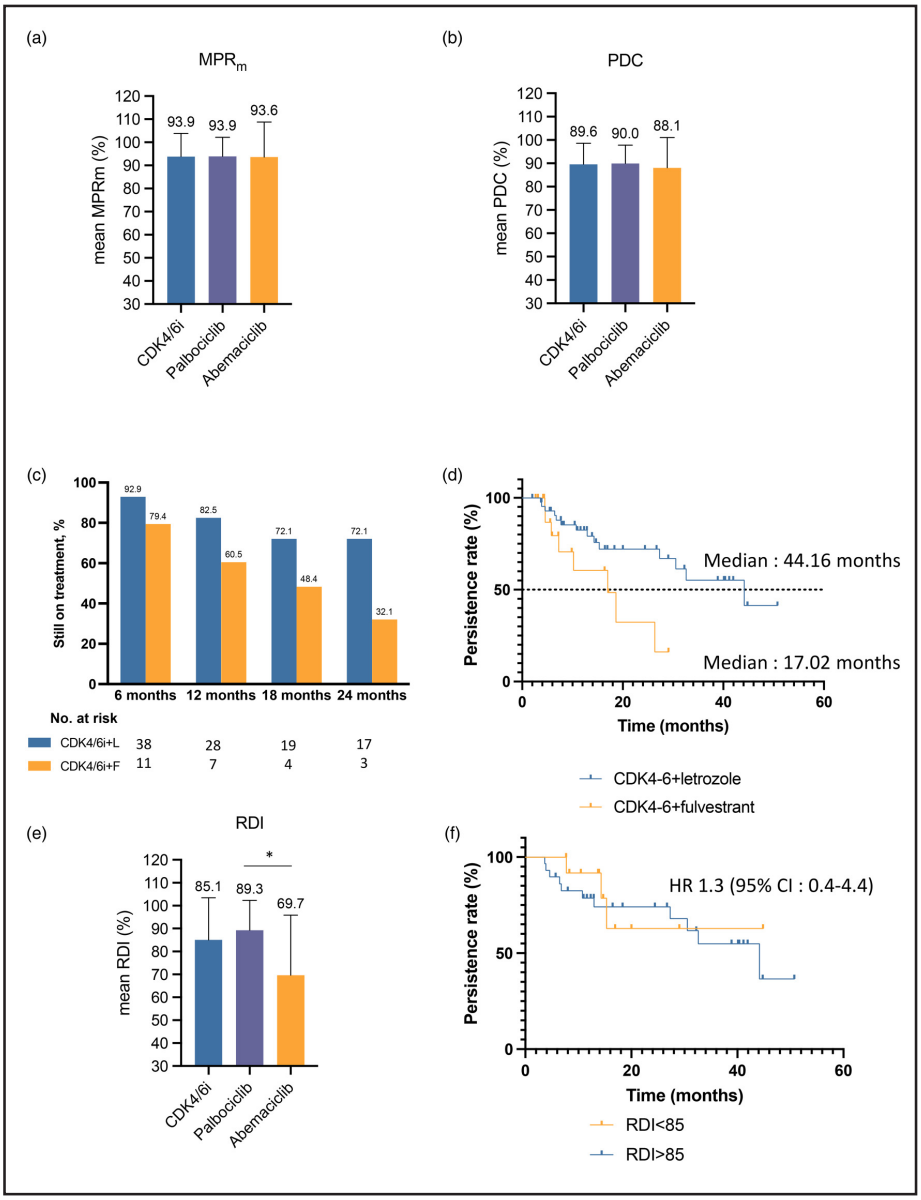

Adherence and duration of treatment data reported in the study: (a) Mean modified medication possession ratio (MPRm) and **(b)** mean proportion of days covered (PDC) are shown in patients treated with either CDK4/6i, palbociclib, and abemaciclib combined with letrozole or fulvestrant. **(c)** Landmark persistence rates are shown in patients treated with either CDK4/6i combined with letrozole or fulvestrant. Rates were estimated using Kaplan-Meier analyses. **(d)** Persistence rates as assessed by the investigators; the median time-to-treatment discontinuation was 44.16 months among 44 patients in the CDK4/6i+letrozole group and 17.02 months among 19 patients in the CDK4/6+fulvestrant group. **(e)** Relative dose intensity is shown for patients treated with either CDK4/6i, palbociclib, and abemaciclib *p=0.023. **(f)** Persistence rates of patients stratified according to their RDI level. Patients achieving and RDI of 85% or higher had similar time-to-treatment discontinuation than patients have an RDI below 85% (HR: 1.3 [95% CI :0.4–4.4]).

Abbreviations: MPRm: modified medication possession ratio; **PDC:** proportion of days covered; **CDK4/6i:** cyclin-dependent kinase 4 and 6 inhibitors; **L:** letrozole; **F:** fulvestrant; **RDI:** relative dose intensity; **HR:** hazard ratio; **CI:** confidence interval.

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SPAIN'S PINK ARCHERS OFFERS BREAST CANCER PATIENTS BOTH THERAPY & EMOTIONAL SUPPORT

By Alejandro Arango Rueda

For women undergoing treatment for breast cancer, surgical options are a daunting prospect, both physically and emotionally.

In cases where both the mammary gland and homologous lymph node in the armpit are removed the accumulation of lymphatic fluid — lymphedema — in the patient's arm can affect activities of daily living.[1]

"The arm becomes inflamed, generating pressure and pain in patients. In some cases, they suffer from chronic skin infections and must be treated preventively with penicillin," said Lucía González-Cortijo, MD, coordinator of the Breast and Gynecological Cancer Unit of the Quirónsalud Madrid University Hospital, and founder of the La Vida en Rosa (Life in Pink) Foundation.[2]

Alejandro Arango Rueda

The inflammatory process can be treated through several avenues, including massage, compression, exercise and raising of the arms.[1] There are also programs like Pink Archers, which specifically emphasize sports and physical activity as a form of therapy.

Starting in 2016, the Infanta Leonor University Hospital in Madrid, in collaboration with the Spanish Association Against Cancer (AECC) of Aranda de Duero and Arco Club Los Mosqueteros (The Archery Club Musketeers or ACM), developed the archery program as a form of physical therapy to reduce the effects of inflammation on the affected arm.[3]

But Pink Archers is more than just physical therapy program. It also acts as support group for women going through breast cancer and mastectomies. And the emotional bond provided by the program has turned out to be just as important as its physical therapeutic benefits.

A participant in the Pink Archers program celebrates her efforts on the archery range. The program was developed as a form of physical therapy to reduce arm inflammation for women going through breast cancer treatment and following mastectomies.

Breast cancer therapy presents a particular challenge in oncology. It is often difficult to advance rehabilitation due to complex mental traumas, such as depression and decreased self-esteem, brought on by the change in the patient's morphology. In many cases, this trauma causes women to lose motivation even for life itself.

Pink Archers helps patients overcome this hurdle by integrating both physical and mental rehabilitation.

The program begins with a preparatory physiotherapy session, where women learn exercises that serve to tone the muscles involved in archery.[4] Next, the patient takes a 20-hour introductory course over two weekends.

After that, the patient begins practicing archery for two hours a week under the supervision of a monitor for the next year.

Every three months, the patient goes through a rehabilitation consultation to

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LYMPHEDEMA

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review her progress.[4]

In addition to archery, the program includes a series of group activities, where women who previously underwent surgery can provide emotional and functional feedback.[5,6,7,8] This social link helps participants recover interest in the aspects of life that motivated them before their cancer treatment.

More than 500 women in Spain have participated in and positively benefited from the program. The project is now being developed in other countries with excellent results.

If you are interested in learning more or developing a program at your practice, please email the author at **arangoarcherycoach@gmail.com**.

▲ **Alejandro Arango Rueda** is an archery coach and sports manager in Chelsea, Massachusetts.

The Pink Archers program provides women going through breast cancer treatment and its aftermath with both physical rehabilitation and emotional support.

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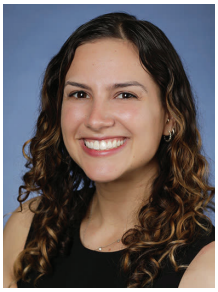
ALL HANDS ON DECK

AN INTERDISCIPLINARY APPROACH IS CRITICAL TO SUPPORT ADHERENCE OF ORAL ANTICANCER MEDICATIONS

By Vera Pervitsky, PharmD, & Ryan Beechinor, PharmD, BCPS, BCOP

It is hard to imagine that the first oral tyrosine kinase inhibitor, imatinib (GLEEVEC®), was approved more than 20 years ago.[1,2] This little orange tablet revolutionized the way we treat cancer, and paved the way for other targeted oral oncolytics.

This success of imatinib has led to a concerted effort by pharmaceutical manufacturers to focus on the development of oral drugs to treat cancer.[3]



Vera Pervitsky

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Because of this growth, as well as the expansion of the number of oral oncolytics approved by the U.S. Food & Drug Administration (FDA), patients can successfully undergo treatment for certain malignancies without requiring hospital admissions or injections, providing convenience and improved quality of life.[4]

However, oral chemotherapy poses its own challenges, particularly with patient adherence. To overcome this challenge, an interprofessional approach is essential.

The implications of patient nonadherence to oral chemotherapy have been demonstrated across several cancer types.[5] Multiple studies have explored the relationship between imatinib adherence for the treatment chronic myeloid leukemia (CML), and found that nonadherence was associated with poorer outcomes and disease progression.[6,7]

One such study found that nonadherent patients had a five-year, event-free survival of 59.8% compared to 76.7% in adherent patients, which underscores the importance of adherence.[8]

Another multivariate analysis revealed that adherence was found to be the only independent risk factor for major molecular response.[9] In the pediatric population, an assessment of mercaptopurine adherence after achieving remission of acute lymphoblastic leukemia (ALL) found that those with lower adherence had a higher risk of relapse.[10]

Low adherence to adjuvant endocrine therapy for hormone receptor-positive breast cancer was associated with a higher risk of death.[11]

Therefore, it is critical that patients understand that nonadherence can detrimentally affect their clinical outcomes, and that cancer centers have a dedicated, well-staffed, multidisciplinary team available to care for prescribed oral oncolytics therapy.

FACTORS IMPACTING ADHERENCE

Many factors can impact patient adherence to oral chemotherapy:

- **Patient misunderstanding:** In a study that included patients prescribed oral capecitabine for either gastrointestinal malignancies or breast cancer, patients cited misunderstanding of the prescription and toxicity as reasons for missing a dose.[12]
- **Reaction to side effects:** When patients perceived their side effects to be too severe, they self-discontinued their oral chemotherapy.[12]
- **Timing:** The timing of oral chemotherapy administration with regards to meals was another identified adherence issue, potentially resulting in deleterious food-drug interactions.[12] For example, patients should avoid proton pump inhibitors with dasatinib to prevent loss of efficacy.[13]
- **Forgetfulness:** In another study conducted in a well-educated population across several cancer types, investigators found that despite the life-threatening nature of their cancer, 30% of patients reported forgetting to take their oral chemotherapy at least sometimes, and 38% of patients reported intentionally skipping their treatment and did not inform their cancer team.[14]

Other factors associated with nonadherence to oral chemotherapies include the cost of oral anticancer agents, regimen complexity, depression and poor patient education.[15]

Given that some of these factors are modifiable, fiduciary relationships between providers and patients, proper patient education and understanding of a patient's chemotherapy regimen is

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INTERDISCIPLINARY

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imperative.[16]

AN INTERDISCIPLINARY APPROACH

Interdisciplinary healthcare teams play a pivotal role in developing methods and interventions to help patients adhere to their chemotherapy regimens.

