ONCOLYTICS TODAY

EMPOWERING THE MEDICALLY INTEGRATED ONCOLOGY PHARMACY PRACTICE | SPRING 2024

FILLING THE DIVERSITY GAP IN CANCER CARE

NCODA

NEW CMS FRAMEWORK FOR HEALTH EQUITY MAY HELP SOLVE THE PUZZLE PAGE 49

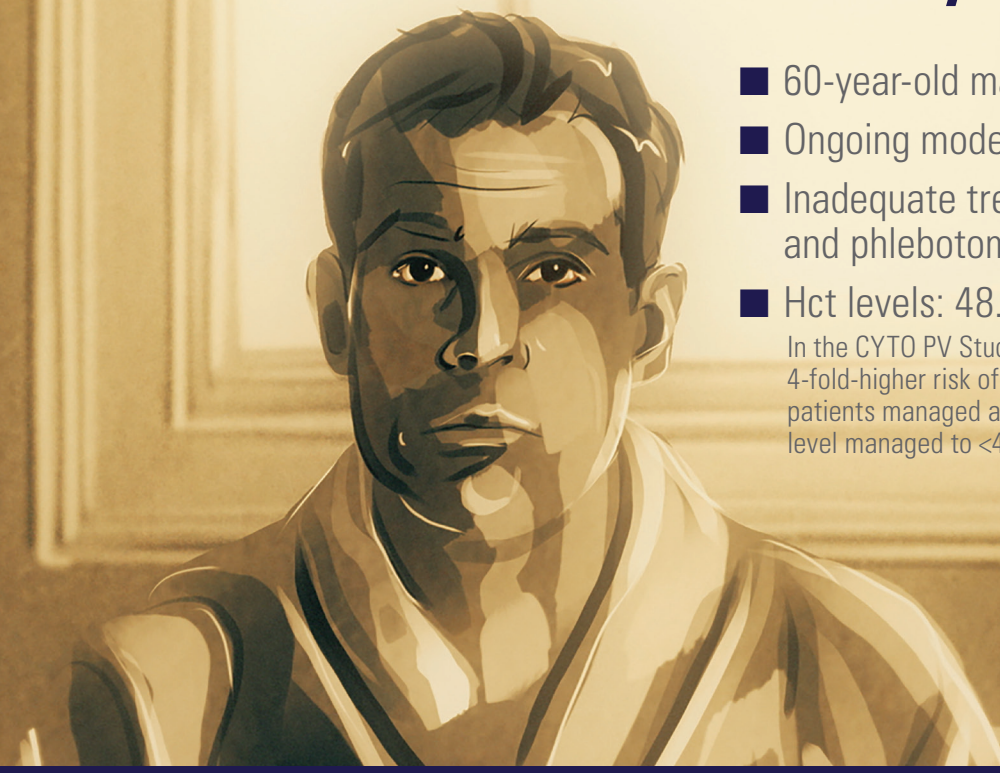
COMMUNICATING ACROSS ECLETIC HEALTHCARE TEAMS TO EFFECT CHANGE PAGE 59

PLUS: THE LATEST NEWS ON ONCOLOGY RESEARCH, RULES & DRUG APPROVALS

Pharmacy directors
and clinical pharmacists...

This is Nick.

He is at an increased risk for a thrombotic event because he has advanced Polycythemia Vera (PV).[1*]



- 60-year-old male
- Ongoing moderate-to-severe fatigue
- Inadequate treatment with HU[†] and phlebotomy
- Hct levels: 48.2%

In the CYTO PV Study[‡] of 365 patients with PV, there was a 4-fold-higher risk of cardiovascular death and major thrombosis in patients managed at an Hct target level of 45% to 50% vs an Hct level managed to <45%[3] (HR, 3.91; 95% CI, 1.45-10.53; $P = 0.007$)

[*]Advanced PV is indicated by Hct ≥45% plus WBC count>11x10^9/L or disease-related symptoms despite treatment with HU at the maximum tolerated dose and phlebotomy.[2-4]

[†]HU at the maximum tolerated dose.[2-6]

[‡]In the CYTO-PV study of 365 adult patients with PV treated with PBT, HU, 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% to 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.[3]

Hct levels ≥45% carry a risk. You can help.

A Quality Initiative can help your care team better manage patients like Nick who have clinical characteristics of advanced PV.

Champion a Quality Initiative

Use your EHR to identify patients who have elevated Hct between 45% to 50% despite HU and phlebotomy, and may also have burdensome symptoms like fatigue.[5,7-10]

SCAN ME

to go to MPNQuality.com to find out how to implement a quality initiative.

CI=confidence interval; CYTO-PV=Cytoreductive Therapy in Polycythemia Vera; EHR=electronic health record; Hct=hematocrit; HR=hazard ratio; HU=hydroxyurea; PBT=phlebotomy; PV=polycythemia vera; WBC=white blood cell.

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How it works:

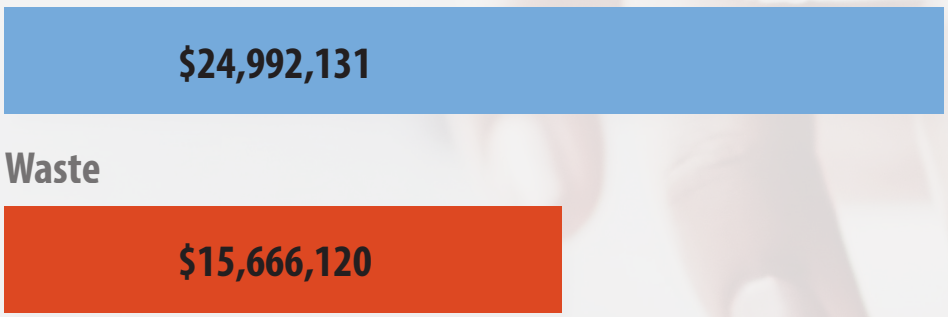
Cost Avoidance: Whenever you perform an intervention for a patient that helps prevent an unnecessary prescription from being given to a patient, ***record the savings.***

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

How to use the data:

Share the information with your administration, payers, employers, and other relevant stakeholders to showcase the benefits of your practice over alternative services.

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



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Filling the Diversity Gap in Cancer Care

Racial inequity in healthcare, particularly in oncology, has been well-documented. Bringing equity to charitable copay assistance and better communication across diverse healthcare teams offer opportunities to improve the situation.

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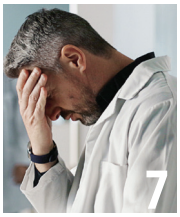
FEATURED ARTICLES



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OUR SPRING 2024 ISSUE FOCUSES ON THE DIVERSITY GAP IN CANCER CARE

Welcome to the Spring 2024 issue of ***Oncolytics Today***, your source for the latest news on oncolytic approvals, indications, clinical updates and best practices, as well as the latest information on NCODA's new and existing initiatives.

The publication, now in its sixth year, explores cancer issues from both the clinical and the human perspective, providing our readers with concise, practical information designed to benefit their patients, practices and personal growth.

Randy Erickson

CLOSING THE DIVERSITY GAP

The lack of diversity, equity and inclusion (DEI) across the oncology spectrum has come to the forefront in recent years. According to the American Cancer Society (ACS) **Cancer Facts & Figures 2023** report, progress in cancer research, care and prevention has led to a 33% decline in U.S. cancer mortality rates since 1991.

Yet despite this progress, an individual's chance of surviving cancer can be profoundly affected by race, gender, socioecomonic status and geography.

For instance, "for most types of cancer, Black people have the highest death rate and shortest survival of any racial/ethnic group in the United States," according to the **ACS Cancer Facts & Figures for African American/Black People 2020-2024** report. Black women alone are 41% more likely to die from breast cancer than their White counterparts, according to the report.

Yet DEI concerns are not limited to patient populations. Recent articles in ***Oncolytics Today*** have examined how the lack of minority representation among healthcare practices and professionals has exacerbated this situation.

This is an issue that runs both broad and deep, and won't be fixed overnight. That said, in this issue of ***Oncolytics Today*** we take a look at solutions designed to remedy two facets of the problem:

▲ **Patricia Falconer**, MBA, **Fred Asiedu Larbi**, MBA, **Samuel Sappor** and **Krista Zodet**, MSW, examine the issue of financial toxicity, and how the Centers for Medicare & Medicaid Services **Framework For Health Equity Priorities** can provide a roadmap for better distribution of charitable copay assistance funds among minority patient populations. Coverage begins on **Page 49**.

▲ **Joni L. Watson**, DNP, MBA, RN, OCN, takes a look at how effective communication is the key to harnessing team and organizational diversity among professional healthcare organizations. Coverage begins on **Page 59**.

ALSO IN THIS ISSUE

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

▲ **Hardeep Phull**, MD, discusses the mental health epidemic in oncology in the wake of the COVID-19 pandemic and offers ideas on how oncologists can overcome burnout and reconnect with their profession on **Page 7**;

▲ The effects of the CMS Final Rulings on **Direct and Indirect Renumeration Fees** and **Prior Authorization** are highlighted on **Page 15** and **Page 17**;

▲ **Joanna Fawzy Doran**, Esq., deciphers 2024 Medicare rules under the Inflation Reduction Act on **Page 23**;

▲ **Nikolas Papadantonakis**, MD, MSc, PhD, summarizes anemia management for patients with lower-risk myelodysplastic neoplasms on **Page 27**;

▲ A healthcare team from **Emory Healthcare/Winship Cancer Institute in Atlanta, Georgia**, outlines the impact of an Antithrombin III replacement protocol in pegaspargase-treated adults with acute lymphoblastic leukemia on **Page 33**;

▲ **Alexandra Minnihan**, MD, and **Alice Rhoton-Vlasak**, MD, review new options to preserve fertility in cancer patients on **Page 39**;

▲ Veterinary oncologist **Renee Alsarraf**, DVM, DACVIM (Onc), reveals how her dog Dusty helped her deal with the challenges of cancer on **Page 83**; and

▲ Fitness expert **Fitz Koehler**, MSESS, recalls how she utilized diet and exercise to overcome 15 months of exhaustive breast cancer treatment on **Page 87**.

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

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

THE MENTAL HEALTH EPIDEMIC IN ONCOLOGISTS

TIME TO INOCULATE OURSELVES FROM THIS CONTAGIOUS ILLNESS AND HIT THE RESET BUTTON

By Hardeep Phull, MD

Oncologists possess some of the highest levels of empathy, humanity and emotional intelligence that I have witnessed in clinical practice.

We see some of the sickest patients in emotionally draining circumstances during some of the most vulnerable moments of an individual's life.

Hardeep Phull

We develop meaningful relationships with these patients, as the person behind the illness emerges, allowing us to empower this soul to undergo the rigors of treatment in the hope of reclaiming their lives which are inevitably changed forever.

When we deal with death and dying, we also handle this difficult event with a spirit of healing, compassion and dignity towards patients and their families.

Though we are not superhuman or immune from the physical and emotional exhaustion of compassion fatigue, we tend to strive daily with a sense of joy, resilient purpose and duty to never lose our empathy or allow ourselves to become cynical or depersonalized.

How then, do we become "burned out" and how does that lead to mental health issues?

HOW TO MORALLY INJURE AN ONCOLOGIST

To understand the problem, we must define fundamentally the crucial terms which often become blurred.

The word "burnout" has become the most common vernacular to describe employee disgruntlement in nearly any industry. The issue with this term is in its implied form of gaslighting in which an individual lacks the necessary resilience to perform the work and therefore the problem insidiously shifts to reside somehow within the deficient individual.

By contrast, moral injury in healthcare practitioners is defined as a fundamental conflict between the needs of healthcare systems and one's own passion, moral beliefs and motivation to serve patients. Such needs may go unmet due to existing demands or restrictions that perpetuate beyond one's control, yet still there is an implied culpability.[1]

In a culture of repetitive, fundamental moral injury, combined with stoicism and "toxic" resiliency, the same positive traits which originally gave an oncologist purpose and compassion can begin to create unrealistic expectations.

This is compounded by not only administrative burdens such as medical notes, EHR clicks and prior authorization

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BURNOUT

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paperwork, but also by physical factors such as the lack of structured breaks in salaried employees, decreased physical activity or time spent outdoors away from computer screens, worsening sleep habits and development of health conditions or illnesses.

Without even accounting for social, gender or personal/family factors, the above process along with a progressive loss of autonomy to practice medicine can lead to a sense of detachment and disconnection from meaningful, rewarding duties, giving way to detrimental feelings of personal failure, imposter syndrome and depression.[2]

Like an infectious disease, these spiraling mental health symptoms can be harmful and even contagious as they infiltrate entire clinics or institutions, trickling down to the entire cancer care team from pharmacists, nurses and medical aides and on to the caregivers and patients themselves.

ENTER THE COVID PANDEMIC

Even before the pandemic, burnout rates were approaching 50% in oncologists and oncology professionals such as physician assistants, nurse practitioners and pharmacists.[3]

However, the COVID pandemic raised even more mental health issues, partially because it added fuel to the already burning fire with additional burdens and stressors.

Beyond the sudden disruption in care, the added fears, expectations and dangers of working as a first responder created literal "life or death" decisions daily.[4]

Moreover, we also started to spend less face-to-face time with patients and colleagues, leading to concerns about job satisfaction, job security and ongoing professional development.

This caused many practitioners to leave clinical practice which exacerbated shortages in the workforce, especially with the influx of post-pandemic patients who delayed care or cancer screenings,

By advocating for a work culture at our institutions in which mental health is not stigmatized, but rather recognized openly, with appropriate resources provided in a nonpunitive fashion, we nurture emotional renewal and promise a sense of authentic well-being that can infiltrate the entire system in pandemic proportions.

resulting in more advanced malignancies and sicker patients overall with fewer (yet more burned out) oncologists and a diminished, exhausted workforce to take care of them.[4]

In 2022, U.S. Surgeon General Vivek Murthy recognized the post-COVID crisis among healthcare workers, declaring it an "urgent need" and writing in the *New England Journal of Medicine* that healthcare workers "continue showing up to battle the pandemic and its sequelae," despite contending with severe symptoms of "insomnia, depression, anxiety, (and) post-traumatic stress disorder," which they were not prepared to face or handle.[5]

Unfortunately, even for the astute clinician or observer, a developing mental health disorder in this milieu was dangerously easy to deny or ignore. Along with the lack of time and availability of easily accessible mental health professionals, there continued to be a perceived stigma around mental health problems in society and in medicine, especially with the latter due to an intuitive instinct of physicians to protect their ability to remain employed.

Subtle clues pointing towards early depression were easily blurred by temporary burnout and denial, sadly leading to increased cases of physician suicide.[2]

RECONNECTING: AUTHENTIC PURPOSE, GENUINE WELLNESS & EMOTIONAL RENEWAL

The first step in solving any problem is to acknowledge that it exists. We must be provided with a system that breaks the status quo, promising safety and immunity with an open, nonpunitive platform to speak candidly about mental health symptoms and disorders.

Indeed, as Murthy stated in 2022, "Burnout manifests in individuals, but it's fundamentally rooted in systems."[5]

Therefore, resilience training and wellness initiatives need to be authentic and practical rather than "contrived wellness" checkboxes.[6] This includes addressing the entire scope of a person beyond their practitioner duties or responsibilities, including practical needs such as physical activity and fitness, childcare and family obligations, sleep habits, coping skills and stress management strategies, among others.

There need to be fewer barriers to getting help, including breaks (beyond a fleeting lunch period mostly spent catching up on EHR tasks or attending conferences) during the daytime for appointments and wellness sessions.

Moreover, colleagues from the entire spectrum of the clinical team should be allowed and taught to recognize symptoms in each other in the spirit of advocacy, empathy and interpersonal relatedness.[6]

Lastly, efforts should be made to harness technology to work for us, rather than the other way around. EHRs, burdensome tasks and paperwork, and patient visits could be simplified perhaps by harnessing the power of artificial intelligence and telemedicine (perhaps one of the positive sequelae of the COVID-19 pandemic).[6]

It is encouraging to see our voices heard on a national level by the American Society of Clinical Oncology's development of an Oncology Clinician Well-Being Task Force to promote mental healthcare services for the entire oncology care team to create a genuinely resilient mental

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BURNOUT

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health culture and workforce.[7]

However, to truly battle detachment, we need to promote attachment on a local level. After all, "Burnout is not only about long hours. It's about the fundamental disconnect between health workers and the mission to serve that motivates them."[5]

In essence, we must recognize our mission of reconnecting each other to meaningful, rewarding duties that enable and empower the entire care team to practice the joy of medicine.

If it took a devastating COVID-19 pandemic to bring these issues to a critical breaking point, then just as the COVID-19 vaccine provided some hope, we too must be willing to inoculate the system with drastic and meaningful reform that results in herd immunity for ourselves and for all of our valuable colleagues including nurses, pharmacists, advance practice providers, technologists, therapists, social workers, support staff and administrators.

Ultimately, we owe it not only to the care team but also to the most important clients in the healthcare business: our patients, whose experience and outcomes depend on the downstream effects of our behaviors and actions.

By advocating for a work culture at our institutions in which mental health is not stigmatized, but rather recognized openly, with appropriate resources provided in a nonpunitive fashion, we nurture emotional renewal and promise a sense of authentic well-being that can infiltrate the entire system in pandemic proportions.

▲ **Hardeep Phull**, MD, is the Director of Medical Oncology at Palomar Health Medical Group in Escondido, California.

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NEW ADVANCEMENTS IN ORAL ONCOLYTICS CREATE NEW PATIENT SUPPORT CHALLENGES

NCODA STUDY SHOWS TREATMENT SUPPORT KITS ENHANCE PATIENTS' ABILITY TO REMAIN ON ORAL THERAPY

By Austin Starkey, PharmD, MBA & Rebecca Bahr, PharmD, MBA

Advancements in cancer research have increased treatment options and improved outcomes, but also present unique challenges.

One such advancement involves the treatment of Myelodysplastic Syndrome (MDS). MDS is a heterogenous group of clonal bone marrow stem cell disorders originating from mutated hematopoietic stem cells, resulting in ineffective hematopoiesis, anemia, neutropenia and/or thrombocytopenia, with an increased risk of transformation to acute myeloid leukemia (AML).[1,2] MDS is one of the most common types of blood cancers with approximately 20,000 new cases reported every year in the United States.[3]

NCCN Guidelines treatment recommendations for MDS include hypomethylating agents (HMAs), azacitidine, and decitabine and cedazuridine (oral DEC-C), hematopoietic stem cell transplant for appropriate candidates, high-intensity chemotherapy, ivosidenib (if mutated IDH1), supportive care, and clinical trials for higher-risk MDS. Lower-risk treatment options include iron chelation, erythropoiesis-stimulating agents, immunosuppressive therapy, HMAs, luspatercept, lenalidomide, and ivosidenib (if mutated IDH1).[4]

A SIGNIFICANT TIME INVESTMENT

In the past, HMA treatments were only available as intravenous infusions or subcutaneous injections. In-clinic infusions require a significant time investment, transportation to and from clinics, and disrupt daily activities for patients and caregivers.

In a survey of 120 patients and 21 caregivers, 64.3% of patents had to take time off work or adjust work duties to accommodate treatments for MDS. In the same study, greater than 40% of individuals receiving care at a medical facility had to travel more than an hour to receive treatments.[5]

When asked about other treatment options, close to 70% of patients in this study indicated that they would prefer to take an oral treatment as opposed to an intravenous therapy or injection.[5]

A patient survey of 150 patients with MDS who had received prior intravenous/subcutaneous (IV/SC) HMAs reported that oral DEC-C interfered less with daily life (91%), improved quality of life (85%) and reduced visits to healthcare facilities (91%).[6]

In 2020, the FDA approved INQOVI® (decitabine and cedazurdine), an oral option for MDS patient. A recent publication in December 2023 updated efficacy and safety data, and reported a median overall survival of 31.8 months for patients taking INQOVI®.[7] This exceeds previously reported overall survival with IV decitabine and parenteral azacitidine.[8]

ORAL TREATMENT CHALLENGES

Oral medications come with

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NCODA TREATMENT SUPPORT KITS SET THE INDUSTRY STANDARD

NCODA's Treatment Support Kits (TSKs) provide patients and caregivers with educational resources and products to help improve medication adherence and compliance during treatment with anticancer medications.

TSKs support patients through their treatment journey by providing information on disease management, and medication side effects and how to manage them, as well as supplying over-the-counter supportive medications and other materials.

NCODA offers TSKs for Abemaciclib, Abiraterone Acetate, Cabozantinib, Capecitabine, Fruquintinib, Mobocertinib, Neratinib, Nirogacestat, Pacritinib, Regorafenib, Tivozanib and Temozolomide.

As an FDA-registered kit manufacturer, NCODA develops and manufactures its TSKs to the highest quality based on current Good Manufacturing Practices.

For more information on TSKs, scan the QR code above.

TSKs

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alternate challenges for patients, such as medication adherence and adverse event support away from the clinic.

When patients are receiving an intravenous regimen, the healthcare team schedules treatment and can manage patient adherence directly in the clinic.

In-person intravenous treatment also allows cancer care professionals to manage any adverse events in the infusion center, premedicating with antiemetics as needed. Patients benefit from the opportunity to speak with the nurses or other cancer care professionals on a regular basis. They may even form connections and find support in other patients, while these opportunities do not arise on oral therapies.[9]

THE INQOVI® TREATMENT SUPPORT KIT

Taiho Oncology, the manufacturer of INQOVI®, recognized these challenges and the need for enhanced patient support. Taiho partnered with NCODA to provide Treatment Support Kits (TSKs) to address this unmet need. NCODA's TSKs are drug-specific kits designed to support patients and anticipate patients' needs during their treatment journey.

The INQOVI® TSK includes patient-centered education, qualitative patient experience survey, medication calendar and supportive care for patients, including over-the-counter antidiarrheal medication, Queasy Drops®, a collapsible water bottle, a digital thermometer, lip balm, heel balm, hydrating cream for very dry skin, and sunscreen.

NCODA provides this complimentary kit, as well as several others, to practices within the NCODA network upon request. Each practice also received the Positive Quality Intervention (PQI) document for INQOVI® with each request for kits. This clinical guidance resource provides an overview of best practices for oral DEC-C patient management.

The kit also includes dose reduction strategies for managing side effects, and highlights additional resources including available patient assistance programs.

PATIENTS PROVIDED TSKS: DEMOGRAPHICS, DISCONTINUATION & THERAPY DURATION

DEMOGRAPHICS		
Gender		
	Male	30
	Female	25
Age		
	> 81	16
	76-80	22
	71-75	11
	66-70	4
	61-65	1
	Unsure	1
THERAPY		
Previous HMA Therapy		
	Yes	16
	No	36
	Unsure	3
Discontinuation		
	Discontinued	34
	On Therapy	21
Cycles Completed		
	4 or Greater	25
	< 4	30

ADHERENCE IS CRUCIAL IN HMA THERAPY

NCODA TSKs deliver information to support patients on oral therapy. In this particular case, they help patients continue HMA therapy and achieve optimal clinical and quality-of-life outcomes. HMAs have been associated with survival benefit, improvement in cytopenias resulting in delayed progression to AML, and improved quality of life.[10,11,12]

It has been shown that patient HMA nonpersistence (<4 cycles or a gap of ≥ 90 days between cycles) incurred higher total monthly per-patient costs compared to the HMA-persistent group.[13,14]

Patients generally require at least four to six cycles to achieve responses to HMA therapy (barring clear progression or unacceptable toxicity). However, real-world evidence has reported that around 33% to 45% of patients received less than four cycles of therapy.[15,16,17,18]

Based on these studies in the traditional IV regimens, oral medication supported by TSKs may provide superior patient outcomes.

A PILOT STUDY OF TSK EFFECTIVENESS

To determine specific definitions on discontinuation and duration of therapy through manageable interventions, 55 patients were assessed to verify if the kits were able to improve the quality of life and time to treatment failure.

The patients came from four different medically integrated pharmacies. Patients received a TSK at the beginning of oral treatment regimens across practices. All patient information was deidentified and maintained at the practice level.

Patient demographics (**Table 1**), resemble those seen traditionally in the disease population, with the primary age of diagnosis between 71 to 76 years of age.[1]

Patients who received the kit had a median time to treatment failure of 105 days and four cycles. Of these, 25 patients (45%) had not met the four-cycle goal. However, eight patients were still on therapy at the study end date.

Dose modifications occurred in 20% of patients, leading to a median time to treatment failure of 130 days. Dose modifications were either lower dosage of drug (fewer days taken) or longer delays between cycles (35 vs 28 days).