First and foremost, to deliver safe and effective care to patients receiving complex anticancer therapies, appropriate training of staff is necessary. An interprofessional training program consisting of modules and workshops focused on several aspects of oncology drug management, including oral chemotherapy adherence, may increase knowledge and confidence amongst interdisciplinary team members.[17]

Interdisciplinary team members can utilize their knowledge to conduct motivational interviews that highlight the importance of adherence to oral chemotherapy agents, and promote behavior changes in nonadherent patients.[18]

Oral anticancer medication programs utilizing multidisciplinary team members may be implemented to increase adherence to oral chemotherapy. These programs consist of several components, including education, counseling, follow-up, dedicated clinical contact, adverse event and toxicity monitoring, adherence monitoring, drug procurement and cost reduction.[19]

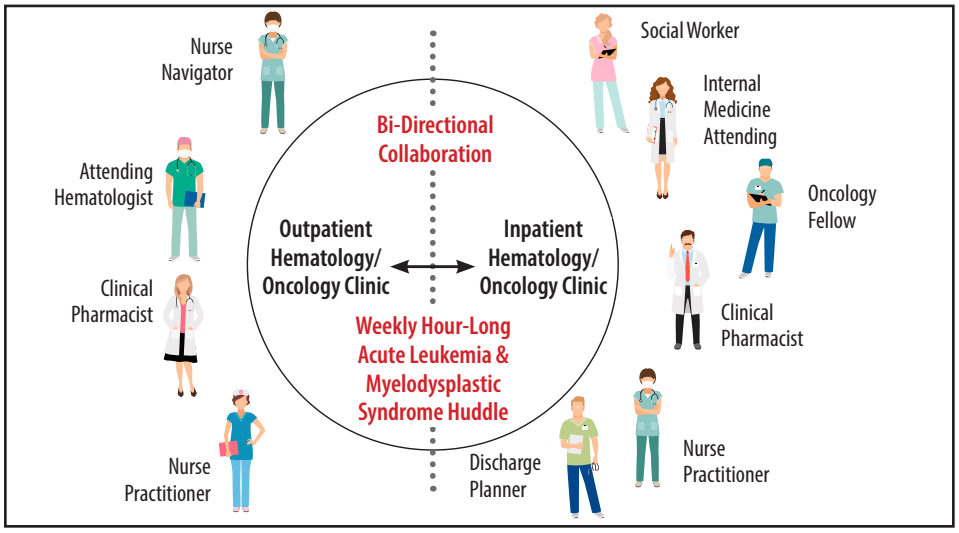
A focus on transitions of care, communication and follow-up may improve a patient's confidence and self-efficacy to adhere to their oral anticancer regimen.[19,20]

Programs that provide dedicated clinician contact through 24/7 telephone lines or messaging systems may help triage side effects and answer questions, further supporting patients to continue taking their medications.[19]

PATIENT EDUCATION

Quality patient education and support from interdisciplinary teams and family members are at the core of adherence interventions.[18]

FIGURE 1: MULTIDISCIPLINARY AML TEAM



An integrated oral chemotherapy program consisting of specialty pharmacists who assist with insurance authorization and clinical pharmacists who perform patient education may improve adherence.[20]

When providing patient education, consideration of a patient's preferences for learning may help tailor the format of the counseling session, materials and teaching method.[18]

Best practices for the management of oral chemotherapy by pharmacists provide detailed recommendations for patient education.[21]

These recommendations include utilizing materials adapted to varying health literacies, discussing patient and caregiver goals for the education session, performing a comprehensive medication review to identify potential drug-drug interactions, highlighting key information about the oral anticancer agent, and emphasizing the importance of adherence.[21]

During counseling sessions, adherence methods incorporating pillboxes, routines, and tracking systems should be discussed.[22]

MANAGING TOXICITIES

Since toxicity has been identified as a cause of nonadherence, a focus on prevention and management of toxicities is necessary. Many team-based nursing and pharmacist communication, education and counseling interventions have been explored.[23,24]

For example, venetoclax, an oral BCL-2 inhibitor, is known to increase the risk of tumor lysis syndrome (TLS). An interdisciplinary team that included pharmacists developed a protocol to manage patients with chronic lymphocytic leukemia (CLL) receiving venetoclax. The protocol — which included weekly appointments, assessment of adherence, management of toxicities and laboratory evaluations — was able to mitigate TLS as well.[25]

Pharmacists and other healthcare providers can emphasize dose reductions for venetoclax and other oral anticancer agents that are substrates of CYP3A4 in the presence of strong CYP3A4 inhibitors like azole antifungals to prevent QTc prolongation.[13]

Toxicity can be due to the oral anticancer agent itself or exacerbated by drug or food interactions, which should be routinely discussed with patients. Patients prescribed drugs such as pazopanib and temozolomide should be counseled to take the medication on an empty stomach to avoid increased adverse effects.[13]

Based on known patient access issues with ability to receive oral antineoplastic agents, we at UC Davis Health have an ongoing study investigating the impact of a multidisciplinary team has on AML patients receiving hypomethylating agents (HMA) + venetoclax **(See Figure 1)**.

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INTERDISCIPLINARY

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The goal of this study is to demonstrate the impact that multidisciplinary teams have on minimizing hospital length of stay for patients receiving this new standard of care. Preliminary results of 78 consecutive patients treated with HMA and venetoclax revealed utilization of an interdisciplinary AML team to target early hospital discharge proved to be safe, and effective, leading to a reduction in costs for the health system (unpublished).

In conclusion, implementing a collaborative approach among patients, physicians, pharmacists and nurses can improve rates of oral anticancer adherence, overcoming a significant barrier in treating patients with oral chemotherapeutics.

Providing care in this structured way will ensure delivery in a manner that is efficient, safe and patient-centered.[26,27]

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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, Inspire & 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.

MEASURING THE COST OF TIME TOXICITY

FOR CANCER PATIENTS WITH A LIMITED LIFE EXPECTANCY, THE TIME INVESTMENT FOR ADDITIONAL TREATMENT MAY OUTWEIGH POTENTIAL SURVIVAL GAINS

"Time toxicity ... includes time spent in coordinating treatments, in travel to treatments, in waiting rooms, in actually getting that treatment, in experiencing anticipated and unanticipated adverse events, follow-up tests and rehabilitations, as well as visits to a healthcare facility."

Arjun Gupta, MD

Oncologists consider a myriad of factors when treating an individual's cancer, including:

- The patient's general health, function and comorbidities;
- The type, extent and behavior of the particular malignancy;
- The expected benefits and side effects of the treatment options; and
- The availability and potential of clinical trials; and a host of other factors.

Up until now, however, one important component often has been left out of this equation: time spent in treatment and its relative value to the patient undergoing therapy.

The issue and potential metrics in future healthcare were explored in "The Time Toxicity of Cancer Treatment," by Arjun Gupta, MD, Elizabeth A. Eisenhauer, MD, and Christopher M. Booth, MD, in the March 2, 2022, edition of the *Journal of Clinical Oncology*.

In the article, the authors maintain that modest average two- to three-month survival gains for patients undergoing treatment

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TIME TOXICITY

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for incurable solid cancers "need to be balanced with potential downsides of therapy."

"Although oncologists commonly discuss side effects and the financial impact of treatment, there is growing recognition that our community does not do a good job of acknowledging, quantifying, or weighing in the discussion (of) the impact of time toxicity," the authors state.

A METRIC FOR TIME

But just what is time toxicity?

Gupta recently explained the concept in a podcast for the American Society of Clinical Oncology:

"Time toxicity is the time spent in pursuing a treatment for cancer," he said. "This includes time spent in coordinating treatments, in travel to treatments, in waiting rooms, in actually getting that treatment, in experiencing anticipated and unanticipated adverse events, follow-up tests and rehabilitations, as well as visits to a healthcare facility. All of the time that a patient and their care partner are spending is what we think of as time toxicity."

Arjun Gupta

"This concept is perhaps applicable to all patients but is probably most applicable to people with advanced solid tumors, who are facing treatment decisions in the context of limited time. In some cases, the overall survival benefit, or the time benefit offered by treatment actually may be overtaken by the time spent in pursuing that treatment."

In a nutshell, patients with advanced cancer with limited life expectancy should be allowed to measure potential survival gains of possible treatment against the amount of time they would be required to invest in that treatment.

For example, the authors state, "A patient may view treatments differently if they knew that, on average, three of their remaining estimated nine months alive would be spent away from home (e.g., in infusions and in the hospital) if they pursue treatment option A, but that all of their estimated remaining seven months would be spent at home if they pursued option B."

But to provide this type of information, oncologists need an effective way to measure time toxicity.

The authors suggest an ideal measure should be patient-centered and comprehensive, including all time burdens associated with the patient's cancer care. They propose a metric of Days with Physical Healthcare System Contact versus Home Days (i.e., days without physical contact).

While the concept will require further study, the authors maintain such a metric could be reliably implemented in clinical trials with minimal additional burden, with digital technology providing an accurate measuring tool.

To view this article in the *Journal of Clinical Oncology*, scan the QR code above.

THE TIME TOXICITY OF CANCER TREATMENT

Time Toxicity: Time spent coordinating treatments and in-visits to a healthcare facility (including travel and waiting), seeking urgent/emergent care for side effects, hospitalizations, and follow-up tests and rehabilitation.

Proposed Metric of Time Toxicity: Days with physical healthcare system contact

Overall Survival = Days with Physical Healthcare System Contact + Home Days

Hypothetical Treatment	Clinical Trajectory	Overall Survival (In Days)	Home Days
Treatment A	Frequent clinic visits, chemotherapy toxicity, hospitalization and rehabilitation	150	90
Treatment B	Short hospitalization for symptom control	120	115

With information on **Time Toxicity** and **Home Days**, a clinician can better guide a patient regarding a treatment strategy that best aligns with the patient's goals.

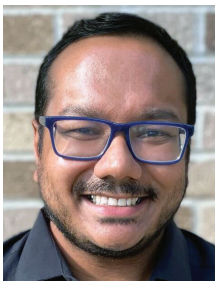
▲ **Arjun Gupta**, MD, is an oncologist in Minneapolis, Minnesota, affiliated with M Health Fairview University of Minnesota Medical Center. **Elizabeth A. Eisenhauer**, MD, FRCPC, is an Emerita professor at the Department of Oncology, Queen's University, Kingston, Ontario, Canada. **Christopher M. Booth**, MD, FRCPC, is a Medical Oncologist and Health Services Researcher at Queen's University in Kingston, Ontario, Canada.

NCODA'S ONCOLOGY RESIDENCY & FELLOWSHIP DIRECTORIES PROVIDE CONVENIENT RESOURCES FOR STUDENT PHARMACISTS

By Sarder Sadid, PharmD

The student-pharmacist's final school year can be a daunting experience as they decide which post-graduation route to pursue.

Some students may feel that this decision determines their future and sets their career in stone. This cannot be further from the truth. One of the perks of being a pharmacist is the fluidity that is enjoyed in terms of career options. The PharmD degree may be utilized in unique ways that many students never considered.



Sarder Sadid

The most common options currently pursued by student pharmacists include residencies, fellowships or positions in a community setting. This is no surprise. Most schools of pharmacy advocate for these pathways as they offer the most abundant number of positions.

There are benefits associated with each role, and the best thing is that there are no wrong answers. Regardless of where you land post-graduation, you are set up for a rewarding and meaningful career.

Yet the versatility of the pharmacy profession also can be a two-edged sword for the graduate. How does one choose the correct path amid so many options?

Sometimes young professionals find themselves in positions or experiences that they do not enjoy as much as they thought they would. Fortunately, we are in a profession that enables us to explore new avenues until we find the right one.

THE BENEFIT FOR NCODA MEMBERS

NCODA has determined that student pharmacists and young professionals can find value in a one-stop resource for opportunities in oncology. For this reason, we set forth to create directories that highlighted residencies and fellowships focused on oncology.

NCODA's website currently provides two separate directories — one for PGY-2 oncology residencies and another for fellowships that focus on oncology. Each directory is easy-to-use, accessible to all NCODA members and enables students to find the right start for their oncology careers.