The qualitative patient experience survey did not generate enough responses to warrant data analysis.

This pilot quality improvement study shows a glimpse of how the use of supportive care resources (i.e., TSKs) for patients receiving an oral therapy may enhance patients' ability to remain on therapy. More research needs to be done to see the full benefit of patient support kits.

Some limitations to this study were the small sample size and collecting data from a limited number of community oncology practices.

Yet it's clear that the use of TSKs can extend care beyond the clinic and, at the same time, empower patients between visits to manage potential adverse events of oral therapies while avoiding the many hours in an infusion chair.

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TSKs

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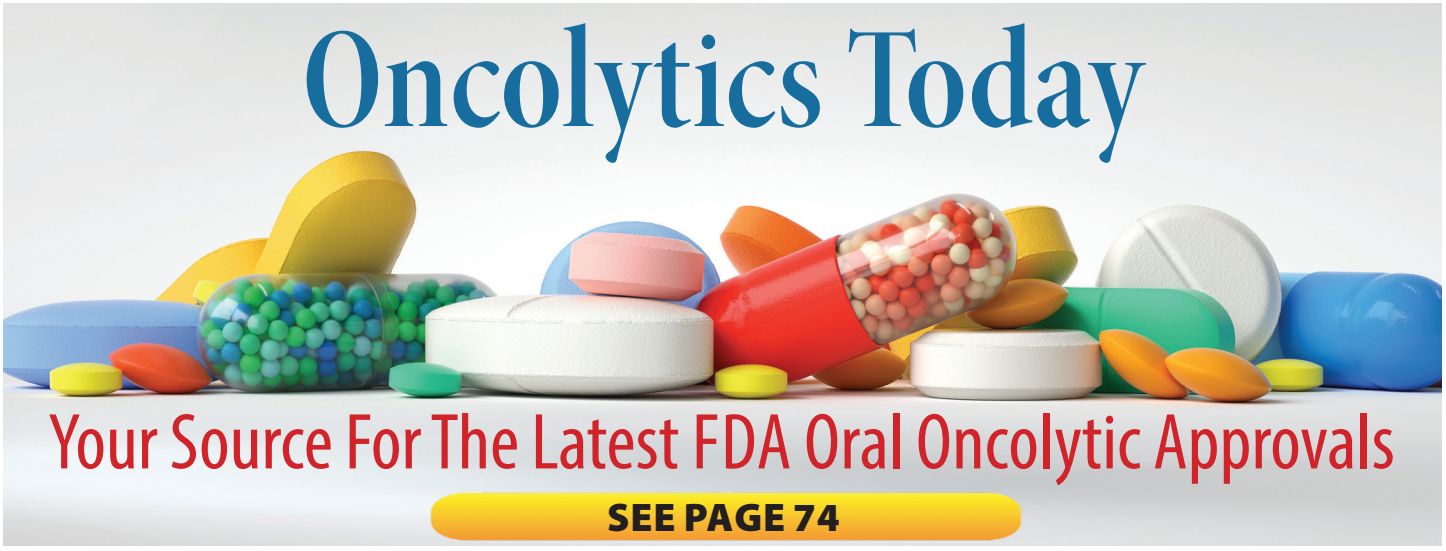

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FINAL CMS RULING ON DIR FEE TRANSPARENCY CUTS BOTH WAYS

HELPS PATIENTS & PHARMACIES, BUT HURTS CASH FLOW FOR PRACTICES IN 2024

Under a federal directive that went into effect January 1, 2024, pharmacy benefit managers (PBMs) can no longer retroactively apply Direct and Indirect Renumeration (DIR) fees to Medicare Part D and Medicare Advantage prescriptions already being sold.

The Centers for Medicare and Medicaid Services (CMS) ruling issued in April 2022 — **"Medicare Program; Contract Year 2023 Policy and Technical Changes to the Medicare Advantage and Medicare Prescription Drug Benefits Programs"** — is designed to help both patients and pharmacies by creating greater transparency in drug costs.

DIR fees are price concessions negotiated between PBMs and pharmacies participating in Medicare Part D and Medicare Advantage networks.

In the past, retroactive DIR fees were assessed weeks, or even months, after Part D beneficiaries' prescriptions were filled. The practice resulted in patients paying higher prices at the pharmacy counter for their prescriptions, as well as pharmacies being unable to recoup costs on prescriptions that had already been filled.

Retroactive DIR fees have become widespread in recent years. According to CMS, retroactive DIR fees increased by 107,400% between 2010 and 2020.[1]

In brief, the ruling requires that DIR fees must be reflected in the negotiated price the patient pays at the pharmacy counter.

The CMS ruling also eliminates a proposal that would have left it up to the health plans and PBMs to decide how much, if any, of the pharmacy price concessions would pass through to patients at the point of sale during the coverage gap in the Medicare Part D or Medicare Advantage program.

CONTINUED ON NEXT PAGE

DIR FEES

CONTINUED FROM PREVIOUS PAGE

BENEFITS BOTH PHARMACIES & PATIENTS

For pharmacies, the new rule means they can immediately see what they will be paid for drugs dispensed. Pharmacies will no longer have to wait weeks or months to learn what they owe the PBMs.

The ruling addresses a regulatory loophole that the CMS opened in 2014 that allowed PBMs to have unlimited license to apply retroactive DIR fees.

For patients, the new rule is intended to reduce out-of-pocket costs by moving all pharmacy price concessions, including retroactive DIR fees, to the point of sale.

The amount that Medicare patients pay for a prescription drug is supposed to be based on the cost of the drug.

In the past, however, payers often calculated drug prices without subtracting the dollars that were taken back from pharmacies. This inflated the patient's drug costs, because the calculation was based on a figure that was higher than what the plans really pay.

ISSUES REMAIN

However, the ruling does not eliminate DIR fees. PBMs still will be able to utilize a bonus payment model that allows them to extract arbitrary fees, except now at the point of sale rather than retroactively.

It also does not address the directive's impact on pharmacy cash flow.

Under the final ruling, pharmacies will receive the "lowest possible reimbursement" in 2024 while PBMs continue to collect pharmacy DIR fees from 2023, which could create significant cash flow issues for pharmacies during the transition.

In its final ruling, the CMS acknowledges the "possibility that changes in cash flow may cause some already struggling pharmacies to decrease services or medication availability, and/or be unable to remain in business, which may impact pharmacy networks."[2]

And while the CMS "encourages Part D plans to consider options, such as payment plans or alternate payment arrangements, to minimize impacts to vulnerable pharmacies and the patients they serve," it makes no provision for Part D plans to address cash flow issues.[2]

Finally, the ruling does not close other PBM loopholes, such as negative reimbursements (through which the PBM reimburses the pharmacy less than it costs to acquire the drug) and steering patients to PBM-affiliated pharmacies for brand, generic and specialty drugs.

"The DIR Transparency Rule is a good start in reducing the opacity of pharmacy pricing that would benefit both pharmacies and patients," said Stacey McCullough, PharmD, Chief Pharmacy Officer for NCODA.

"However, much work still needs to be done to level the playing field for medically integrated pharmacies. We encourage our members to stay committed to engaging their elected officials and educating their peers and the public on this important issue."

The CMS acknowledges the "possibility that changes in cash flow may cause some already struggling pharmacies to decrease services or medication availability, and/or be unable to remain in business, which may impact pharmacy networks."

HOW HAS THE NEW DIR FEE TRANSPARENCY RULE AFFECTED YOUR PRACTICE?

With the recent implementation of the DIR Fee Transparency Rule, NCODA is surveying members regarding its impact on their practices.

The rule marks a significant shift in pharmacy reimbursement processes, with specific implications for our members in the community sector.

NCODA supports this law's intent to enhance transparency and predictability in pharmacy reimbursements. We believe that these changes, although challenging in the short term, may represent a positive step towards a more understandable and equitable financial environment for our member pharmacies.

This new reimbursement model poses challenges in terms of reduced upfront payments and cash flow challenges.

In response to the complexities of the new ruling, NCODA is engaging with all key stakeholders to empower members in proactively assessing complex contractual agreements and achieving enhanced precision in financial planning.

We encourage member to reach out with any questions or to delve deeper into understanding the profound impact of this new rule.

To participate in NCODA's **DIR Fee Transparency Rule Survey**, scan the QR code above.

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CONTENTION OR MEANINGFUL REFORM?

By Hardeep Phull, MD

Most would agree with the American Medical Association's (AMA) recent statement that "Prior authorization is costly, inefficient and responsible for patient care delays ... leading to potential setbacks in care including practice hassles and even patient harm."[1]

In fact, of more than 1,000 physicians surveyed by the AMA, one in three doctors reported that the prior authorization process led to a serious adverse event in their patients.

This has prompted some physicians to state that prior authorization is a form of practicing medicine without a license, with no substantive consequences to payers' denials or delays in care for a patient that they have not seen or examined.[2]

Though its original intent was to eliminate unnecessary or inappropriate care, there were likely some monetary incentives provisioned as well. Indeed, by virtue of its effectiveness in reducing bottom-line healthcare spending, "Prior authorization is one of the most enduring, infuriating … tools in the United States."[3]

Unfortunately, the prior authorization process has concurrently evolved into an obstacle for otherwise appropriate, time-sensitive patient care that is needed by doctors practicing evidence-based medicine as advocates for their patients the vast majority of the time.[3]

In January 2024, the Centers for Medicare & Medicaid Services (CMS) passed the much-awaited "Interoperability and Prior Authorization Final Rule" (CMS-0057-F), expected to save $15 billion by streamlining and digitizing the process while promising to reduce burdens on patients, providers, and payers. The following will soon become necessary parameters for payers to meet:[4]

▲ Send decisions within 72 hours for urgent requests, and seven days for nonurgent ones.

▲ Include specific reason(s) for denying a request, to allow for timely appeal.

EFFECT OF PRIOR AUTHORIZATION RULE REMAINS TO BE SEEN

▲ Report prior authorization metrics publicly in order to anticipate whether a planned treatment/procedure/diagnostic requires prior authorization and to make the process more transparent.

▲ Implement a HL7 interface with EHRs to facilitate electronic communication and automation, helping to avoid unnecessary paperwork that is difficult to track and easily misplaced.

Although this reform certainly feels like a step in the right direction, there has been some healthy skepticism about how this will pan out in "real world" practice.[3]

Will the burden and incentive be shifted to a less defined and less efficient appeals or denials process, which could be more difficult to navigate than the initial prior authorization process itself due to a lack of set guidelines or streamlined workflows?

To whom (patients or payers) will the program's cost savings be passed on to?

Will the costs of medications, diagnostics, or procedures themselves rise paradoxically due to the unanticipated effect of more efficient (and thereby increased) care utilization?

Will certain specialties or physicians be "penalized" more, due to the costs of their unique therapies, diagnostics or procedures?

Would requiring patients to have oversight over their portion of the revised process put certain populations at risk of receiving less equitable care — especially disadvantaged patients such as those with disabilities, less disposable time, lower education, communication/language barriers, or fewer resources overall?

Ultimately, the prior authorization reform rules seem to be a step in the right direction, with steps incorporated to help reduce burdens for clinicians, patients and payers.

However, to truly impact daily clinical practice, the reform will need to accomplish more than just reduce administrative burdens. It should uphold the concept of value-based healthcare which holds the system accountable towards addressing the root cause of the problems by coupling medical and financial responsibility with transparent pricing to physicians and consumers in a free market.[5]

Once implemented, it will need regular audits of its efficacy in accomplishing the primary intent of the reform. This will require systematic review of downstream compensatory behaviors including free market responses, the appeals/denials process and providers' prescribing preferences or patterns in "real world" clinical practice.

Lastly, the reform also will need to stand up to the bigger challenge of improving the quality and equity of care provided, perhaps through judicious use of the program's promised cost savings trickling down to patients.

What other fundamental issues could we be overlooking, and what other improvements must be demanded to ensure that the genuine intent of this law does not become diluted in due time?

▲ **Hardeep Phull**, MD, is the Director of Medical Oncology at Palomar Health Medical Group in Escondido, California.

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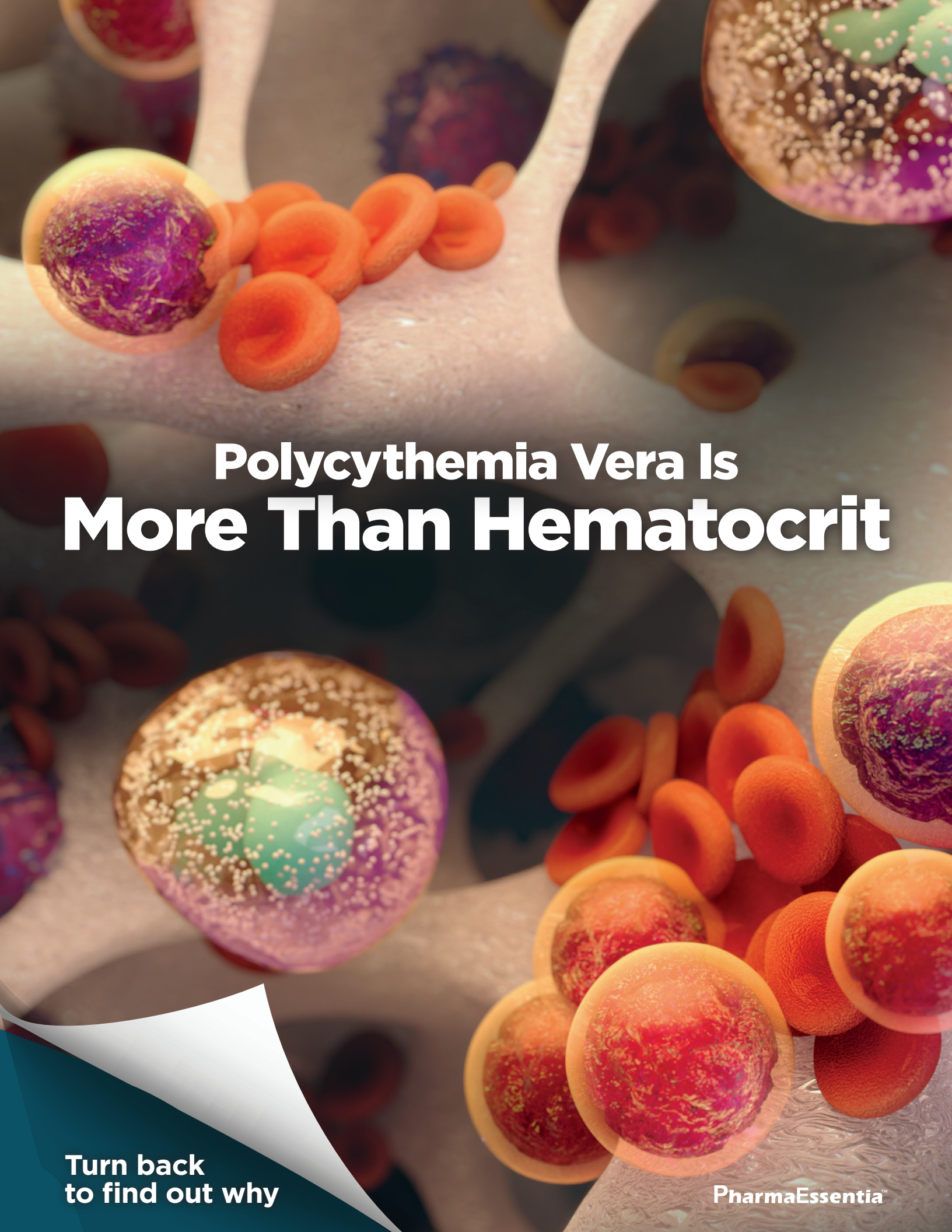
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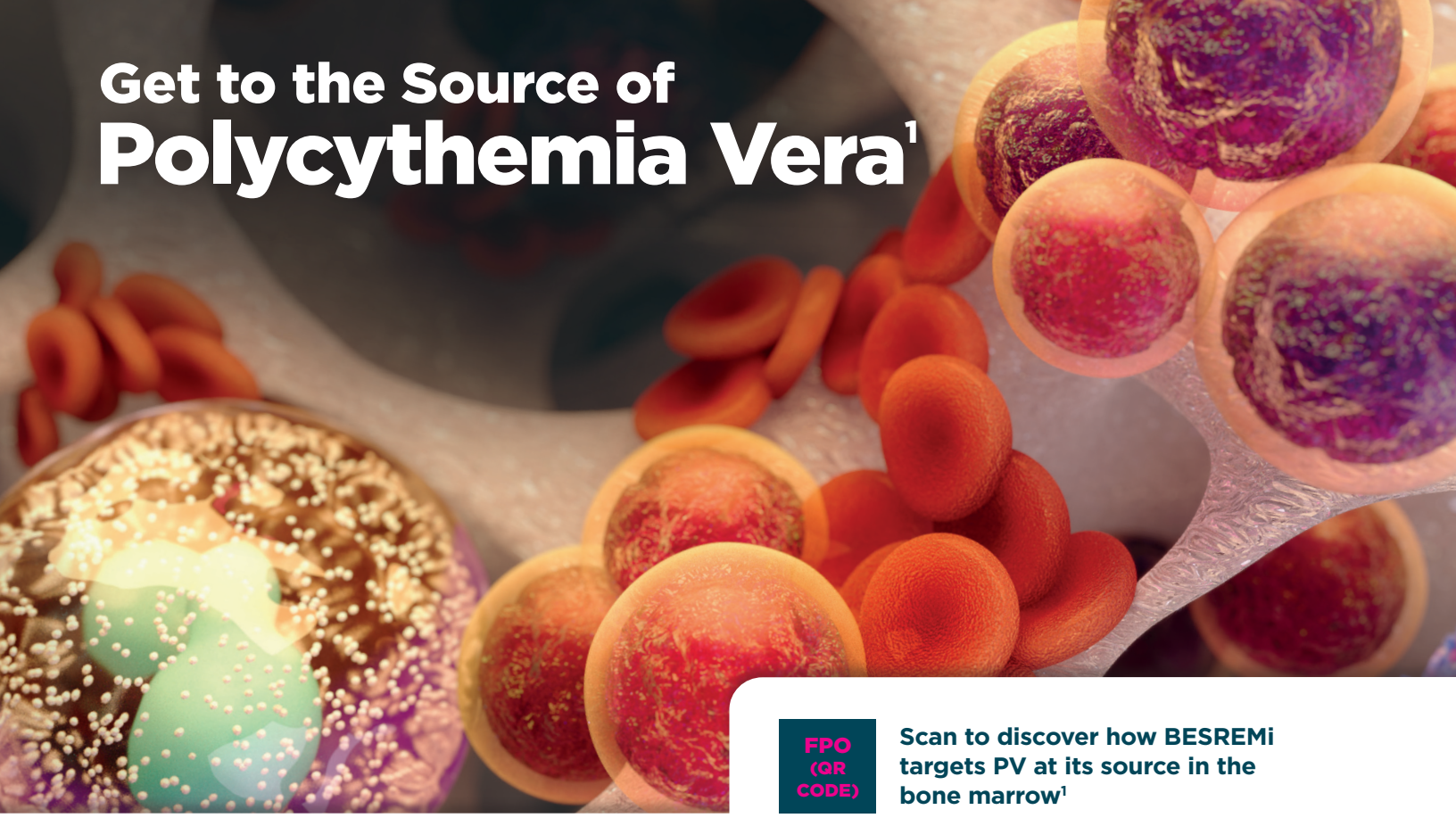

FPO (QR CODE)

Scan to discover how BESREMi targets PV at its source in the bone marrow[1]

INDICATION

BESREMi is indicated for the treatment of adults with polycythemia vera

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DISORDERS

Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy.

CONTRAINDICATIONS

- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt
- Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of BESREMi.
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment
- History or presence of active serious or untreated autoimmune disease
- Immunosuppressed transplant recipients

WARNINGS AND PRECAUTIONS

- Depression and Suicide: Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa-2b products, including BESREMi. These reactions may occur in patients with and without previous psychiatric illness.
  Other central nervous system effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa products. Closely monitor patients for any symptoms of psychiatric disorders and consider psychiatric consultation and treatment if such symptoms emerge. If psychiatric symptoms worsen, it is recommended to discontinue BESREMi therapy.
- Endocrine Toxicity: These toxicities may include worsening hypothyroidism and hyperthyroidism. Do not use BESREMi in patients with active serious or untreated endocrine disorders associated with autoimmune disease. Evaluate thyroid function in patients who develop symptoms suggestive of thyroid disease during BESREMi therapy. Discontinue BESREMi in patients who develop endocrine disorders that cannot be adequately managed during treatment with BESREMi.
- Cardiovascular Toxicity: Toxicities may include cardiomyopathy, myocardial infarction, atrial fibrillation and coronary artery ischemia. Patients with a history of cardiovascular disorders should be closely monitored for cardiovascular toxicity during BESREMi therapy. Avoid use of BESREMi in patients with severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction.
- Decreased Peripheral Blood Counts: These toxicities may include thrombocytopenia (increasing the risk of bleeding), anemia, and leukopenia (increasing the risk of infection). Monitor complete blood counts at baseline, during titration and every 3-6 months during the maintenance phase. Monitor patients for signs and symptoms of infection or bleeding.
- Hypersensitivity Reactions: Toxicities may include serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis). If such reactions occur, discontinue BESREMi and institute appropriate medical therapy immediately. Transient rashes may not necessitate interruption of treatment.
- Pancreatitis: Pancreatitis has occurred in 2.2% of patients receiving BESREMi. Symptoms may include nausea, vomiting, upper abdominal pain, bloating, and fever. Patients may experience elevated lipase, amylase, white blood cell count, or altered renal/hepatic function. Interrupt BESREMi treatment in patients with possible pancreatitis and evaluate promptly. Consider discontinuation of BESREMi in patients with confirmed pancreatitis.
- Colitis: Fatal and serious ulcerative or hemorrhagic/ischemic colitis have occurred in patients receiving interferon alfa products, some cases starting as early as 12 weeks after start of treatment. Symptoms may include abdominal pain, bloody diarrhea, and fever. Discontinue BESREMi in patients who develop these signs or symptoms. Colitis may resolve within 1 to 3 weeks of stopping treatment.
- Pulmonary Toxicity: Pulmonary toxicity may manifest as dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis. Some events have resulted in respiratory failure or death. Discontinue BESREMi in patients who develop pulmonary infiltrates or pulmonary function impairment.
- Ophthalmologic Toxicity: These toxicities may include severe eye disorders such as retinopathy, retinal hemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion which may result in blindness. During BESREMi therapy, 23% of patients were identified with an eye disorder. Eyes disorders ≥5% included cataract (6%) and dry eye (5%). Advise patients to have eye examinations before and during BESREMi therapy, specifically in those patients with a retinopathy-associated disease such as diabetes mellitus or hypertension. Evaluate eye symptoms promptly. Discontinue BESREMi in patients who develop new or worsening eye disorders.
- Hyperlipidemia: Elevated triglycerides may result in pancreatitis. Monitor serum triglycerides before BESREMi treatment and intermittently during therapy and manage when elevated. Consider discontinuation of BESREMi in patients with persistently, markedly elevated triglycerides.
- Hepatotoxicity: These toxicities may include increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and bilirubin. Liver enzyme elevations have also been reported in patients after long-term BESREMi therapy. Monitor liver enzymes and hepatic function at baseline and during BESREMi treatment. Discontinue BESREMi in patients who develop evidence of hepatic decompensation (characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage) during treatment
- Renal Toxicity: Monitor serum creatinine at baseline and during therapy. Avoid use of BESREMi in patients with eGFR <30 mL/min. Discontinue BESREMi if severe renal impairment develops during treatment.
- Dental and Periodontal Toxicity: These toxicities may include dental and periodontal disorders, which may lead to loss of teeth. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with BESREMi. Patients should have good oral hygiene and regular dental examinations.
- Dermatologic Toxicity: These toxicities have included skin rash, pruritus, alopecia, erythema, psoriasis, xeroderma, dermatitis acneiform, hyperkeratosis, and hyperhidrosis. Consider discontinuation of BESREMi if clinically significant dermatologic toxicity occurs.
- Driving and Operating Machinery: BESREMi may impact the ability to drive and use machinery. Patients should not drive or use heavy machinery until they know how BESREMi affects their abilities. Patients who experience dizziness, somnolence or hallucination during BESREMi therapy should avoid driving or using machinery.
- Embryo-Fetal Toxicity: Based on the mechanism of action, BESREMi can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended in females of reproductive potential prior to treatment with BESREMi. Advise females of reproductive potential to use an effective method of contraception during treatment with BESREMi and for at least 8 weeks after the final dose.