Oncology is a vast, developing field, and it can be daunting to find information that will potentially shape one's career. NCODA purposefully chose a minimalist approach when it came to summarizing the information about the programs.

The website is aesthetically pleasing and enables users to learn the key points quickly. It's "accordion-style" web design allows users to quickly tab through programs in all 50 states and the District of Columbia.

Any NCODA member can access this complimentary tool. Students — or professionals — who are not already a member of NCODA can register at **www.ncoda.org/register**.

Down the road, NCODA plans to add a third directory for oncology-related internships from the pharmaceutical industry, clinical settings, associations and other organizations. New directory features, including search and multi-filter options, also are in the mix.

NCODA's biggest driver in creating the directories was to enable our young members to find the right start for their oncology careers. We want students to utilize this resource to learn about their options and determine the right career pathway for them.

NCODA wants students to have a strong passion and zeal when it comes to oncology. We believe this will help them become the best possible professionals in their field. That, in turn, will enhance the field of oncology and, ultimately, improve the quality of care for patients.

MANAGING THE DIRECTORY

As an Oncology | Advocacy | Health Policy & Equity fellow at NCODA, I was tasked with bringing this initiative to life. Having just graduated from pharmacy school, I was thrilled to have the opportunity to give back to student pharmacists.

From the start, I realized that the greatest challenge of creating and maintaining the directories would be the coordination needed to ensure that everything is updated.

As you may know, there already exists a vast number of residencies and fellowships. Therefore, there was an immense amount of data to collect for current residency and fellowships. In addition, the landscape for residencies and fellowships is ever-changing. Keeping track of all the new information is a challenge.

Directory updates would not be possible without the diligence of the NCODA staff and Advanced Pharmacy Practice Experience (APPE) students on rotation with NCODA, who are always on alert to inform the team about any new information that becomes available.

The marketing team at NCODA has also been instrumental in ensuring that the directories come to life.

As you can see, this has been very much a team effort, and I am very grateful to everyone who has helped me these last few months.

▲ **Sarder Sadid**, PharmD, is an Oncology | Advocacy | Health Policy & Equity Fellow at NCODA and a 2022 graduate of Albany College of Pharmacy and Health Sciences in Albany, New York.

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Scan to learn more, or visit **ncoda.org/Spring-Forum**

FDA ANNOUNCES 8 ORAL ONCOLYTIC APPROVALS

By Olivia Bukowski, Ethan Shell, Ashley Dorale, Kirollos Hanna, PharmD, BCPS, BCOP, & Derek Gyori, PharmD, BCOP

Eight oral oncolytic approvals were announced by the U.S. Food & Drug Administration (FDA) during Q1, Q2 and Q3 of 2022 (March 12, 2022 through Sept. 16, 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	POTENTIAL ADVERSE EFFECTS	CLINICAL PEARLS
VIJOICE® (alpelisib)[1-3]	4/5/2022*	• Severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy • **Adults:** 250 mg orally once daily • **Pediatric** (2-18 years): 50 mg orally once daily; can increase to 125 mg once daily after 24 weeks of treatment in patients < 6 years of age	**EPIK-P1 Trial** • Retrospective non-interventional medical chart review • Percent of patients achieving ≥20% reduction in target lesion volume during treatment: 37.5 (95% CI 21.1-56.3) • Mean reduction of target lesion volume: 13.7% • Symptom improvement at week 24 (percent of patients): pain (90.9%); fatigue (76.2%); vascular malformation (78.9%); limb asymmetry (69.0%); disseminated intravascular coagulation (55.2%)	• ≥10%: Diarrhea, stomatitis, hyperglycemia	• Administer with food at about the same time each day • Swallow tablets whole (tablets should be intact prior to ingestion); do not chew, crush or split • Monitor fasting blood glucose (FBG) and HbA1c prior to alpelisib treatment initiation; monitor FBG at least once each week for the first two weeks, then at least once every four weeks, and as clinically indicated; monitor HbA1c every three months and as clinically indicated • Available as 50 mg, 125 mg, 200 mg tablets
TIBSOVO® (ivosidenib)[1,4-5]	5/25/2022*	• Newly diagnosed acute myeloid leukemia (AML) with a susceptible IDH1 mutation in patients aged 75+ or who have comorbidities that preclude use of intensive induction chemotherapy • 500 mg by mouth once daily (in combination with azacitidine for injection)	**AGILE Trial** • Double-blind, placebo-controlled, phase 3 trial • Randomization 1:1 between ivosidenib + azacitidine group and placebo + azacitidine group • Event-free survival (EFS): Significantly longer in the ivosidenib group (HR 0.33; 95% CI 0.16-0.69; P=0.002) • Overall survival (median): Significantly longer in the ivosidenib group (24.0 months) compared to placebo group (7.9 months) (HR 0.44; 95% CI 0.27-0.73; P=0.001) • Complete remission achievement: Significantly higher percentage of patients achieved remission in the ivosidenib group (47%; 95% CI 35-59) compared to the placebo group (15%; 95% CI 8-25) (P<0.001) • Median duration of response: 22.1 months with ivosidenib group compared to 9.2 months with placebo group	• Black box warning: life-threatening or fatal differentiation syndrome • ≥25%: diarrhea, fatigue, edema, nausea, vomiting, decreased appetite, leukocytosis, arthralgia, dyspnea, abdominal pain, mucositis, rash, EKG QT prolongation, differentiation syndrome, myalgia, neutropenia	• Taken with or without food • Not approved in combination with ONUREG® (azacitidine) tablets • Available as 250 mg tablets

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	POTENTIAL ADVERSE EFFECTS	CLINICAL PEARLS
TAFINLAR® (dabrafenib) & **MEKINIST®** (trametinib)[1,6-11]	6/22/2022*	• Unresectable or metastatic solid tumors with BRAF(V600E) mutation who have progressed following prior treatment without satisfactory alternative treatment options • **Adults:** 150 mg dabrafenib by mouth twice daily in combination with 2 mg trametinib by mouth once daily • **Pediatric** (6-18 years): dosing is based on body weight	**Study BRF117019 and NCI-MATCH Trial** • N=131 adult patients • Open-label cohort trials • Objective Response Rate (ORR): 41% (95% CI 33-50) across 24 tumor types • Highest-responding tumor types: Biliary tract cancer (46%; 95% CI 31-61), combined high-grade glioma (33%; 95% CI 20-48), combined low-grade glioma (50%; 95% CI 23-77) **Study CTMT212X2101** • N=36 pediatric patients • ORR: 25% (95% CI 12-42)	• **Adults** ≥20%: pyrexia, fatigue, nausea, rash, chills, headache, hemorrhage, cough, vomiting, constipation, diarrhea, myalgia, arthralgia and edema • **Pediatrics** ≥20%: pyrexia, rash, vomiting, fatigue, dry skin, cough, diarrhea, dermatitis acneiform, headache, abdominal pain, nausea, hemorrhage, constipation, paronychia	• Dabrafenib available as 50 mg and 75 mg capsules • Administer at least one hour before or two hours after a meal; doses should be ~12 hours apart • Trametinib available as 0.5 mg and 2 mg tablets • Administer at least one hour before or two hours after meal • Trametinib doses should be administered ~24 hours apart • Store refrigerated at 2°C to 8°C (36°F to 46°F). Dispense in original bottle; do not remove desiccant • Protect from light and moisture • Do not transfer to pillboxes
XALKORI® (crizotinib)[1]	7/14/2022*	• Unresectable, recurrent or refractory inflammatory anaplastic lymphoma kinase (ALK)-positive inflammatory myofibroblastic tumors (IMTs) in patients one year of age and older • **Adults:** 250 mg by mouth twice daily until disease progression or unacceptable toxicity • **Pediatric:** 280 mg/m^2 by mouth twice daily until disease progression or unacceptable toxicity	**Study A8081013** • ORR: 5/7 **Study ADVL0912** • Pediatric patients • ORR: 12/14 (86%, 95% CI: 57-98) • Both multicenter, single-arm, open label	• **Adults:** • ≥35%: vision disorders, nausea and edema • **Pediatrics:** • ≥35%: vomiting, nausea, diarrhea, abdominal pain, rash, vision disorder, upper respiratory tract infection, cough, pyrexia, musculoskeletal pain, fatigue, edema, constipation and headache	• Take with or without food, swallow whole • Antiemetics are recommended to prevent nausea and vomiting • Avoid grapefruit and grapefruit juice • Available as 200 mg and 250 mg capsules

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	POTENTIAL ADVERSE EFFECTS	CLINICAL PEARLS
NUBEQA® (darolutamide)[1, 13-14]	8/5/2022*	• Used in combination with docetaxel for adult patients with metastatic hormone-sensitive cancer (mHSPC) • Dosing: take 600 mg (two 300 mg tablets) by mouth twice daily with food until unacceptable toxicity or disease progression	**ARASENS Trial** • Randomized, multicenter, double-blind, placebo-controlled clinical trial • Overall survival: Darolutamide plus docetaxel arm (95% CI: NR, NR) docetaxel plus placebo arm (HR 0.68; 95% CI: 0.57, 0.80; p<0.0001)	• Adverse reactions (≥10% with ≥2% increased over placebo with docetaxel): constipation, decreased appetite, rash, hemorrhage, increased weight and hypertension • Abnormal laboratory values (≥30%): anemia, hyperglycemia, decreased lymphocyte count, decreased neutrophil count, increased AST, increased ALT and hypocalcemia	• Administer with food • Swallow tablets whole • Available as 300 mg tablets
TABRECTA® (capmatinib)[1,15-16]	8/10/2022*	• Metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation leading to mesenchymal-epithelial transition (MET) exon 14 skipping in adult patients • **Adults:** 400 mg by mouth twice daily with or without food	**GEOMETRY Mono-1 Trial** • Multicenter, non-randomized, open-label, multi-cohort study **Treatment naive patients:** • ORR: 68% (95% CI: 55, 80) • Duration of response: 16.6 months (95% CI: 8.4, 22.1) **Previously treated patients:** • ORR: 44% (95% CI: 34, 54) • Duration of response: 9.7 months (95% CI: 5.6, 13)	≥20%: edema, nausea, musculoskeletal pain, fatigue, vomiting, dyspnea, cough and decreased appetite	• Administer with or without food • Swallow whole • Available as 150 mg and 200 mg tablets
IMBRUVICA® (ibrutinib)[1,17]	8/24/2022*	• Previously treated Pediatric patients ≥ 1 year of age with chronic graft versus host disease (cGVHD) • Patients ≥12 years old: 420 mg orally once daily • Patients 1 to <12 years old: 240 mg/m^2 orally once daily (up to a dose of 420 mg), until cGVHD progression, recurrence of an underlying malignancy, or unacceptable toxicity	**iMAGINE Trial** • ORR: 60% (95% CI: 44, 74) • Median DoR: 5.3 months (95% CI: 2.8, 8.8) • Median time from first response to death: 14.8 months (95% CI: 4.6 - not evaluable)	• ≥20%: anemia, musculoskeletal pain, pyrexia, diarrhea, pneumonia, abdominal pain, stomatitis, thrombocytopenia and headache	• Administer at approximately the same time each day • Swallow tablets or capsules whole with a glass of water • Capsules: 70 mg and 140 mg • Tablets: 140 mg, 280 mg, 420 mg and 560 mg • Oral suspension: 70 mg/mL

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	POTENTIAL ADVERSE EFFECTS	CLINICAL PEARLS
PEMAZYRE® (pemigatinib)[1,18]	8/26/2022*	• Relapsed or refractory myeloid/lymphoid neoplasms with FGFR1 rearrangement • 13.5 mg orally once daily until disease progression or unacceptable toxicity	**FIGHT-203 Study** • N=28 • CR: 78% (95% CI: 52, 94) • Median time-to-CR: 104 days (range, 44 to 435) • Median duration was not reached (range: 1+ to 988+ days)	• ≥20%: hyperphosphatemia, nail toxicity, alopecia, stomatitis, diarrhea, dry eye, fatigue, rash abdominal pain, anemia, constipation, dry mouth, epistaxis, serous retinal detachment, extremity pain, decreased appetite, dry skin, dyspepsia, back pain, nausea, blurred vision, peripheral edema and dizziness	• Perform ophthalmological examination prior to initiation of therapy • Swallow tablet whole, with or without food • Available as 4.5 mg, 9 mg and 13.5 mg tablets

▲ **Olivia Bukowski** and **Ethan Shell** are 2024 PharmD Candidates at University of Toledo College of Pharmacy and Pharmaceutical Sciences. **Ashley Dorale** is a 2023 PharmD Candidate at University of Minnesota College of Pharmacy. **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.