ADVERSE REACTIONS

The most common adverse reactions reported in > 40% of patients in the PEGINVERA study (n=51) were influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis, and musculoskeletal pain. In the pooled safety population (n=178), the most common adverse reactions greater than 10%, were liver enzyme elevations (20%), leukopenia (20%), thrombocytopenia (19%), arthralgia (13%), fatigue (12%), myalgia (11%), and influenza-like illness (11%).

DRUG INTERACTIONS

Patients on BESREMi who are receiving concomitant drugs which are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs. Avoid use with myelosuppressive agents and monitor patients receiving the combination for effects of excessive myelosuppression. Avoid use with narcotics, hypnotics or sedatives and monitor patients receiving the combination for effects of excessive CNS toxicity.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on mechanism of action and the role of interferon alfa in pregnancy and fetal development, BESREMi may cause fetal harm and should be assumed to have abortifacient potential when administered to a pregnant woman. There are adverse effects on maternal and fetal outcomes associated with polycythemia vera in pregnancy. Advise pregnant women of the potential risk to a fetus.
- Lactation: There are no data on the presence of BESREMi in human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children from BESREMi, advise women not to breastfeed during treatment and for 8 weeks after the final dose.
- Females of Reproductive Potential: BESREMi may cause embryo-fetal harm when administered to a pregnant woman. Pregnancy testing prior to BESREMi treatment is recommended for females of reproductive potential. Advise female patients of reproductive potential to use effective contraception during treatment with BESREMi and for at least 8 weeks after the final dose.
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established.
- Geriatric Use: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent pages.

PV, polycythemia vera.

Reference: 1. Besremi. Package insert. PharmaEssentia Corporation; 2021.

BESREMi® (ropeginterferon alfa-2b-njft) INJECTION

PharmaEssentia™

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US-BSRM-2200190 (v1.0) 01/2023

Brief Summary of Prescribing Information for BESREMi (ropeginterferon alfa-2b-njft)

BESREMi (ropeginterferon alfa-2b-njft) injection, for subcutaneous use

See package insert for full Prescribing Information

WARNING: RISK OF SERIOUS DISORDERS

Risk of Serious Disorders: Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy [*see Warnings and Precautions (5.1, 5,2, 5.3, 5.4) and Adverse Reactions (6.1)*].

1 INDICATIONS AND USAGE

BESREMi is indicated for the treatment of adults with polycythemia vera.

4 CONTRAINDICATIONS

BESREMi is contraindicated in patients with:

- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt
- Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of BESREMi
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment
- History or presence of active serious or untreated autoimmune disease
- Immunosuppressed transplant recipients

5 WARNINGS AND PRECAUTIONS

5.1 Depression and Suicide

Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa products, including BESREMi. These reactions may occur in patients with and without previous psychiatric illness. Serious neuropsychiatric reactions have been observed in 3% of patients treated with BESREMi during the clinical development program. Among the 178 patients in the clinical development program of BESREMi, 17 cases of depression, depressive symptoms, depressed mood, and listlessness occurred. Of these seventeen cases, 3.4% of the patients recovered with temporary drug interruption and 2.8% stopped BESREMi treatment.

Other central nervous system effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa products. BESREMi is contraindicated in patients with a history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt *[see Contraindications (4)]*.

Closely monitor patients for any symptoms of psychiatric disorders and consider psychiatric consultation and treatment if such symptoms emerge. If psychiatric symptoms worsen, it is recommended to discontinue BESREMi therapy.

5.2 Endocrine Toxicity

Endocrine toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include worsening hypothyroidism and hyperthyroidism. Autoimmune thyroiditis and hyperglycemia, including new onset type 1 diabetes, have been reported in patients receiving interferon alfa-2b products. Eight cases of hyperthyroidism (4.5%), seven cases of hypothyroidism (3.9%) and five cases (2.8%) of autoimmune thyroiditis/ thyroiditis occurred in the development program of BESREMi.

Do not use BESREMi in patients with active serious or untreated endocrine disorders associated with autoimmune disease *[Contraindications (4)]*. Evaluate thyroid function in patients who develop symptoms suggestive of thyroid disease during BESREMi therapy. Discontinue BESREMi in patients who develop endocrine disorders that cannot be adequately managed during treatment with BESREMi.

5.3 Cardiovascular Toxicity

Cardiovascular toxicity has occurred in patients receiving interferon alfa products, including BESREMi. Toxicities may include cardiomyopathy, myocardial infarction, atrial fibrillation and coronary artery ischemia *[see Adverse Reactions (6.1)]*. Patients with a history of cardiovascular disorders should be closely monitored for cardiovascular toxicity during BESREMi therapy. Avoid use of BESREMi in patients with severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction.

5.4 Decreased Peripheral Blood Counts

Decreased peripheral blood counts have occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include thrombocytopenia (increasing the risk of bleeding), anemia, and leukopenia (increasing the risk of infection). Thrombocytopenia of grade 3 (platelet counts <50,000 – 25,000/mm^3) or greater occurred in 2% of BESREMi-treated patients. Anemia of grade 3 (Hgb < 8 g/dL) or greater occurred in 1% of BESREMi-treated patients. Leukopenia of grade 3 (WBC counts <2,000 – 1,000/mm^3) or greater occurred in 2% of BESREMi-treated patients. Infection occurred in 48% of BESREMi-treated patients, while serious infections occurred in 8% of BESREMi-treated patients. Monitor complete blood counts at baseline, during titration and every 3-6 months during the maintenance phase. Monitor patients for signs and symptoms of infection or bleeding.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions have occurred in patients receiving interferon alfa products, including BESREMi. BESREMi is contraindicated in patients with hypersensitivity reactions to interferon products or any of the inactive ingredients in BESREMi *[see Contraindications (4)]*. Toxicities may include serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis). If such reactions occur, discontinue BESREMi and institute appropriate medical therapy immediately. Transient rashes may not necessitate interruption of treatment.

5.6 Pancreatitis

Pancreatitis has occurred in patients receiving interferon alfa products, including BESREMi. Pancreatitis was reported in 2.2% of patients receiving BESREMi. Symptoms may include nausea, vomiting, upper abdominal pain, bloating, and fever. Patients may experience elevated lipase, amylase, white blood cell count, or altered renal/hepatic function. Interrupt BESREMi treatment in patients with possible pancreatitis and evaluate promptly. Consider discontinuation of BESREMi in patients with confirmed pancreatitis.

5.7 Colitis

Fatal and serious ulcerative or hemorrhagic/ischemic colitis have occurred in patients receiving interferon alfa products, some cases occurring as early as 12 weeks after start of treatment. Symptoms may include abdominal pain, bloody diarrhea, and fever. Discontinue BESREMi in patients who develop these signs or symptoms. Colitis may resolve within 1 to 3 weeks of stopping treatment.

5.8 Pulmonary Toxicity

Pulmonary toxicity has occurred in patients receiving interferon alfa products, including BESREMi. Pulmonary toxicity may manifest as dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis. Some events have resulted in respiratory failure or death. Discontinue BESREMi in patients who develop pulmonary infiltrates or pulmonary function impairment.

5.9 Ophthalmologic Toxicity

Ophthalmologic toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include severe eye disorders such as retinopathy, retinal hemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion which may result in blindness. During BESREMi therapy, 23% of patients were identified with an eye disorder. Eyes disorders ≥5% included cataract (6%) and dry eye (5%). Advise patients to have eye examinations before and during BESREMi therapy, specifically in those patients with a retinopathy-associated disease such as diabetes mellitus or hypertension. Evaluate eye symptoms promptly. Discontinue BESREMi in patients who develop new or worsening eye disorders.

5.10 Hyperlipidemia

Hyperlipidemia has occurred in patients treated with interferon alfa products, including BESREMi. Hyperlipidemia, hypertriglyceridemia, or dyslipidemia occurred in 3% of patients receiving BESREMi. Elevated triglycerides may result in pancreatitis *[see Warnings and Precautions (5.6)]*. Monitor serum triglycerides before BESREMi treatment and intermittently during therapy and manage when elevated. Consider discontinuation of BESREMi in patients with persistently, markedly elevated triglycerides.

5.11 Hepatotoxicity

Hepatotoxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include increases in serum ALT, AST, GGT and bilirubin. BESREMi is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[see Contraindications (4)]*.

Increases in serum ALT ≥3 times the upper limit of normal (ULN), AST ≥3 times the ULN, GGT ≥3 times the ULN, and bilirubin >2 times the ULN have been observed in patients treated with BESREMi.

In the clinical development program of BESREMi, 36 patients (20%) experienced liver enzyme elevations, 33 of whom had elevations of 1.25-5x ULN. Patients were able to resume BESREMi upon resolution of liver enzyme elevations. Liver enzyme elevations have also been reported in patients after long-term BESREMi therapy.

Monitor liver enzymes and hepatic function at baseline and during BESREMi treatment. Reduce BESREMi dosage by 50 mcg for increased AST/ALT/GGT then monitor AST/ALT/GGT weekly until the values return to baseline or grade 1 (ALT and AST < 3 x ULN if baseline was normal; 1.5 - 3 x baseline if baseline was abnormal, and GGT < 2.5 x ULN if baseline was normal; 2 - 2.5 x baseline if baseline was abnormal) *[see Dosage and Administration (2.3) in*

the full prescribing information]. If toxicity does not improve, continue decreasing the BESREMi dose at biweekly intervals until recovery to grade 1. Hold if AST/ALT/GGT > 20 x ULN and consider permanent discontinuation if increased liver enzyme levels persist after four dose-reductions. Discontinue BESREMi in patients who develop evidence of hepatic decompensation (characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage) during treatment *[see Use in Specific Populations (8.7)].*

5.12 Renal Toxicity

Renal toxicity has occurred in patients receiving interferon alfa products, including BESREMi. During BESREMi therapy, <1% of patients were reported to develop renal impairment and <1% of patients were reported to have toxic nephropathy. Monitor serum creatinine at baseline and during therapy. Avoid use of BESREMi in patients with eGFR <30 mL/min. Discontinue BESREMi if severe renal impairment develops during treatment *[see Use in Specific Populations (8.6)].*

5.13 Dental and Periodontal Toxicity

Dental and periodontal toxicities may occur in patients receiving interferon alfa products, including BESREMi. These toxicities may include dental and periodontal disorders, which may lead to loss of teeth. In addition, dry mouth could have a damaging effect on teeth and oral mucous membranes during long-term treatment with BESREMi. Patients should have good oral hygiene and regular dental examinations.

5.14 Dermatologic Toxicity

Dermatologic toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities have included skin rash, pruritus, alopecia, erythema, psoriasis, xeroderma, dermatitis acneiform, hyperkeratosis, and hyperhidrosis. Consider discontinuation of BESREMi if clinically significant dermatologic toxicity occurs.

5.15 Driving and Operating Machinery

BESREMi may impact the ability to drive and use machinery. Patients should not drive or use heavy machinery until they know how BESREMi affects their abilities. Patients who experience dizziness, somnolence or hallucination during BESREMi therapy should avoid driving or using machinery.

5.16 Embryo-Fetal Toxicity

Based on the mechanism of action, BESREMi can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in the full prescribing information and Use in Specific Populations (8.1)]*. Pregnancy testing is recommended in females of reproductive potential prior to treatment with BESREMi. Advise females of reproductive potential to use an effective method of contraception during treatment with BESREMi and for at least 8 weeks after the final dose *[see Dosage and Administration (2.1) in the full prescribing information and Use in Specific Populations (8.1, 8.3)].*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

- Depression and Suicide *[see Warnings and Precautions (5.1)]*
- Endocrine Toxicity *[see Warnings and Precautions (5.2)]*
- Cardiovascular Toxicity *[see Warnings and Precautions (5.3)]*
- Decreased Peripheral Blood Counts *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Pancreatitis *[see Warnings and Precautions (5.6)]*
- Colitis *[see Warnings and Precautions (5.7)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.8)]*
- Ophthalmologic Toxicity *[see Warnings and Precautions (5.9)]*
- Hyperlipidemia *[see Warnings and Precautions (5.10)]*
- Hepatotoxicity *[see Warnings and Precautions (5.11)]*
- Renal Toxicity *[see Warnings and Precautions (5.12)]*
- Dental and Periodontal Toxicity *[see Warnings and Precautions (5.13)]*
- Dermatologic Toxicity *[see Warnings and Precautions (5.14)]*
- Driving and Operating Machinery *[see Warnings and Precautions (5.15)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.16)]*

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

The pooled safety population described in the Warnings and Precautions section reflects exposure to BESREMi as monotherapy for the treatment of polycythemia vera dosed every two to four weeks in 178 patients in two open-label trials [*PEGINVERA, PROUD/CONTINUATION PV*]. The mean age at baseline was 58.6 years (range 30-85 years), 88 (49.4%) women, 90 (50.6%) men, 177 (99%) Caucasian and 1 (1%) Asian. Among 178 patients who received BESREMi, 80% were exposed for 12 months or longer. The mean dose of BESREMi was 334 mcg SD ± 121 during the treatment period. In this pooled safety population, the most common adverse reactions greater than 10%, were liver enzyme elevations (20%), leukopenia (20%), thrombocytopenia (19%), arthralgia (13%), fatigue (12%), myalgia (11%), and influenza-like illness (11%).