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BHAVESH ASHAR | SpringWorks Therapeutics

Bhavesh Ashar, MBA, is the Chief Commercial Officer for SpringWorks Therapeutics, a biotech company headquartered in Stamford, Connecticut.

Prior to joining SpringWorks Therapeutics in March 2021, he served as Senior Vice President and General Manager of US Oncology at Bayer, as well as in other executive positions at Sanofi Genzyme, and as Engagement Manager at McKinsey & Co.

Ashar grew up in in Zambia, in Central Africa. He completed his undergraduate studies in mathematics and worked as an actuary in the United Kingdom before moving to the U.S. to pursue his MBA.

How did you get involved in the pharmaceutical industry?

My interest in healthcare started back when I was thinking about my post-undergrad focus, and at one point it became a decision between going to medical school and the actuarial field. And while I decided on the actuarial route, that healthcare interest always lingered in the back of my mind.

I later decided to combine both of my interests ... and had the good fortune to obtain a role as a healthcare consultant at McKinsey & Co.. I was inspired by the impact our industry had during my four years there, as well as gaining an appreciation for the still many unmet needs that existed in the healthcare spectrum. That really solidified my resolve to work in the biotech pharmaceutical space.

Why did you decide to pursue a career in oncology, specifically?

My "why" is helping make a change in oncology patients' lives. It is gratifying to see the lives of patients and their families transformed by medications that I've had the privilege of working on. And I use that word privilege deliberately, because I see it as that. That is what energizes me to work harder every day.

As most people who work in this field would agree, it's just great to see drug development done right. Working in oncology, where the mortality rate from cancer can be quite high, it's been a truly meaningful experience to hear patient success stories.

I remember receiving a letter from a father of someone who was getting married. He said it is because of our drug that he was able to walk down the aisle with his daughter, help her get married and enter a new phase of her life. I mean, it doesn't get better than that.

What advancements in oncology treatments are you most excited about?

Precision medicine is one area that I find very exciting. It's an approach that SpringWorks applies to our drug development programs, often using a combination therapy approach.

For example, multiple myeloma is a large evolving market where there has been significant advancement with drugs like anti-CD38s, which has really transformed the market. When you see there are approximately 40,000 newly diagnosed multiple myeloma patients, and the outcomes that they're seeing today even compared to 10 years ago are significantly improved.

Unfortunately, many of them will advance because these conditions are hard to treat. But now there are more people who are surviving five years down the line. So, the need for treatment options for relapsed refractory patients is even higher because now there's a larger pool of survivors.

Combination therapy is the gold standard for treating multiple myeloma and while significant advances have been made, there is still a need for more innovation.

At SpringWorks, we are evaluating our gamma secretase inhibitor, nirogacestat, in combination with BCMA targeted agents across key modalities, including an ADC, CD3 bispecific, CAR-T cell therapy, and a monoclonal antibody.

CONTINUED ON NEXT PAGE

"My 'why' is helping make a change in oncology patients' lives. It is gratifying to see the lives of patients and their families transformed by medications that I've had the privilege of working on. And I use that word privilege deliberately, because I see it as that. That is what energizes me to work harder every day."

PARTNER PROFILE

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What makes SpringWorks Therapeutics different from other pharmaceutical manufacturers?

We're a young company and we're getting ready to launch our first product for desmoid tumors. We're about five years old, and that's in some ways unique in this space because it usually takes 15+ years to develop a drug and bring it to market.

So how did that happen for us? We got a sort of a head start, if you like, because we in-licensed two products with promising science in rare tumors with significant unmet need.. We recognized the opportunity to advance these products.

We've been able to move them along into late-stage studies and advance the science around them at a faster rate by bringing the right focus and the right expertise in the tumor types that we were investigating.

We built our company around exceptional people who really work with an urgency to help impact the lives of people with devastating cancer.s. SpringWorks has five core values:

- Good enough is never enough;
- Care hard;
- Think deeply, act quickly,
- In it together; and
- Ambition without ego.

It differentiates us. It makes us give our best. And it makes us do that in an urgent matter, because the clock is ticking for the patients that that we're looking to serve.

These values are really core to how we work and how we operate in every interaction, whether its hiring new people, managing our performance process, working with strategic partners or even simply executing our overall strategies. That's what makes us different.

How do those values translate into supporting external customers, such as patients and cancer centers?

We thrive in an atmosphere of passion and tenacity, and we're driven to work with urgency because of that.

And so, in desmoid tumors, for example, we strive to help educate patients, physicians and other stakeholders about these rare tumors so that they get a rapid and accurate diagnosis. We just recently launched **desmoidtumors.com**, which is meant to provide information and resources to patients.

We also work with patient advocacy organizations, such as the Desmoid Tumor Research Foundation, to help raise awareness and provide support for the desmoid tumor community.

Finally, we share data from our trials. Results from our Phase 3 DeFi trial were showcased at the ESMO Congress and again at the Desmoid Tumor Research Foundation. DeFi is evaluating nirogacestat, an oral, small-molecule gamma secretase inhibitor (GSI) in adult patients with progressing desmoid tumors.

For more information about **SpringWorks Therapeutics**, scan the QR code above.

How did you become involved with NCODA?

I had the opportunity to work with NCODA at both of my prior organizations, as did some of our other team members. So, we at SpringWorks were early to recognize the value of a symmetric partnership with aligned missions. We both put patients at the center of our efforts and we are both driven to help patients live longer, better lives.

We take care very seriously every day. And if you attend NCODA meetings or interact with NCODA leadership, it's clear that everyone at NCODA also cares about helping patients.

Which NCODA tools or initiatives do you find most useful?

The Positive Quality Interventions (PQIs) are a great tool for providers. We are also looking at Treatment Support Kits (TSKs) for our patients.

RESEARCH INITIATIVES AT SPRINGWORKS THERAPEUTICS

SpringWorks Therapeutics is a clinical-stage biopharmaceutical company that applies a precision medicine approach to acquiring, developing and commercializing life-changing medicines. Current focus areas include:

RARE ONCOLOGY

SpringWorks' late-stage rare oncology programs have the potential to be best-in-class treatments for patients with devastating diseases, including desmoid tumors, neurofibromatosis type 1-associated plexiform neurofibromas (NF1-PN) and low-grade gliomas.

BCMA COMBINATIONS IN MULTIPLE MYELOMA

SpringWorks believes that by inhibiting gamma secretase with nirogacestat, membrane-bound BCMA can be preserved, thereby increasing target density while simultaneously reducing levels of soluble BCMA, which may interfere with BCMA-directed therapies.

In preclinical models of human multiple myeloma, nirogacestat has shown the ability to meaningfully enhance the activity of BCMA-targeted therapies. SpringWorks is currently studying nirogacestat in multiple myeloma patients through clinical collaborations with eight industry-leading developers of BCMA therapies.

BIOMARKER-DEFINED METASTATIC SOLID TUMORS

SpringWorks is collaborating with BeiGene to take a vertical inhibition approach to the mitogen-activated protein kinase (MAPK) pathway. A study combining its MEK inhibitor with BeiGene's RAF dimer inhibitor represents a unique opportunity to treat patients with MAPK-driven cancers, particularly those with RAS mutations, where rational targeted therapies are urgently needed for patients. We believe that through a potent and optimized vertical inhibition combination therapy approach, we may be able to address several biomarker-defined patient subsets within the broader MAPK-mutated solid tumor space.

SO, YOU'RE A PHARM TECH . . . NOW WHAT?

A LOOK AT GROWTH OPPORTUNITIES FOR PHARMACY TECHNICIANS

By Kara Sammons, MSPharmReg, CPhT, RPhT

Historically, a pharmacy technician is an assistant-based role that supports operations, adherence, customer service, accreditation or procurement.

Pharmacy technicians work in many settings, including hospitals, retail, call centers, doctors' offices and community support. Job requirements vary by state, but usually consists of some form of school, and state licensing and/or a professional certification. Duties can include mixing chemicals, counting pills or running a cash register — yes, math!

Kara Sammons

As with many healthcare-related careers, pharmacy technician jobs are in high demand. The field is projected to grow by 30,000 job openings a year through 2030 due to higher rates of chronic illnesses and an aging population, according to the U.S. Bureau of Labor Statistics.

Individuals that choose this career path often follow a family tradition of healthcare, pick the profession based on a passion for serving others or, like me, stumble into the opportunity because the availability worked with my school schedule.

Working as a pharmacy technician has humbled me in many ways. At first, it was a part-time job running a cash register and ensuring that patients received their medication in a seven-day time frame prior to the order being returned to stock.

But I soon learned that it was much more than that.

I've watched patients of all ages take medication in the short- and long-term, and witnessed and participated in their struggles with insurance, cost, side effects and quality of life. I, as a pharmacy technician, was an important part in their journey.

My regular patients were always happy to see me. They'd share updated news on their illnesses, cholesterol counts or blood pressure, and discuss medication changes based on their diet or lifestyle.

Some days, I'd add fruitful flavors to their children's antibiotics in the hope that it would help the family rest after a long distressful day or night. On other days, I would compound mouthwashes, gels and creams to assist patients with pain or discomfort resulting from their chemotherapy or radiation.

Every day that I worked I learned a small piece of the puzzle that would soon land me at a community oncology practice, Florida Cancer Specialists & Research Institute, and as a part of their oncology pharmacy, Rx To Go, LLC.

Working at Rx To Go took me out of the face-to-face interaction environment I was used to, and put me into a call center role. The experience taught me how to verbally build customer service and patient relationships. It was a big transition, and something every pharmacy technician should think about when moving into another industry setting.

As we continued to grow and expand, the pharmacy was able to invest in new opportunities. Our leadership team allowed technicians to take ownership in such tasks as medication adherence, financial/patient assistance, payer contracting, state licensing, drug purchasing and negotiations, accreditation, customer service, sales and compliance.

Our pharmacy technicians created workflows for many of these tasks. Some eventually became leaders within our organization.

For me, this is when I realized that I really enjoyed the operations and compliance aspects of the job. I joined NCODA and OPTA, enrolled in a master's degree program, spoke at several conferences and joined several panels for NCODA and the International Oncology Network (ION). My niche became applying accreditation and pharmacy board standards to our day-to-day operations.

These topics are opportunities that we all have as pharmacy technicians. If you have a passion or interest, dive in. Learn the lingo, gain an understanding of the topics, lean on leaders and find mentors that will support you in your drive.

TAKING THE NEXT STEP: CAREER OPPORTUNITIES FOR PHARMACY TECHNICIANS

For pharmacy technicians needing that next push or are looking for additional training/participation opportunities, here are some options my peers and I have participated in that have enhanced our careers:

- Complete continuing education certificate programs;
- Advance the basic Pharmacy Technician Certification Board certificate to one of the many areas of advanced training and certificates now being offered;
- Join the Oncology Pharmacy Technician Association (OPTA);
- Participate in organizations that advocate on behalf of a specific practice, like NCODA;
- Go back to school for a master's degree in various areas of study, including healthcare administration, pharmaceutical regulation or social work;
- Complete Project Management or Sales Representative certification offered by various organizations;
- Participate in committees or volunteer within your organization for networking opportunities.

USEFUL WEBSITES

- www.ncoda.org
- www.ncoda.org/opta

▲ **Kara Sammons**, MSPharmReg, CPhT, RPhT, is Associate Director of Pharmacy Services at RxToGo, Florida Cancer Specialists & Research Institute's Medically Integrated Specialty Pharmacy.

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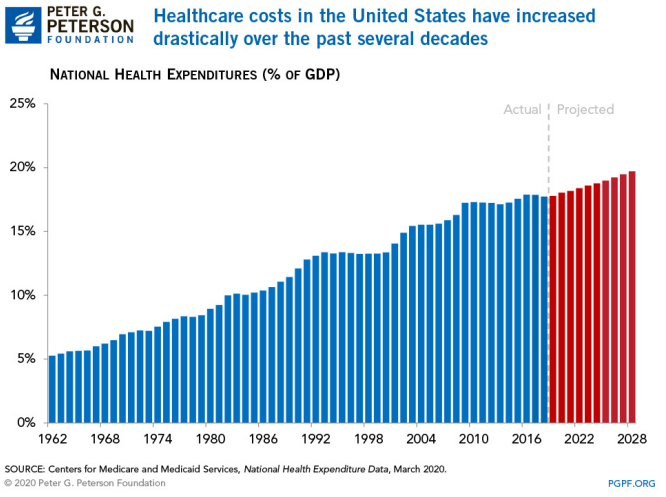
DOSE ROUNDING: AN EFFECTIVE COST-AVOIDANCE INITIATIVE

By Kristie Fox, PharmD, Taylor Moore, MHA, & Bijoy Telivala, MD



Cancer care in the United States is one of the fastest-growing costs in our current healthcare system, climbing to approximately $160 billion in 2018.[1]

Specifically, the cost of oncology drugs has outpaced other areas, making cost control a priority for practices. As a community-based oncology practice, Cancer Specialists of North Florida (CSNF) takes responsibility to implement initiatives that will save healthcare expenditures while maintaining quality of care.

Drug waste occurs when doses fall between vial sizes that are available from the manufacturer. The Hematology/Oncology Pharmacy Association (HOPA) recently released guidelines showing the importance of dose rounding, where appropriate.

Rounding doses to the nearest vial size (for single-use vials), when less than an established percentage, can help minimize drug waste and assist physicians and pharmacy by providing more accurate and precise amounts for patient doses.[2]

Based on published data, HOPA recommends that monoclonal antibodies and other biologic agents be dose rounded to the nearest vial size within 10% of the prescribed dose.[2] They also recommend that cytotoxic agents be considered on a case-by-case basis.

METHODS

At CSNF, we piloted a dose-rounding program beginning in June 2021. A team was assigned to this program to ensure quality, efficacy and compliance were maintained. The team consisted of three physicians from CSNF's Value-Based Committee (Bijoy Telivala, MD, Sejal Kuthiala, MD, and Suprith Badarinath, MD), one pharmacist (Kristie Fox, PharmD) and one reimbursement specialist (Taylor Moore, MHA).

Kristie Fox

Taylor Moore

Bijoy Telivala

CSNF's current electronic medical records (EMR) system calculates a patient's dose based off their most recent weight.

For example, a patient weighing 77.9kg is scheduled to receive daratumumab (DARZALEX®) at a regimen dose of 16 mg/kg. Calculated, this dose would be 1,246 mg. As a practice purchasing this drug (prior to rounding), we would need to purchase 1,300 mg, giving 1,246 mg to the patient and wasting 54 mg.

By rounding this dose, we could save 100 mg (the smallest vial size) and purchase 1,200 mg, which is a 3.7% dose reduction.

To put this into perspective, 100 mg of DARZALEX® is purchased for $550 (based on average wholesale price) and costs the healthcare system approximately $570 (based on Medicare allowance).

In the months prior to implementation, the team evaluated the most common drugs that were appropriate to dose rounding. We used the HOPA position statement mentioned previously as our guidepost in making recommendations.

The team then created a list of different phases, which allowed our practice to fine-tune the process along the way. We spent approximately two weeks at each phase before adding the next. The phases were:

Phase 1: pemetrexed, nivolumab, bevacizumab (and biosimilars)

Phase 2: trastuzumab, daratumumab, isatuximab-irfc

Phase 3: cetuximab, panitumumab, bendamustine

Phase 4: rituximab (and biosimilars)

Phase 5: carfilzomib, elotuzumab

Phase 6: paclitaxel protein-bound, durvalumab

Working together, the reimbursement specialist and pharmacist identified upcoming doses of the listed drugs and calculated potential doses to be rounded. The pharmacist had the authority to change the dose, if appropriate, in

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DOSE ROUNDING

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the patient's chart. If there were clinical concerns with rounding, the pharmacist would request approval from the physician.

Any patients currently involved in clinical trials were excluded from the rounding program.

RESULTS

As stated previously, our practice began this project in June 2021. The initial results (June 2021 – September 2021) were presented by Fox as a poster at the NCODA Fall Summit in October 2021.

We are continuing the program for the foreseeable future; however, the data in **GRAPH 1** reflects the time period of June 14 to December 31, 2021.

During the time frame, our practice was able to round 907 doses across all drugs included in the pilot program, as shown in **GRAPH II**. The program helped CSNF to achieve total healthcare dollar savings (payer and patient) of approximately $600,000 (based on Medicare reimbursement), also shown in **GRAPH 1**.

The program allowed CSNF to achieve the most drug savings with rituximab (RITUXAN®) and its biosimilar (Ruxience).

In addition to the total healthcare dollars saved, CSNF was able to spend less on drug purchases based on average wholesale prices (AWP) of about $570,000.

DISCUSSION

Upon implementation of the program, CSNF experienced some push-back from the physicians across our practice. Using the supported literature as a guide, we were able to circumvent most of these issues and collaborate agreement to this rounding project.

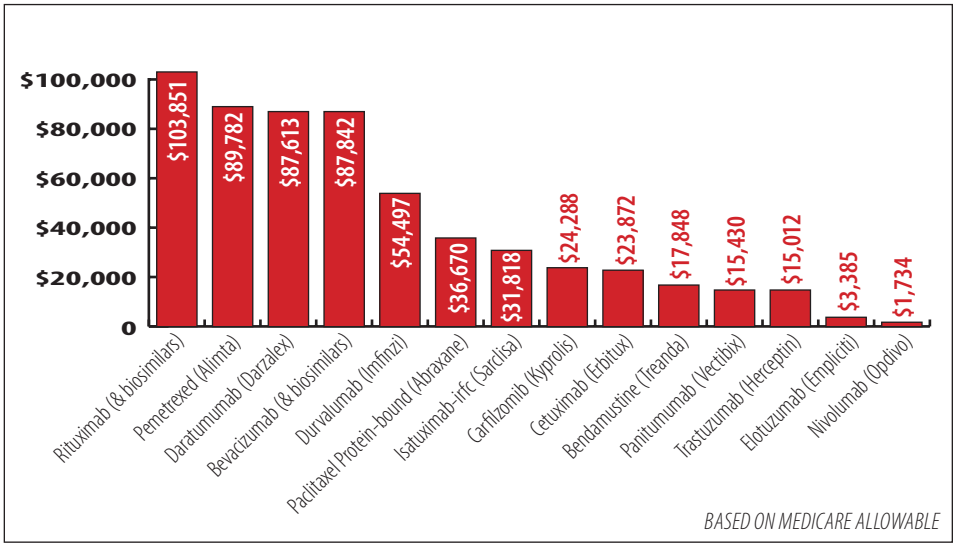
The key to success was the teamwork between the physicians, pharmacy and reimbursement team. Given the complications and challenges of oncology, collaboration between team members is essential.

With healthcare costs continually rising, reducing drug waste and controlling expenditures should be an area of continual focus. Dose rounding to the nearest vial size — within a 10% threshold — can yield substantial benefits from cost avoidance to reduced waste.

Not only were we able to show cost savings, but we also reduced financial toxicity to the patient and healthcare system.

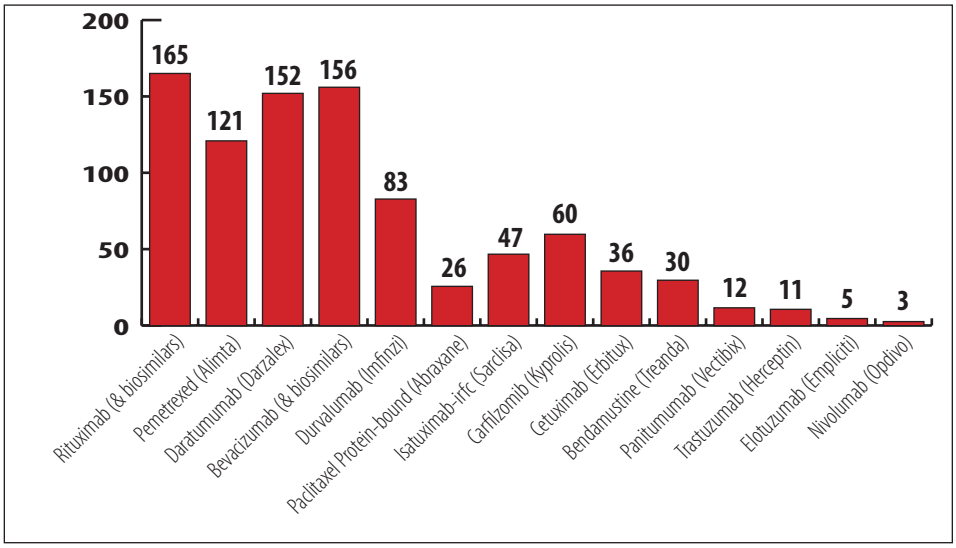
We anticipate that CSNF will carry on with this program and continue to see the benefits of the implementation. Our clinics will remain "patient-centric" by focusing on cost, quality and access to ensure great success.

GRAPH I | HEALTHCARE DOLLARS SAVED



BASED ON MEDICARE ALLOWABLE

GRAPH II | DOSES ROUNDED



▲ **Kristie Fox**, PharmD, was previously a clinical oncology pharmacist at Cancer Specialists of North Florida who helped to start this pilot program. She is a Manager of Clinical Initiatives at NCODA. **Taylor Moore**, MHA, is a Managed Care Reimbursement Specialist and **Bijoy Telivala**, MD, is a Partner Physician with Cancer Specialists of North Florida in Jacksonville, Florida.