The safety findings described below reflect exposure to BESREMi as monotherapy for the treatment of polycythemia vera in 51 patients in the PEGINVERA study *[see Clinical Studies (14) in the full prescribing information].* Among the 51 patients receiving BESREMi, 71% were exposed for 12 months or longer, 63% were exposed for three years or longer, and 53% were exposed for greater than five years.

Serious adverse reactions were reported in 16% of patients in the PEGINVERA study. The most common serious adverse reactions observed during the study (≥ 4%) included urinary tract infection (8%), transient ischemic attack (6%) and depression (4%).

Adverse reactions requiring permanent discontinuation in >2% of patients who received BESREMi included depression (8%) arthralgia (4%), fatigue (4%), and general physical health deterioration (4%) In the PEGINVERA study, patients were not pre-screened for depression or anxiety disorders.

The most common adverse reactions reported in ≥10% of patients in the PEGINVERA study are listed in Table 2.

Table 2 Adverse Reactions in > 10% of Subjects with Polycythemia Vera in the PEGINVERA Study Over 7.5 Years.

Adverse Reactions*	BESREMi N=51 %
Influenza-like illness [a]	59
Arthralgia	47
Fatigue [b]	47
Pruritus	45
Nasopharyngitis [c]	43
Musculoskeletal pain [d]	41
Headache [e]	39
Diarrhea	33
Hyperhidrosis [f]	29
Nausea	28
Upper respiratory tract infection [g]	27
Local administration site reactions	26
Dizziness	22
Abdominal pain [h]	20
Depression	20
Sleep disorder [i]	20
Leukopenia	18
Decreased appetite	18
Alopecia	16
Edema [j]	16
Hypertension [k]	16
Muscle spasms	16
Neutropenia	16
Rash [l]	16
Transaminase elevations [m]	16
Urinary tract infection	16
Thrombocytopenia	12
Vertigo	12

*Adverse Reactions defined as all treatment emergent adverse events

Grouped Term Definitions

[a] Includes pyrexia, chills, and influenza-like illness.
[b] Includes asthenia, malaise, and fatigue.
[c] Includes pharyngitis and nasopharyngitis.
[d] Includes musculoskeletal pain, back pain, pain in extremity, bone pain, flank pain, and spinal pain.
[e] Includes headache, migraine, and head pain.
[f] Includes night sweats and hyperhidrosis.

[g] Includes upper respiratory tract infection, rhinitis, bronchitis, and respiratory tract infection.
[h] Includes abdominal pain upper, abdominal pain lower, and abdominal pain.
[i] Includes insomnia, sleep disorder, and abnormal dreams.
[j] Includes peripheral edema and generalized edema.
[k] Includes hypertension and hypertensive crisis.
[l] Includes rash, maculopapular rash, and pruritic rash.
[m] Includes transaminase increase, hepatic enzyme increase, GGT increase, AST increase, and ALT increase.

Clinically relevant adverse reactions in < 10% of patients include:
Cardiovascular System: Atrial fibrillation

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other interferon alfa-2b products may be misleading.

The incidence of binding antibodies to ropeginterferon alfa-2b-njft was 1.4% (2/146) and they were observed as early as 8 weeks post-dosing. Among the patients who tested positive for binding antibodies, none developed neutralizing antibodies.

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450

Certain proinflammatory cytokines, including interferons, can suppress CYP450 enzymes resulting in increased exposures of some CYP substrates *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Therefore, patients on BESREMi who are receiving concomitant drugs that are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs.

7.2 Myelosuppressive Agents

Concomitant use of BESREMi and myelosuppressive agents can produce additive myelosuppression. Avoid use and monitor patients receiving the combination for effects of excessive myelosuppression *[see Warnings and Precautions (5.4)]*.

7.3 Narcotics, Hypnotics or Sedatives

Concomitant use of BESREMi and narcotics, hypnotics or sedatives can produce additive neuropsychiatric side effects. Avoid use and monitor patients receiving the combination for effects of excessive CNS toxicity *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available human data with BESREMi use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal studies assessing reproductive toxicity of BESREMi have not been conducted. Based on mechanism of action and the role of interferon alfa in pregnancy and fetal development, BESREMi may cause fetal harm and should be assumed to have abortifacient potential when administered to a pregnant woman. There are adverse effects on maternal and fetal outcomes associated with polycythemia vera in pregnancy *(see Clinical Considerations)*. Advise pregnant women of the potential risk to a fetus.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Untreated polycythemia vera during pregnancy is associated with adverse maternal outcomes such as thrombosis and hemorrhage. Adverse pregnancy outcomes associated with polycythemia vera include increased risk for miscarriage.

8.2 Lactation

There are no data on the presence of BESREMi in human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children from BESREMi, advise women not to breastfeed during treatment and for 8 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

BESREMi may cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing prior to BESREMi treatment is recommended for females of reproductive potential.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with BESREMi and for at least 8 weeks after the final dose.

Infertility

Females

Based on its mechanism of action, BESREMi can cause disruption of the menstrual cycle *[see Clinical Pharmacology (12.1) in the full prescribing information]*. No animal fertility studies have been conducted with BESREMi.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of BESREMi did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

8.6 Renal Impairment

No dose adjustment is necessary in patients with estimated glomerular filtration rate (eGFR) ≥30 mL/min *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid use of BESREMi in patients with eGFR <30 mL/min *[see Warnings and Precautions (5.12)]*.

8.7 Hepatic Impairment

BESREMi is contraindicated in patients with hepatic impairment (Child-Pugh B or C) *[see Contraindications (4)]*.

Increased liver enzyme levels have been observed in patients treated with BESREMi. When the increase in liver enzyme levels is progressive and persistent, reduce the dose of BESREMi. If the increase in liver enzymes is progressive and clinically significant despite dose-reduction, or if there is evidence of hepatic impairment (Child-Pugh B or C), discontinue BESREMi *[see Dosage and Administration (2.2) in the full prescribing information and Warnings and Precautions (5.11)]*.

10 OVERDOSAGE

Overdosage of BESREMi may result in influenza-like symptoms or other adverse reactions. There is no antidote to BESREMi overdosage. In case of an overdose, frequently monitor signs and symptoms for adverse reactions.

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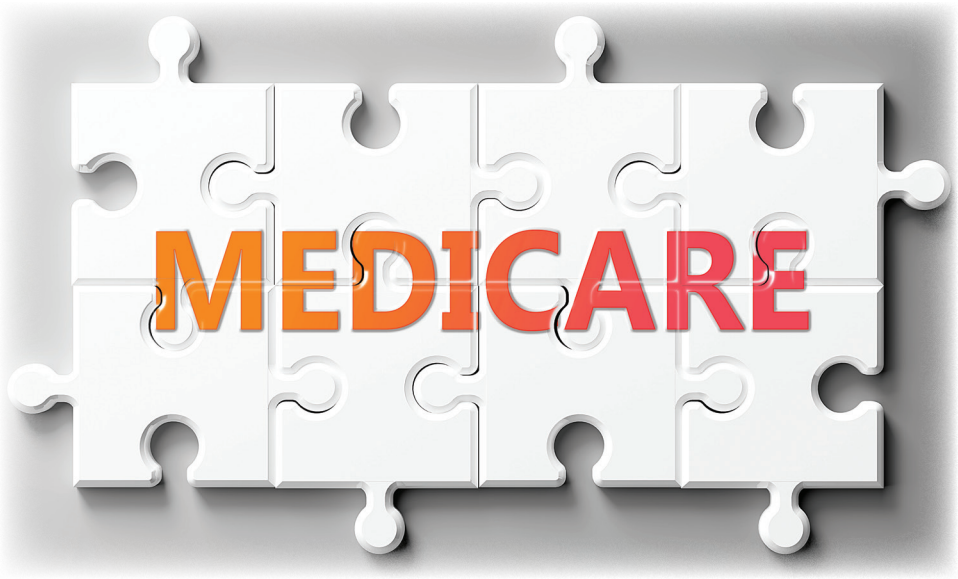
DECIPHERING THE 2024 MEDICARE RULES UNDER THE INFLATION REDUCTION ACT

By Joanna Fawzy Doran, Esq.



In the arena of health insurance in the United States, things are always changing.


Joanna Fawzy Doran

Those changes may be about what type of care is covered, who is eligible for that care or how much patients have to pay out-of-pocket for that care.

Staying on top of those changes can feel challenging for patients, caregivers and other members of the healthcare community.

Navigating changes to Medicare coverage is no different. Medicare is a federal health insurance program that covers more than 65 million Americans. Each year, there are changes to Medicare costs, and people who have Medicare coverage have to make decisions about how they want to access that coverage.

In addition to these annual changes, in April 2022, Congress passed the Inflation Reduction Act (IRA). This bill included a wide array of provisions, including specific changes to Medicare Part D that may benefit the cancer community.

PARTS OF MEDICARE

Medicare coverage is broken down into four parts:

▲ **Part A of Medicare** is hospital insurance. It includes coverage for care received in the hospital and hospice care. It also provides limited coverage for skilled nursing facilities, nursing homes, and home healthcare.

▲ **Part B of Medicare** is medical insurance. It includes coverage for items such as outpatient services, preventive care, labs, mental healthcare, ambulances and durable medical equipment. It also covers intravenous chemotherapy.

Part A and Part B are referred to as Original Medicare, because that is what was included in the original Medicare and Medicaid Act of 1965.

Over time, Congress added:

▲ **Part D of Medicare**, which covers prescription drugs. Medicare Part D plans are separate plans sold by Medicare-approved private insurance companies.

▲ **Part C of Medicare**, also referred to as Medicare-managed care plans or Medicare Advantage Plans, which provides an alternative to Original Medicare. Medicare Part C plans are separate managed care plans sold by Medicare-approved private insurance companies. However, Part C plans include the benefits and services covered under Parts A and B and usually Part D.

2024 COSTS OF MEDICARE

▲ **Part A:** For individuals who have paid into Medicare while working over their lifetime, the monthly premium is free. If individuals haven't paid into the system or haven't done so long enough, it is still possible to get Medicare Part A coverage, but they will have to pay a monthly premium. In 2024, the Part A monthly premium can be up to $505. There is also a deductible per benefit period of $1,632. Individuals may also be responsible for paying co-payments based on the number of days spent in a hospital.

▲ **Part B:** In 2024, the Part B monthly premium is generally $174.70 (individuals with higher incomes pay higher premiums) and there is a deductible of $240 per year. The co-insurance for Part B coverage is 80/20. This means that once an individual has paid their deductible, Medicare will cover 80% of their healthcare costs under Part B, and the patient will be responsible for 20%. With Part B coverage, there is no out-of-pocket maximum.

▲ **Part C:** Premiums for Part C plans are usually at least the same as Part B or more, but vary based on the plan chosen. The deductibles, co-insurance and out-of-pocket maximums also will depend on your plan. However, the most that a Part C plan out-of-pocket

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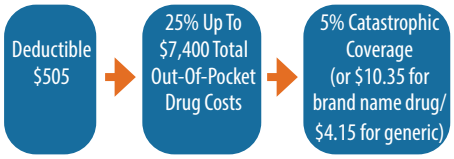
maximum may be for services covered by Part B in 2024, is $8,850.

▲ **Part D:** Part D premiums vary by plan and are higher for those with higher-income levels. Prior to the IRA, a standard Part D plan was structured with a maximum deductible of $505 (in 2023). After paying the deductible, an individual would pay 25% of their drug costs. When the total out-of-pocket drug costs reached $7,400, then the patient would enter catastrophic coverage. Then, patients would pay the greater of 5% of the drug costs, or $10.35 for brand-name drugs ($4.15 for generics) for the remainder of the year. There was no out-of-pocket maximum for Part D prescription drug costs.