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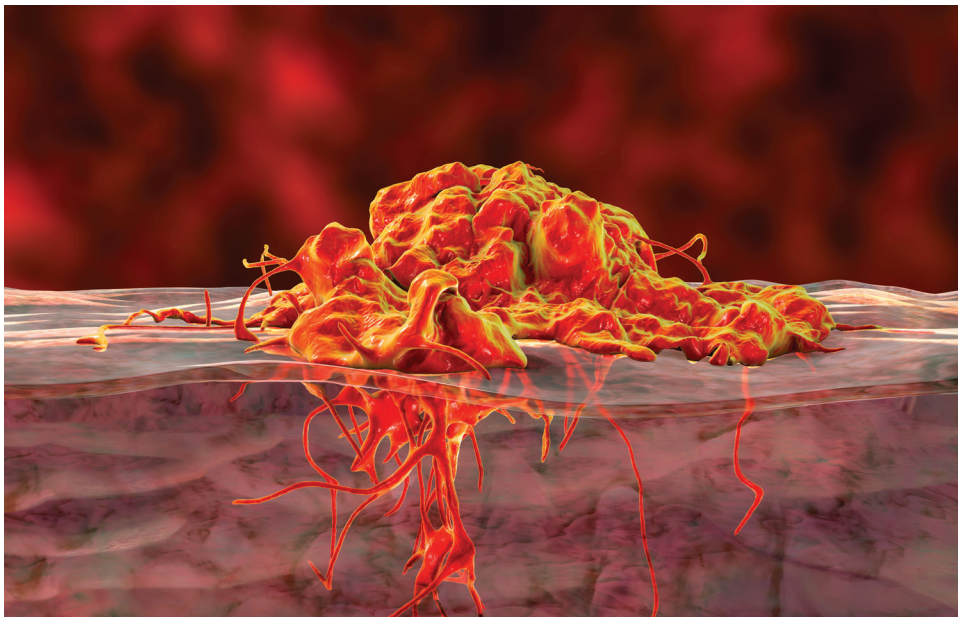
SELECTED TREATMENT UPDATES INVOLVING METASTATIC OR UNRESECTABLE MELANOMA

By Dane Fritzsche, PharmD, BCOP, Andrew Ruplin, PharmD, & Stephanie Pang, PharmD

Malignant melanoma is a tumor of the melanin-producing cells, melanocytes. The vast majority of these arise from melanocytes found in the skin, however these tumors may arise from other sites such as mucosal surfaces or the uveal tract which consists of the iris, ciliary body, and choroid in the eye.

Although cutaneous and uveal melanomas arise from melanocytes, their incidence, prognosis, molecular markers, and treatment vary significantly.[1,2]



Melanoma is the most invasive skin cancer with the highest risk of death. While it's a serious skin cancer, it's highly curable if caught early. Prevention and early treatment are critical, especially if the patient has fair skin, blonde or red hair, and blue eyes.

Cutaneous Melanoma

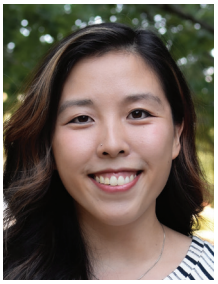
Cutaneous melanoma (CM) is the most common subtype of melanoma.[3] It is most associated with ultraviolet (UV) exposure in fair-skinned individuals.[4] Although the frequency of cutaneous melanoma continues to increase, treatment advances harnessing immunotherapy and targeted agents have led to a decrease in mortality from advanced disease over the past 10 years.[5]

Although the basic treatment of CM has not changed significantly over the past few years, new treatment options and strategies continue to be developed. A thorough understanding of the treatment of CM is required to understand where these new treatment options fit into the current treatment landscape.

More than 90% of patients diagnosed with melanoma present with local or local-regional disease.[5] While surgical management remains the gold standard of treatment, systemic treatment is an important component of those with stage IIB and above. Historically, systemic treatment consisted of chemotherapy, such as dacarbazine or temozolomide.

Dane Fritzsche

Andrew Ruplin



Stephanie Pang

Typically, chemotherapy would lead to an initial response, however rapid resistance would develop, ultimately leading to only a modest improvement in progression-free survival (PFS) and no improvement in overall survival (OS).[6] With the advent of immunotherapy and targeted therapy, significant improvements in five-year survival and OS have been seen in patients with metastatic melanoma.

Currently, non-metastatic CM of stages IIB and above is treated with surgical management with the option of adjuvant therapy.[7] For patients with lower risk disease, stage IIB/C, a new treatment option is pembrolizumab. It was FDA-approved in December 2021 based on an interim analysis of the now published KEYNOTE-716 trial.[8]

For patients with higher risk disease, stages IIIA-C, adjuvant systemic therapy options include: ipilimumab, nivolumab, pembrolizumab, and, for patients who harbor BRAF mutations, the combination of dabrafenib and trametinib.[7]

Management of metastatic CM is dependent on the feasibility of metastasis-directed therapy via surgery with or without radiation. If complete resection is achieved, adjuvant therapy, as previously described, is indicated; otherwise, systemic therapy is utilized in unresectable or metastatic CM.

Options for first-line systemic

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therapy include pembrolizumab or nivolumab monotherapy or in combination with ipilimumab, or nivolumab and relatlimab-rmbw (Opdualag™). The combination of nivolumab and relatlimab-rmbw was recently approved by the FDA in March 2022 based on the RELATIVITY-047 trial.[9]

For patients who harbor BRAF mutations, combination targeted therapy is indicated with either dabrafenib and trametinib, vemurafenib and cobimetinib, or encorafenib and binimetinib. Treatment of progressive melanoma is dependent on what was given in the first line and if the patient harbors a BRAF mutation.

In patients with an activated BRAF mutation, switching between targeted agents and immunotherapy is often the next step, while in those without a BRAF mutation switching between immunotherapy agents and combinations is often done.[10]

Although the foundation of melanoma treatment through targeted therapy and immunotherapy has not changed recently, new medications, like the combination of nivolumab and relatlimab-rmbw, or new combinations of targeted agents and immunotherapy such as vemurafenib + cobimetinib with atezolizumab (VCA) are newer first-line therapeutic options in metastatic melanoma.

The remainder of this section will be devoted to these new combinations and their role in the treatment of metastatic cutaneous melanoma and future directions for the management of this disease.

NIVOLUMAB AND RELATLIMAB-RMBW

The combination of nivolumab and relatlimab-rmbw contains the novel anti-lymphocyte activation gene 3 (LAG-3) blocking antibody.[11,12] The immune checkpoint inhibitor (ICI) LAG-3 suppresses T cell activation and cytokine secretion and in combination with anti-PD-1, has shown exciting efficacy in fighting programmed death-1 (PD-1) resistance.[13]

The combination was approved by the FDA for patients with unresectable or metastatic melanoma based on the RELATIVITY-047 trial. This phase 2-3 trial enrolled patients with previously untreated, unresectable stage III or IV melanoma where patients received either nivolumab 480 mg and relatlimab-rmbw 160 mg in a fixed-dose combination or nivolumab 480 mg monotherapy.

The median PFS was 10.1 months with nivolumab and relatlimab-rmbw compared to 4.6 months with nivolumab alone with a 25% lower risk of disease progression or death than nivolumab alone [hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.62 - 0.92; p=0.006]. Follow-up showed that nivolumab and relatlimab-rmbw demonstrated a 20% reduction in risk of death but did not reach statistical significance.[14]

Notably, nivolumab and relatlimab-rmbw was also shown to be superior to nivolumab in patients with high tumor burden, elevated baseline LDH, and visceral non-lung metastases. Grade 3 or 4 treatment-related adverse events occurred in 18.9% in the nivolumab and relatlimab-rmbw group and in 9.7% of patients in the nivolumab alone group, appearing to be better tolerated than combination ipilimumab and nivolumab.[15,16]

The introduction of a novel ICI expands the available treatment for patients with unresectable or metastatic melanoma; however, the sequencing of nivolumab and relatlimab-rmbw with other combination ICIs and its place in therapy is unclear given the discordance in treatment experience between the FDA approval for unresectable or metastatic melanoma and the treatment-naïve study population.

At Fred Hutchinson Cancer Center (FHCC), nivolumab and relatlimab-rmbw use is largely in the treatment-experienced population per the broader FDA approval indication.

VEMURAFENIB/COBIMETINIB/ATEZOLIZUMAB

The individual agents contained in the combination of VCA are not new in the treatment of metastatic melanoma. However, giving BRAF/MEK and immunotherapy concomitantly is relatively new. VCA was approved by the FDA in July 2020 for the treatment of BRAF positive, unresectable or metastatic melanoma based on results from the IMspire150 trial.[17,18]

This trial enrolled patients with previously untreated, metastatic, or unresectable stage IIIC melanoma with a documented BRAFv600 mutation where patients either received combination of vemurafenib + cobimetinib with placebo or atezolizumab.

Median PFS favored the atezolizumab containing group with 15.1 months versus 10.6 months with the placebo arm (HR 0.78, 95% CI 0.63 - 0.97; p=0.025). At the time of the publication, the OS analysis data was not yet mature but demonstrated a trend towards improvement with the atezolizumab containing group compared with the placebo arm (HR 0.85, 95% CI 0.64 - 1.11; p=0.23).

Updated OS results were presented at the ASCO 2022 annual meeting and demonstrated a continued trend favoring the atezolizumab group.[19]

Adverse effects seen in the clinical trial were expected based on previous experience with these agents, with arthralgias, myalgias, elevations of creatine phosphokinase and thyroid hormone dysfunction occurring more frequently than in the placebo group.[18]

Uptake of the VCA regimen has been limited at the FHCC and largely our practice has been — depending on the patient case, wishes and setting — to go with either immunotherapy or BRAF/MEK therapy and not use them in combination. The rationale for this is likely multifactorial, with at least some hesitancy over using vemurafenib and cobimetinib due to this combination's unique toxicities, such as photosensitivity reactions.[20]

The FHCC more regularly use the other BRAF/MEK combinations of dabrafenib + trametinib and encorafenib + binimetinib for BRAF/MEK inhibition. Additionally,

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there is currently no clear benefit to the VCA combination instead of sequential therapy with only a modest impact on PFS and no mature OS data supporting its use.

FUTURE OPTION: INTRATUMORAL INJECTIONS

Despite the progress made in developing new treatments for advanced and metastatic melanoma, disease progression continues to threaten long-term, durable responses. Intratumoral injections, notably toll-like receptor 9 (TLR-9) agonist injections in combination with ICIs, are a promising combination of agents being studied in both treatment-naïve as well as treatment-experienced, including anti-PD-1 resistant, disease.[21-24]

TLR-9 is expressed on dendritic cells and B cells and when activated, it stimulates the production of proinflammatory cytokines by both the adaptive and innate immune responses.[25] The intratumoral injection of TLR-9 agonists could selectively activate tumor-specific dendritic cells and induce an antitumor effect by presenting tumor antigens to CD8+ T-cells.[26]

Furthermore, the combination with other ICIs further potentiates the antitumor response due to the release of PD-1-mediated inhibition. The phase III clinical trial ILLUMINATE-301 studying tilsotolimod (IMO-2125) and ipilimumab versus ipilimumab alone failed to meet its primary endpoint of overall response rate for patients with anti-PD-1 refractory advanced melanoma and is pending further review whether the trial will continue investigating OS benefit.[27]

However, multiple other early-phase studies are continuing to investigate the benefit of this combination. A phase Ib clinical trial investigating vidutolimod (CMP-001) intratumoral injection in combination with pembrolizumab in patients with previous resistance to anti-PD-1 therapy showed an ORR of 23.5% and a median duration of response (DOR) of 25.2 months with an acceptable safety profile.[28]

To date, immunotherapy and targeted therapy have produced some of the largest benefits for patients diagnosed with advanced melanoma, and novel treatments undergoing investigation continue to involve these therapeutic paradigms.

Intratumoral injections have gained traction as an option for patients with advanced melanoma due to their manageable, non-overlapping safety profile and efficacy when combined with ICIs, However, given the latest failure of tilsotolimod with ipilimumab, cautious optimism is recommended until confirmatory clinical trials are completed.

Uveal Melanoma

Uveal melanoma (UM) is a rare form of melanoma compared to cutaneous but represents the most common type of primary intraocular malignancy of adults.[29] New cases occur in five to 10 people per million per year, with most UMs arising in the choroid or ciliary body.[29-34]

The majority of UM is diagnosed as localized disease, and metastases at initial diagnoses are rare, occurring less than 3% of the time.[31,35-37]

Likewise, early stage at diagnosis confers a substantially lower risk of metastases at five years with only a 3% to 5% risk for stage I disease. Meanwhile, a stage III diagnosis carries a 44% or greater risk of metastasis at five years.[33,36] Metastatic UM remains difficult to treat, and the estimated five-year survival rate is often reported as less than 20%.[36,38-40]

The main goals of treatment in early-stage disease include destruction of the tumor, prevention of recurrence and metastasis and preservation of vision. Decisions around treatment of UM depends on tumor size, location, extension, visual function, health status and function of the patient, and the presence of metastasis.[41,42]

The presence or absence of metastasis is a primary driver of the available modalities of treatment, and in localized disease, options may range from observation to surgery or radiation.

Metastatic UM may receive systemic treatment with immunotherapy, targeted therapy, or cytotoxic chemotherapy, though survival benefits have traditionally been minimal.[43,44]

SURGERY AND RADIATION

Enucleation remains an extensively utilized treatment in UM, especially for tumors with thickness >2.5 mm or diameter >19 mm, but radiation is often considered as well.[42,45-47]

Risks and complications differ among the various treatments. Pre-enucleation radiation is not often used as it has not shown a benefit to 10-year survival compared to enucleation alone.[48,49] Local recurrence associated with enucleation is rare and seems to be lower compared to primary local resection.[50-53]

Enucleation has demonstrated equivalent survival outcomes when compared to other non-systemic treatments, including versus iodine-125 brachytherapy, cobalt plaque brachytherapy, a mixture of brachytherapy plaque types, stereotactic radiosurgery/radiation and proton beam radiotherapy.[54-57]

PHARMACEUTICAL TREATMENT

Treatments for metastatic UM that demonstrate a clear benefit to survival remain scarce, and only the recently FDA-approved treatment, tebentafusp-tebn (KIMMTRAK®), has done so.

Tebentafusp-tebn is a novel bispecific gp100 peptide-HLA-A*02:01 directed T cell receptor CD3 T-cell engager

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approved by the FDA for treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic UM.

It is the first treatment approved for UM based on positive phase 3 trial results showing a benefit to overall survival at one year (73%) compared to the investigator's choice of monotherapy as the control group (59%) (HR for death 0.51, 95% CI 0.37 - 0.71; p<0.001) in the intention-to-treat population.

Adverse events were common, especially rash (83%), pyrexia (76%) and pruritus (69%) but rarely led to treatment discontinuation (2%). Cytokine release syndrome (CRS) of any grade occurred in 89% of patients, but only 2% had grade ≥3.[58]

Due to the risks of CRS, the target dose of 68 mcg weekly is reached by standardized titration over three weeks. The prescribing information requires a 16-hour observation period after the first three infusions due to the risk of CRS during initiation of treatment.

Outside of tebentafusp-tebn use in the first line setting in HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma, no other treatments have demonstrated a clear benefit to overall survival. Clinical trials should be carefully considered in any patient, and since efficacy of most treatments is limited, patients' goals, prognosis, as well as the location and extent of disease should help to guide selection of treatment.

For patients with isolated liver metastasis, liver-directed, locally administered pharmaceutical therapy such as melphalan, TNF-alpha, or cisplatin, as well as embolization, ablation, or resection are options.[59-63]

For patients with more widespread metastatic disease, suggested systemic therapies largely resemble those available for treatment of metastatic cutaneous melanoma.

While multiple trials for different regimens have been undertaken, these are often small phase II trials, and most demonstrate remarkably poor response rates <10%.[58,64-66]

Due to the lack of approved therapies, consensus guideline recommendations for suggested treatments by the National Comprehensive Cancer Network (NCCN) will be mentioned in this review.

Among cytotoxic chemotherapy, proposed treatments include dacarbazine, temozolomide, paclitaxel or albumin-bound paclitaxel, or the combination of carboplatin and paclitaxel.[67-73]

At this time, the only targeted small-molecule therapy recommended by NCCN for metastatic UM is the MEK inhibitor trametinib.[74,75]

Immune checkpoint inhibitor monotherapy (pembrolizumab, nivolumab, or ipilimumab) or combination therapy with nivolumab and ipilimumab produce modest benefits, however these are again in the context of phase II trials without direct comparators.[76-81]

In one trial of nivolumab and ipilimumab, the OS and PFS were 12.7 and 3 months, respectively.[83] In another, the OS and PFS were 19.1 and 5.5 months, respectively.[84]

CONCLUSION

To date, immunotherapy and targeted therapy have produced some of the largest benefits for patients diagnosed with advanced melanoma, and novel treatments undergoing investigation continue to involve these therapeutic paradigms.

That said, advanced uveal melanoma continues to be in dire need of life-extending therapies. However, it brings optimism that the therapeutic armamentaria for both advanced cutaneous and uveal melanoma have expanded just this year alone.

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NURSES AN ESSENTIAL COMPONENT IN THE MEDICALLY INTEGRATED PHARMACY SPACE

By Dawn Landolph, RN, BSN, OCN, MPA

Nursing in a medically integrated, specialized pharmacy provides a novel, innovative way for nurses to impact patient outcomes through medication education, reinforcement of adherence and side-effect management.

The opportunity to engage a Medically Integrated Pharmacy (MIP) nurse to assist patients through their health journey could significantly impact the patient's adherence, tolerance and response to therapy.

Dawn Landolph

MIPs have a unique opportunity to utilize nurses to reinforce medication education and side-effect management strategies.

MEDICATION ADHERENCE

According to the World Health Organization, medication adherence can have a more direct impact on patient outcomes than the specific treatment itself.[1] So, why are patients not adherent to their therapy? For oncology patients, the main reasons include age, complexity of treatment, tolerance of therapy and cost.

According to the National Cancer Institute, the average age of a patient diagnosed with cancer is 66, and a quarter of all new cancer cases are diagnosed in people between 65 and 74 years of age. By 2030, an estimated 70% of all cancers will occur among adults aged ≥ 65 years.[2]

Advanced age, coupled with illness and the shock of diagnosis, can impact an individual's ability to effectively listen to, comprehend and retain information. Toss in the complexity of many oncology treatment regimens, and this is a prime setup for confusion.

Additional barriers to medication adherence relate to the patient's social determinants, such as language barriers, health literacy, financial toxicities, healthcare system navigation and resource management.

Patients may not fill their prescriptions due to cost or lack of knowledge regarding financial assistance programs. To help patients secure means to afford their medications, providers and pharmacies often utilize nurse navigators or specialized teams to assist them.

Rx to Go Pharmacy, LLC., part of the Florida Cancer Specialists system, identifies patients experiencing high copays and refers them to the pharmacy patient assistance team, which searches for foundation dollars to help cover the costs.

Most nurses can describe a personal experience they have had with a patient who has misunderstood the meaning of dosing directions and taken three pills once daily instead of one pill three times daily, or the patient who decided to take their BID (twice a day) medication once a day to save pills.

Specialized, oncology pharmacy nurses are trained in disease state and oral medication regimens. They understand that the potential side effects may differ from IV therapy, and that side effects on day one may differ from those at day 60 or 90.

Specialized, oncology pharmacy nurses can assess provider notes for information regarding employment or insurance changes, follow medication fill histories and reach out to patients to discuss discrepancies or potential adherence concerns.

These nurses can be utilized to reinforce pharmacist-initiated patient education on medication use, storage and handling, and side-effect management.

THERAPY TOLERANCE

The innovation of precision medicine, combination therapies and targeted therapies have vastly improved treatment outcomes and changed the landscape of side effects experienced by the patient.

Cytotoxic modalities — which are known for extreme, intolerable effects on the body — are being replaced with immunotherapy or targeted therapies with less intense side effect profiles.

Consolidation or maintenance therapies often utilize oral oncolytic, targeted regimens. Patients may be on oral oncolytics for years or until progression or intolerance to therapy. Minimizing the experienced side effects may keep patients on therapy longer at maximum dosing, thus optimizing response to therapy.

Specialized, oncology pharmacy nurses are trained in disease state and oral medication regimens. They understand that the potential side effects may differ from IV therapy, and that side effects on day one may differ from those at day 60 or 90.

Rx to Go Pharmacy utilizes a team of RN specialists who review and assess the patient's tolerance to current oral therapies with every fill of medication the patient requests.

This assessment is focused on medication-specific toxicities. Nursing interventions are designed to notify

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NURSING

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providers of potential hematologic or non-hematologic side effects that may indicate a need for dosing reevaluations or other clinical interventions.

Additionally, this team targets a subgroup of oral oncolytics that pose a high risk for extreme side effects and may impact the patient's ability or desire to continue therapy.

Nurses call patients every two weeks for the first two months of therapy to ensure they are utilizing any supportive care modalities and home care advice to minimize side effects such as diarrhea, nausea and vomiting, fatigue and pain. The team will reinforce the provider's recommendations of when to contact the office for uncontrolled side effects and relay concerns directly to the team.

For more information about **NCODA Oral Chemotherapy Education (OCE) sheets**, scan the QR code above.

Nursing teams have many resources that can supplement their evidence-based interventions, including medication package inserts, nursing, and medical research articles, and NCODA's PQI articles and Oral Chemotherapy Education (OCE) sheets.

WASTE & FINANCIAL TOXICITY PREVENTION

Providers, insurers and MIPs understand the dangers of automatic refill dispensing in the oral oncolytic space. Patient conditions can change dramatically during treatment and treatments may change abruptly.

Because of this possibility, MIP pharmacies typically dispense a 28- to 30-day supply of oral oncolytics per fill. Rarely will insurers approve multi-month supplies and some medications — such as REVLIMID®, POMALYST® or THALOMID® — are restricted by the U.S. Food & Drug Administration (FDA) and manufacturer due to the public safety concerns resulting from large, on-hand supplies of these medications.

Patients are motivated to fill their medications based on a number of factors. These may include a personal drive to continue therapy and desire to follow instruction from the provider or family members. The absence of barriers in obtaining the prescriptions will also impact the patient's motivation to fill.

For example, picture a 70-year-old cancer survivor who has been on treatment for a month. This patient has undergone extensive IV therapy with resulting chemotoxicities — including fatigue and neurologic changes — and is continuing to fight for their life. The pharmacy calls to schedule the next shipment of their lifesaving medication. The patient is eager to set up delivery because they know they cannot just go to the local pharmacy and pick this up-and they have only five days of pills remaining on hand. The patient arranges delivery, unaware that their recent blood work indicates a hold in treatment or dose reduction.

Rx To Go employs a team of specialized pharmacy technicians dedicated to evaluating patient adherence issues and collecting information on current medication, dosing regimen and recent admissions to facilities. The pharmacy technician sometimes collects this information from an elderly, confused, ill patient or the spouse of a hospitalized patient. The medical record, however, may tell a different story.

At RX to Go, a nurse will reevaluate the patient status prior to the order shipping. Often there can be multiple days between the technician's conversation with the patient and the day the order actually ships. For instance, the nurse may see the order was scheduled Monday, but the EMR indicates a hospitalization or significant hematologic side effect on Thursday — the date the order is set to ship. Swift nursing intervention may save the patient from a large copay, or worse, taking a medication that may cause harm.

Waste prevention initiatives in the specialty pharmacy space are aimed at preserving optimal patient outcomes and mitigating financial toxicities for the patient and pharmacy. And nurses can be the driver of this initiative.

At RX to Go, the nurse has the responsibility to assess every order and stop the processing or delivery of medications deemed not suitable to be dispensed. Patient education regarding the clinical rational for the intervention is also best delivered by a member of the pharmacy clinical team. Interventions coupled with patient education ensure the patient is informed of the potential consequences of refilling their medications.

Tracking orders can yield data related to drug-specific toxicities and place a numeric financial value to the initiative. Calculating drug pricing per unit plus the number of units not dispensed, (units saved), will yield a cost per order that the patient, insurer and pharmacy did not incur.

For more information about **NCODA's Cost Avoidance & Waste Tracker tool**, scan the QR code above.

NCODA's Cost Avoidance & Waste Tracker tool provides a similar function.

Nurses act as advocates, navigators, collaborators and educators, as well as deliver patient care with compassion and purpose. Along with providers, they are one of the most visible, tangible aspects for a patient on their journey.

▲ **Dawn Landolph**, RN, BSN, OCN, MPA, is Associate Director of Specialty Pharmacy Nursing Services at Rx to Go Pharmacy, LLC.