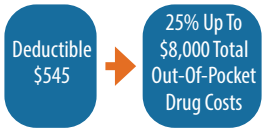
PATIENT MEDICARE DRUG COSTS IN 2023



IRA CHANGES TO MEDICARE

▲ **2024:** This year, the structure of the standard Part D drug benefit changes.[1] In 2024, the maximum deductible for a Part D plan is $545. After paying the deductible, patients pay 25% of their drug costs, until their total out-of-pocket drug costs reach $8,000. On its face, you would think that the math would then look like this:

PATIENT MEDICARE DRUG COSTS IN 2024



However, the devil is in the details. The total out-of-pocket drug costs include what patients have actually spent out-of-pocket, plus the value of the 70% manufacturer price discount on brand-name drugs in the former coverage gap.

This means that individuals who take only brand-name drugs in 2024, will reach the $8,000 catastrophic coverage threshold by spending a total of $3,333 out-of-pocket. And, they will then have no additional costs for their Part D prescriptions for the rest of the year.

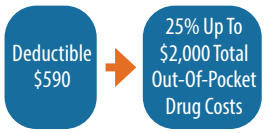
TABLE 1: PART D COSTS FOR A $12,000 BRAND-NAME DRUG IN 2024

Deductible $0-545	$545
Initial Coverage Period (ICP) $545-$5,030	25% of cost of covered drugs = $1,121.25 **How you get there:** •$545 up to $5,030 in total drug costs (what a patient and their plan pays together) = $4,485 • $4,485 * 25% = $1,121.25
Former Coverage Gap (FCP) $5,030 - $8,000	25% of cost of covered drugs = $1,666.75 **How you get there:** • $8,000 catastrophic threshold - $545 deductible already paid - $1,121.25 ICP amount already paid = $6,333.75 left to pay (95% of total drug costs) However, the total amount a patient gets credit for spending during the former coverage gap = 95% of total drug costs. This includes the 25% actually paid by patient and a 70% drug manufacturer's discount on brand-name drugs. The 5% paid by the plan is not included. • 100% of the costs during this period are $6,667.11 • $6,667.11 * 25% = $1,666.75
Catastrophic Coverage	$0
Total amount a patient actually pays out-of-pocket if they only take brand-name drugs	$3,333 **How you get there:** • $545 deductible + $1,121.25 ICP + $1667.75 FCP = $3,333

The brand-name discounts and the math involved are causing a lot of confusion. So, let's look at an example of a patient who is taking an oral chemotherapy brand-name drug covered under Part D that costs $12,000. **See Table1 for a breakdown of what the patient will pay.**

▲ **2025:** In 2025, the structure for patient out-of-pocket drug costs will be simplified considerably. Patients will pay a deductible of $590 and then will pay 25% of their drug costs until they have spent a total of $2,000 out-of-pocket. They will then have no additional costs for their Part D prescriptions for the rest of the year.

PATIENT MEDICARE DRUG COSTS IN 2025



It is important to note that under the IRA, the $2,000 cap on drug costs will be indexed to rise each year after 2025, at the rate of growth in per capita Part D costs.

Also starting in 2025, individuals will have the option of spreading out their out-of-pocket prescription drug costs over the year, rather than face high out-of-pocket costs in any given month.

For example, if a patient takes an expensive brand-name drug in January, instead of paying the full $2,000 out-of-pocket

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MEDICARE

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cost in January, they can make payments throughout the year.

We are still waiting on a final rule from the Centers for Medicare & Medicaid Services to explain the details of how this process will work for patients.

EDUCATING PATIENTS ABOUT MEDICARE CHANGES

Key stakeholders in the continuum of a patient's care are uniquely positioned to help patients understand how the IRA has changed their Part D coverage and what they will need to pay for their prescription drugs. That includes members of healthcare teams, pharmacists, community health workers and patient advocates. This information can be shared with patients throughout the continuum of a patient's care.

To learn more about, Medicare and cancer, scan the QR code above.

Although the Part D changes in the IRA will substantially decrease the maximum of what patients have to pay out-of-pocket for their prescription drugs — particularly for oral chemotherapy brand-name drugs — many patients will still find it financially challenging to afford $3,333, or even $2,000.

EDUCATING PATIENTS ABOUT FINANCIAL HELP

It is also important for stakeholders to ensure that patients are aware of other programs and resources that can help offset those expenses.

For patients who are struggling to pay their Medicare out-of-pocket costs for prescriptions drugs, they may be eligible for the **Extra Help Program**. This program is also referred to as the low-income subsidy or LIS. It helps people with limited income and resources pay prescription drug costs, such as premiums, deductibles and co-insurance.

If patients don't qualify for Extra Help, some states also have state pharmaceutical assistance programs and there are private organizations that provide financial assistance to offset the cost of prescriptions drugs.

Helping patients successfully understand and navigate the changes to Medicare will not only improve the chances that patients get access to the care that they need, but also mitigate the financial burden of a cancer diagnosis.

▲ **Joanna Fawzy Doran**, Esq., is a cancer rights attorney and Chief Executive Officer of Triage Cancer in Chicago, Illinois.

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ANEMIA MANAGEMENT IN LOWER-RISK MDS PATIENTS

AN OVERVIEW OF CURRENT PRACTICES, EMERGING RESEARCH AND FUTURE DEVELOPMENTS

By Nikolaos Papadantonakis, MD, MSc, PhD

Anemia is the most prevalent cytopenia among lower-risk myelodysplastic neoplasms (MDS). Lower-risk MDS patients typically do not harbor complex karyotypes and have low blast burden.[1] Management of symptomatic anemia beyond supportive care constitutes a major objective in clinical practice.

Nikolaos Papadantonakis

ESA

Erythropoietin stimulating agents (ESAs) such as darbepoetin alfa[2] and epoetin alfa[3] have been established as key treatment modalities in MDS over decades. Despite advances in molecular annotation of MDS, the Nordic score — which is based on degree of transfusion dependency and erythropoietin (EPO) levels — remains the gold standard in predicting responses to ESA.[4,5]

Regarding the impact of myeloid gene mutations, a seminal study described inferior responses to ESA in the presence of more than two mutations.[6] ESA can elicit responses in 20% to 60% of patients.[7,8]

It has been reported that among MDS patients with primary resistance to ESA, the refractory anemia with ring sideroblasts (RARS) subgroup was enriched.[9] Median duration of response to ESA can span a year and a half to two years[7] and depends on the response criteria. For example, median duration was 29 months for patients with complete response.[4] ESA-responding patients had improved global quality of life, social functioning and fatigue.[5]

Granulocyte colony stimulating factor (G-CSF) in conjunction with ESA has been utilized for MDS-related anemia.[10] A metanalysis supported the additional benefit of the combination for at least the low to intermediate doses of ESA.[11] The impact of the ESA and G-CSF combination in patients with RARS has been favorable. In one study, 50% of RARS patients had a response.[4]

The mechanisms that lead to ESA loss of response in MDS patients have not been elucidated, and such loss of response does not always translate to progression to higher-risk MDS.[12] However, primary ESA response failure or response lasting less than six months has been associated with higher propensity to acute myeloid leukemia (AML) progression.[9]

Hence, from a translational research standpoint there is an unmet need to identify mechanisms of resistance/loss of response to ESA in the context of MDS. It will be intriguing to explore if any of potential mechanisms of ESA resistance[13] in patients with renal failure are also applicable in the context of MDS.

LUSPATERCEPT

MDS also is associated with upregulated transforming growth factor beta (TGF-β) signaling through SMAD2/3 that ultimately impairs late-stage erythropoiesis. **Luspatercept** was engineered by the fusion of activin receptor type IIB extracellular domain to the Fc domain of human immunoglobulin[14] and it is able to interact with TGF-β superfamily ligands such as growth differentiation factor 11 (GDF11). Luspatercept interaction with GDF11 ameliorates the enhanced SMAD2/3 downstream signaling noted in MDS.[15]

Our understanding of luspatercept's mechanisms of action continues to evolve. Recent reports indicate that luspatercept

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response was associated with higher baseline levels of the short form of GATA1 protein. A putative mechanism involves GDF11 mediated binding of SMAD2 in a specific area of GATA1, leading to production of the short form of GATA1.[16] Luspatercept interference with GDF11 signaling could beneficially modulate GATA1 short form production resulting in amelioration of erythropoiesis.

Furthermore, luspatercept was recently reported to impact expression of several cytokines with key roles in the bone marrow inflammatory pathways.[17,18]

Luspatercept was initially approved for lower-risk MDS patients with RARS based on the phase 3 placebo-controlled MEDALIST trial.[19] The registration trial included patients with RARS (according to WHO 2016 classification) who did not respond to ESA or were unlikely to respond based on their EPO level.

Thirty-eight percent of patients in the luspatercept arm had transfusion independence of at least eight weeks (during weeks 1-24), which was the primary endpoint. Moreover, 35% of patients in the luspatercept arm had an increase in hemoglobin of at least 1g/dL during the first 24 weeks of the trial.[19]

COMMANDS TRIAL

The interim analysis of the phase III COMMANDS trial[20] was pivotal for the approval of luspatercept in patients with lower-risk non-del5q MDS regardless of ring sideroblast status. The study randomized lower-risk MDS patients to epoetin alfa or luspatercept. Dosing was reflective of clinical practice: epoetin alfa up to 1,050 IU/kg (total dose maximum 80,000 IU) weekly and luspatercept up to 1.75 mg/kg every three weeks. Notably, G-CSF was not allowed in conjunction with epoetin alfa.

The COMMANDS trial enrolled treatment-naïve lower-risk MDS patients. The mean age of the 356 patients was 74 years old (range 69-80 years old). EPO level was required to be less than 500 U/L (in both arms, 79% had EPO level below 200 U/L).

Both arms were enriched with patients with SF3B1 mutation or were ring sideroblasts positive (defined as SFR3B1 mutation and at least 5% but less than 15% sideroblasts encompassing the erythroid precursors, or ring sideroblasts encompassing at least 15% of erythroid precursors); 61% of the patients had SFR3B1 mutation and 73% had ring sideroblasts.

The primary endpoint of the clinical trial was red blood cell (RBC) transfusion independence for a minimum of 12 weeks with concurrent hemoglobin increase of at least 1.5 g/dL during weeks 1-24.

In the interim analysis, 59% of patients in the luspatercept arm reached the primary end point but only 31% in the epoetin alfa arm.[20] An abstract presented at the American Society of Hematology (ASH) 2023 conference included data from the full analysis.[21] Primary endpoint was attained in 60% of patients in the luspatercept arm vs. 34% with epoetin alfa.

Perhaps not surprisingly, the luspatercept arm had higher response rates in patients with SF3B1 mutated/ring sideroblasts positive (RS+) over epoetin alfa. In the interim analysis, the primary endpoint was met by 65% of RS+ and 70% of SF3B1 mutated patients in the luspatercept arm compared to 26% and 31% respectively in the epoetin alfa arm.[20] Full analysis reported similar outcomes.[21]

However, in the interim analysis, patients without ring sideroblasts (RS-) had similar responses in both arms: 41% vs 46% for luspatercept and comparator arm, respectively.[20] The results for the SF3B1 unmutated patients also were not superior for luspatercept (44%) vs 36% for epoetin alfa in the full efficacy analysis.[21]

In the ASH 2023-presented abstract of full efficacy analysis, RBC transfusion independence for at least 12 weeks was achieved by 68% vs 48% patients on luspatercept vs epoetin alfa, respectively. The median duration of treatment in the full analysis was 51 weeks vs. 37 weeks for luspatercept and epoetin alfa, respectively.[21]

Regarding mutational data, in the intention to treat population (encompassing the RS+ subgroup), a mutational burden of up to three mutations was associated with favorable response to luspatercept over ESA.[22]

This correlation was not observed in the RS- subgroup or in patients with four mutations. In addition, more luspatercept responses were seen compared to ESA in a range of the Molecular International Prognostic Scoring System (IPSS-M) score risk subgroups.[22]

The published interim analysis of the COMMANDS trial did not report on quality-of-life metrics. An ASH 2023 conference abstract provided insights regarding patient reported outcomes (PRO). Two different instruments were used: the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy — Anemia (FACT-An).