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NEW HEALTHCARE RESOURCES SUPPORT ORAL ANTICANCER MEDICATION ADHERENCE

By Kristine B. LeFebvre, DNP, RN, NPD-BC, AOCN

A collaborative effort in 2021 by professional from three organizations has developed resources that healthcare workers can use to support patient adherence for oral anticancer medications.

Members of the NCODA Nursing Committee, the Hematology/Oncology Pharmacy Association (HOPA), and the Oncology Nursing Society (ONS) participated in this interprofessional work, which was published by ONS in July 2022.

Kristine B. LeFebvre

A systematic review and meta-analysis served as the evidence base for this work. PICO (Population, Intervention, Comparison, Outcome) questions addressed aspects of oral adherence, including patient assessment, education, follow-up, coaching, motivational interviewing, technology and program structure. This study was a comprehensive review of the current knowledge of interventions used to support oral anticancer medication adherence.

The interprofessional team of oncology healthcare professionals and patients used data from the systematic review to develop the ONS Guidelines to Support Patient Adherence to Oral Anticancer Medications. In addition to usual care, the guidelines recommend integrating patient education, adherence risk assessment, proactive follow-up, coaching, motivational interviewing and a structured oral anticancer medication program as methods shown to improve adherence.

The Oncology Nursing Society's Oral Anticancer Medication Toolkit has tools on patient education and assessment, drug interactions, resources for caregivers, follow-up and monitoring, and much more.

Several pharmacy and nursing experts who participated in the guidelines noted that they often receive inquiries on how to structure an oral therapies program. To address this topic, a concurrent literature review was conducted to identify domains of such a program.

The scoping review of 21 studies revealed successful programs are proactive and include follow-up, patient education, counseling, toxicity, adherence and adverse event monitoring, as well as assistance with drug procurement and cost reduction.

Last of these new resources is the ONS Oral Anticancer Medication Toolkit. Nursing and pharmacy experts provided the feedback and recommendations needed to update the former ONS Oral Adherence Toolkit, and resources developed by the NCODA Nursing Committee helped to form some of the tools.

This new revision has tools on patient education and assessment, drug interactions, resources for caregivers, follow-up and monitoring, and much more. A printable wallet card can be personalized for patients to share at care transitions.

Each of these resources was developed through the collaboration of pharmacists and nurses. Find these and many other resources in the ONS Oral Anticancer Medication Learning Library, available at **www.ons.org/learning-libraries/oral-anticancer-medication**. *Please note that the resources are available free of charge, but you will be required to register and login to the ONS website to download the resources.*

▲ **Kristine B. LeFebvre**, DNP, RN, NPD-BC, AOCN, is an Oncology Clinical Specialist at the Oncology Nursing Society in Pittsburgh, Pennsylvania.

The Oncology Nursing Society Releases **New Oral Anticancer Medication Adherence Guidelines, a Scoping Review, and a Toolkit!**

The toolkit features the following:

- Pretreatment assessment and patient and caregiver education
- Safety concerns, including drug-drug and drug-food interactions
- Financial and reimbursement resources
- Tips for motivational interviewing
- Follow-up monitoring and wallet card

ONS Guidelines™ to Support Patient Adherence to Oral Anticancer Medications

Developed by experienced oncology nurses and oncology pharmacists, the oral adherence guidelines incorporate published research with expert consensus on the certainty of the evidence, the balance of benefits and harms, and patient preferences and values.

Domains of Structured Oral Anticancer Medication Programs: A Scoping Review

This scoping review identifies oral anticancer medication programs in the literature to provide examples and propose a framework intended to improve adherence.

Oral Anticancer Medication Toolkit

The toolkit provides evidence-based strategies and resources to help clinicians facilitate adherence among patients prescribed oral anticancer therapy.

Learn more at
ons.org/OAM-Guidelines

ONS®
Oncology Nursing Society

YOUNG ADULT CANCER SURVIVORS HELP PEERS RECONNECT WITH THE JOY OF LIFE

Kaitlyn Ash and Lauren Stafford have a lot in common. They're both young women from the Jacksonville, Florida, area.

They're both professionals — Ash is a restaurant manager and Stafford, a former clinical pharmacy manager at a regional hospital group.

Both survived bouts with Ewing sarcoma, a rare pediatric bone cancer.

Kaitlyn Ash

Lauren Stafford

And both know full well the challenges faced by young adults with cancer.

Ash has been in remission since 2001, a year after she was first diagnosed with the disease at age 12. She has given back to the cancer community ever since, through speaking engagements, serving on boards for numerous nonprofits and organizations, and connecting young adults suffering from cancer with support.

"Once you survive the cancer, you think everything's going to go back to normal, but life is forever changed," Ash said.

In addition to its physical, mental, and emotional impacts, a cancer diagnosis can be particularly devastating for young adults. Cancer can interrupt school, relationships and careers, as well as getting married and having children.

According to the National Cancer Institute, more than 70,000 young adults are diagnosed with cancer each year in the United States – almost eight times the total number of pediatric cancers.[1]

In 2013 — along with fellow survivors Katie Pearsall and Todd Blake — Ash founded the Live For Today Foundation, a nonprofit dedicated to providing support to young adults with cancer, as well as to create adventure, encourage new experiences, and inspire healthy lifestyles.

To participate in the program, members must be between the ages of 18 and 39, diagnosed with or treated for cancer and a resident of northeast Florida. The group currently has around 120 members.

The foundation specializes in Life Adventures, a wish-granting experience tailored to young adult cancer patients. Recipients have experienced customized trips to Disney World, seaside resorts, cruise ships, concerts and other events.

Stafford joined the Live For Today Foundation after experiencing the organization's work firsthand as a recipient of a customized Life Adventure following completion of her bone cancer treatment in 2014.

"My husband and I were going to California to celebrate our 10-year anniversary. Live For Today gave us an incredible day, including a hot air balloon ride over Napa Valley and an incredible chauffeured wine-tasting tour," Stafford recalled. "It was just amazing to get to experience that, and it was very life-affirming."

Stafford was so inspired by the event that she became a board member. She now chairs the group's Life Adventure program.

Live For Today also hosts a Group Event every couple of months, including bowling nights, cooking classes, restaurant rendezvous, trips to sporting events, and parties. Healthy Living events emphasize proper nutrition and exercise, including yoga, spa, and workouts.

"We also serve childhood cancer survivors," Ash noted. "And while long-term survivors aren't eligible for Life Adventures, they still often attend our Group Events many often deal with lifelong setbacks from their cancer treatments."

The social aspects of the program have proven to be particularly beneficial.

"Cancer effects your mental health, so you need to be able to connect with other people," Ash said. "And while there are things to facilitate that, like social workers and group sessions, our idea was a more casual interaction with food and a fun activity where those conversations just happen naturally."

"It doesn't have to be 'Hi, I'm Kaitlyn, I was diagnosed with cancer when I was 12. I've been in remission for XYZ.' Instead, it's 'What are you up to? What do you do in life?' It's proven to be a great opportunity for a lot of our members to get together."

It also provides a place for patients and survivors to focus on goals, dreams and visions beyond their cancer experience.

"When you're going through cancer treatment, all you can really think about is the fight itself, and it can become a very difficult, depressing place," Stafford explained. "Our goal is to help members — especially ones that are fresh out of their cancer treatment journey, or maybe still going through it — get out of that survival mode and remember the importance of living and the joy of life."

For more information about the **Live For Today Foundation**, scan the QR code above.

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NCODA AT EIGHT: HOW COMBINING NEED WITH PASSION IS CHANGING THE WORLD OF ONCOLOGY

Since its inception in 2015, NCODA has empowered the medically integrated oncology community by following one simple formula: **NEED + PASSION = VALUE**.

The **NEED** quickly became apparent to me back in 2013 when we created one of the first medically integrated dispensing practice in the country. Our practice had been flawlessly performing IV infusions for more than four decades.


Michael Reff

Yet when it came to the rapidly emerging field of oral oncolytics, many of those methodologies no longer applied. From the moment I began filling prescriptions, it was clear that a lot of things needed correcting. Things like access, financial toxicity, adherence and education.

So, from the outset, the **NEED** was clearly identified. We anticipated those needs by having a nurse, pharmacist and pharmacy technician to help ensure that the patient had a great experience. We focused on continuity of care, and especially on the need to keep the first fill and subsequent fills within our practice.

Ultimately, that focus on patient-centered care was to become the wellspring of NCODA, and its driving **PASSION**. That **PASSION** was formalized with the launch of NCODA in 2015 and the creation of our four Quality Standards: Patient-Centered, Positive Quality Interventions, Foundational Elements and Health Information Technology.

NCODA reached a milestone in December 2019 with the creation and publication of the **ASCO/NCODA Patient-Centered Standards for Medically Integrated Dispensing**. That achievement, in turn, lead to the launch of the **NCODA Center of Excellence (CoE) Medically Integrated Pharmacy (MIP) Accreditation** program in 2022.

As we enter our eighth year, the growth of these and NCODA's many other initiatives bear witness to the **VALUE** our organization has brought to patients, providers and industry partners:

▲ **MEMBERSHIP:** NCODA's rise in membership has been nothing short of meteoric. We started with 100 members representing 47 practices. Today we represent more than 6,000 members from over 900 community, academic, hospital, integrated delivery networks (IDN) and urology practices in 50 states, six Canadian provinces and 14 countries.

▲ **ACCREDITATION:** Since the launch of NCODA CoE MIP Accreditation Program in January, one practice has become accredited, while another 37 are pursuing accreditation. The program is the preferred accreditation body by Prime Therapeutics. Plans are for a multi-specialty accreditation by January 2023 and collaboration with additional PBMs to expand the program's reach.

▲ **TREATMENT SUPPORT KITS (TSKs):** NCODA currently offers three generic and seven branded oral oncolytic TSKs. To date, more than 10,000 kits have been distributed to 120 cancer centers. NCODA has been an FDA-registered kit manufacturer for the past three years. We plan to continue working with our pharmaceutical partners to create TSKs for new drugs and existing compounds. We also plan to implement Malcolm Baldridge Quality Framework for the TSK platform.

▲ **MENTORING:** NCODA oversees 49 Professional Student Organization (PSO) chapters in the U.S. and Canada. Along with our pharmaceutical partners, we also sponsor four fellowships. Our program is proudly supported by Bristol Myers Squibb, Exelixis and Pharmacyclics/Janssen.

▲ **OCE/IVE SHEETS:** NCODA initiated Oral Chemotherapy Education (OCE) and Intravenous Cancer Treatment Education (IVE) sheets because there was a need for standardized patient and caregiver education. Currently there are 100+ OCE sheets and 30+ IVE sheets, generating more than 80,000 webpage views each month. In the future, we plan to translate the sheets into other languages and expand both libraries.

▲ **LEGISLATIVE AWARENESS:** NCODA's Legislative Policy & Advisory Committee (LPAC) was created to increase education and engagement by healthcare providers at the state and national level through our Oncology Legislation Tracker, legislative sessions at meetings and collaboration with the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Patient Access Network (PAN) Foundation. We plan to expand LPAC and enhance the tracker in the months to come.

▲ **POSTIVE QUALITY INTERVENTIONS (PQIs):** PQIs were created to meet the need for concise and precise, peer-reviewed clinical guidance for healthcare professionals in order to provide better patient care. Currently, there are 95+ published PQIs for oral and IV anticancer medications. International authorship, IV-specific PQIs and PQIs that focus on Diversity, Equity & Inclusion are in the works.

NCODA initiatives are changing the face of oncology. The **NEED** is great, but our **PASSION** is greater, while its **VALUE** to the patients we serve is limitless.

Michael J. Reff, RPh, MBA
Executive Director & Founder | NCODA

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Lit No. 1SS22-2092125 (08/2022)