Patients treated with luspatercept had increased probability of improvement in several domains of the PRO instruments, including dyspnea, compared to ESA-treated patients.[23]

Fatigue was the most reported suspected treatment-related event in the luspatercept arm (impacting at least 3% of patients), with asthenia, dyspnea and hypertension also reported.[20] Grade 3/4 adverse events impacting at least 10% of patients were not frequent in both arms and included fatigue, hypertension, dyspnea and COVID-19 infection. Treatment-emergent adverse events associated with death were reported in 5% of the luspatercept arm vs. 7% of the ESA arm.

COMMANDS LIMITATIONS

The COMMANDS trial has provided important and novel insights in the management of anemia in lower-risk

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MDS patients. Limitations of the trial were that epoetin alfa could not be used in conjunction with G-CSF, the study included only 1% black patients, the open label design, and a high percentage of RS+ patients and/or SF3B1 mutations.

Moreover, the study did not provide information regarding post-study treatments to provide insights of therapeutic avenues utilized and whether a sequential approach was pursued or was successful (i.e., luspatercept transition to epoietin-alfa). The study did not include patients with baseline EPO level more than 500 U/L.

Hence, it is unclear whether the response rates (and the extent/duration of response) for patients without RS or SF3B1 mutations to luspatercept are impacted by very high EPO levels. In the seminal MDS -PACE trial, three out of the four RS negative and non-responder patients had a very high baseline EPO (more than 900 U/L). Several insightful commentaries highlighting the open questions following the COMMANDS trial have been published.[24,25]

POTENTIAL SYNERGY

Luspatercept and ESA act in different stages of erythropoiesis, and a potential synergy has been explored in seminal studies.

A patient series[26] from Moffitt Cancer Center included 28 lower-risk MDS patients with the majority (n=25) having prior exposure to ESA and which were refractory or had lost response to luspatercept. Overall response was modest (36%) and with a median duration of response of 16.6 months. Patients without SF3B1 mutation (n=4) or ESA naïve (n=4) with luspatercept exposure or EPO level higher than 500 U/L did not respond. Two out of three patients treated upfront with ESA/luspatercept combination responded.

A smaller series from Italy also reported responses to the combination of ESA/luspatercept in patients with SF3B1 mutation/ MDS with ring sideroblasts.[27] All non-responders had EPO levels > 500 U/L.

The management of anemia in lower-risk MDS has evolved and the results of several ongoing clinical trials are eagerly awaited. Clinical challenges will include balancing toxicities and determining optimal sequencing of treatments.

ONGOING TRIALS

Luspatercept clinical trials are ongoing:

▲ The ELEMENT-MDS trial (NCT05949684) will randomize patients who are ESA naïve and anemic (but non-transfusion-dependent) to luspatercept or ESA.

▲ Another phase 2 trial of lenalidomide and luspatercept (NCT04539236) explores this combination for lower risk MDS patients without del5q.

▲ A clinical trial conducted in France (NCT05181735) recruited patients with lower risk MDS without ring sideroblasts after loss of response to ESA/ESA failure (or having EPO level above 500 U/L). Patients will receive luspatercept monotherapy in arm A and a combination of luspatercept and ESA in arm B.

▲ The QOL-ONE Phoenix trial (NCT05924100) explores the impact of luspatercept on patients with del5q who have not responded or are intolerant to lenalidomide.

OTHER DEVELOPMENTS

Apart from the approval of luspatercept for anemia in lower-risk MDS patients irrespective of ring sideroblasts status or SF3B1 mutation, several developments are noted in the lower-risk MDS field:

Imetelstat[28] is a telomerase inhibitor that has been tested in an array of myeloid malignancies including MDS and myeloproliferative neoplasms.[29] It acts by interfering with telomerase activity in the malignant stem cells.

Recently, the results of the IMerge study were published. IMerge is an international, randomized, double-blind, clinical trial comparing imetelstat to placebo.[30]

One hundred seventy-eight adult non-del5q MDS patients with up to intermediate risk by IPSS, transfusion-dependent and ESA refractory/ relapsed or ESA ineligible (based on EPO level) were randomized to imetelstat or placebo infusions every four weeks. Patients were required to have at least four pRBC transfusions over eight weeks in a time frame of 16 weeks prior to randomization. The study did not allow prior hypomethylating or lenalidomide exposure, but 6% of patients had luspatercept exposure.

The primary endpoint was transfusion independence for eight consecutive weeks. The majority of patients in both arms had very low/low R-IPSS risk category (77% in imetelstat vs. 80% in placebo arms). Most patients were white, with only ~ 1% being black.

Sixty-two percent of patients had RS in both arms. Median serum EPO level was 361 U/L in the imetelstat arm vs. 472 U/L in placebo, and 22% of patients in the imetelstat arm had EPO levels above 500 U/L compared to 37% in the placebo arm. Six percent in the imetelstat arm and 7% in the placebo arm had prior exposure to luspatercept.

After a median follow up of approximately 18 months, a median of eight cycles were administrated in both arms. Forty percent of imetelstat patents and 9% of patients in the placebo arm achieved

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the primary endpoint. Focusing on patients with RS, primary endpoint was achieved in 45% of those enrolled in the imetelstat arm compared to 19% in the placebo arm.

In RS negative patients, primary endpoint was achieved in 32% of patients in the imetelstat arm and 9% in the placebo arm.

Patients that met the primary objective of the study had a different trajectory regarding maintaining transfusion independency. Median duration of transfusion independency in the imetelstat arm was ~ 51 weeks, while on placebo only 13 weeks.

Interestingly, ring sideroblast burden was reduced in 40% of patients who responded to imetelstat.

More than 90% of patients in the imetelstat arm had Grade 3/4 adverse events, with ~ 1/3 of imetelstat-treated patients having a serious adverse event. Neutropenia (68% of patients) and thrombocytopenia (62% patients) were notable hematological toxicities in the imetelstat arm. Subsequently, imetelstat was dose adjusted in 49% of patients secondary to these cytopenias. However, very few patients had to discontinue the study.

Pyruvate kinase (PK) activity was reported to be decreased in lower-risk MDS patient samples,[31] and PK activators have attracted attention in an array of hematologic disorders.[32] In the context of lower risk MDS, studies, including AG-946[33] and etavopitat,[34] are exploring the impact of PK activators in anemia.

Canakinumab is a potent IL-1B inhibitor and its role is explored in lower-risk MDS.[35] Canakinumab either as monotherapy[36] or in combination with ESA[37] has so far yielded modest results in early clinical trials. More mature results will elucidate the role of canakinumab in lower-risk MDS.

Hypoxia inducible factor -1 (HIF-1) has been shown to have a role in MDS-related anemia through multiple mechanisms including modulation of bone marrow environment[38] and iron metabolism.[39] Several HIF-1 inhibitors have been developed.

Matterhorn phase 3 randomized placebo controlled trial results were reported at the ASH 2023 conference[40] utilizing the oral HIF-1 inhibitor roxadustat.

The study enrolled anemic MDS patients with intermediate risk and lower risk by R-IPSS and low transfusional needs and with randomization to roxadustat or best supportive care.

Primary endpoint was transfusion independence for at least 56 days in the first 28 weeks of treatment. There was no statistical difference between roxadustat and placebo arm responses (47% vs 33%, respectively).

The management of anemia in lower-risk MDS has evolved and the results of several ongoing clinical trials are eagerly awaited. Clinical challenges will include balancing toxicities and determining optimal sequencing of treatments.

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TO REPLACE OR NOT TO REPLACE?

THE IMPACT OF AN ANTITHROMBIN III REPLACEMENT PROTOCOL IN PEGASPARGASE-TREATED ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

By Haleh Bakhtiari, PharmD, Belinda Li, PharmD, BCOP, William Blum, MD, Colin A. Vale, MD, Yichun Cao, MPH, Jeffrey Switchenko, PhD, & Danielle Schlafer, PharmD, BCOP

ABSTRACT

Background: Pegaspargase is a modified form of L-asparaginase that interferes with hemostatic and anticoagulant pathways leading to an increased risk of thrombosis. Depletion of anticoagulation factors such as antithrombin III (AT III) can cause life-threatening thromboembolisms (VTE). Due to limited data and a lack of guideline recommendations, institution specific guidelines have been utilized to support the use of AT III replacement.

Objective: The purpose of this retrospective review was to compare the incidence of venous TE in acute lymphoblastic leukemia (ALL) patients treated with pegaspargase before and after implementation of an ATIII monitoring and replacement protocol designed to reduce thrombotic complications during induction therapy in the front-line setting.

Methods: This was a single center, retrospective chart review of patients with ALL treated with pegaspargase at our center between January 1, 2016 and July 17, 2021. The study included an intervention group with implementation of AT III replacement, and a historical control group treated with pegaspargase prior to initiation of AT III replacement protocol. The primary objective for the study was to examine the overall incidence of thrombosis during induction chemotherapy with pegaspargase before and after the implementation of AT III monitoring replacement protocol. The secondary objectives included incidence of major/minor bleeding, incidence of VTE and central nervous system (CNS) thrombosis after induction, dose and amount of AT III administered, number of AT III doses administered per patient and incidence of cryoprecipitate replacement.

Results: Forty-one patients were included. Thrombotic events occurred during therapy for four out of 24 patients (16.7%) from the treatment group and five out of 17 patients (29.4%) from the historical control group (p=0.45). There was no statistically significant difference between the two groups regarding the occurrence of thrombotic events.

Conclusion: This was a retrospective pilot study focused on comparing outcomes between the study group with implementation of AT III replacement and the historical control group. This study was not powered to detect a difference in the incidence of VTE before and after the implementation of the AT III replacement protocol. AT III monitoring and replacement is feasible and may reduce thrombotic complications, but future prospective studies are necessary to establish efficacy.

The prognosis of adolescents and young adult patients with Philadelphia chromosome negative ALL has improved substantially with utilization of pediatric-inspired regimens.

These multiagent chemotherapy regimens incorporate L-asparaginase or pegylated asparaginase and have been associated with improved four-year overall survival up to 67%.[1]

Pegaspargase is a modified form of L-asparaginase that depletes asparagine in leukemic cells by catalyzing the conversion of asparagine to aspartic acid and ammonia.[2] This leads to inhibition of DNA- and RNA-syntheses, inhibition of protein synthesis, and apoptosis of leukemic cells.

Pegaspargase interferes with the physiologic balance between the hemostatic and anticoagulant pathways as low levels of asparagine can lead to decreased synthesis of procoagulant and thrombolytic proteins.[3] This results in decreased levels of fibrinogen, antithrombin III (AT III), protein C and protein S.[4]

Pegaspargase is a cornerstone of multiagent chemotherapy regimens, and the side effect profile, including thrombotic complications, has recently been well-described. Venous thromboembolism (VTE) occurs most frequently in deep limb veins and cerebral venous sinuses.[5]

In previous clinical trials, the incidence of thrombosis in patients initiated on pegaspargase was reported between 1% and 36% depending on the treatment protocol and study design.[2] Cerebral thrombosis is a life-threatening form of VTE that occurs in approximately 4% of patients with ALL treated with pegaspargase and is associated with increased morbidity and mortality of 6.2%.[5,6]

Antithrombin III is an anti-coagulant protein that can lead to life-threatening thromboembolisms when depleted. Current guideline recommendations do not address the use of AT III replacement

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to mitigate pegaspargase toxicity, and data is conflicting regarding the overall efficacy of AT III replacement.

The International Society of Thrombosis and Haemostasis (ISTH) provides recommendations for an antithrombin repletion regimen based on an approximate 60% reduction in VTE.[6] Guidance recommends prophylactic therapy with anticoagulation and AT III replacement for levels <50%-60% with a repletion target in the range of 80%-120%.[6]

In the CAPELAL trial, adult patients received replacement therapy when antithrombin levels were <60%.[8] The rate of thrombosis in the AT III-treated group was 5% compared to 12% in the non-AT III treated group (p=0.04).[7]

The incidence of major bleeding is approximately 5% in pegaspargase-treated patients and can be worsened by low levels of prothrombotic proteins such as fibrinogen.[2]

Recommendations for cryoprecipitate prophylaxis vary and largely depends on hypofibrinogenemia, while replacement is utilized in the setting of active bleeding.[4] Depending on the severity of the hemorrhage, cryoprecipitate therapy is recommended by some (but not by others) when fibrinogen levels have declined.[4]

The French Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) recommends prophylactic cryoprecipitate when fibrinogen levels are <50 mg/dL, while Mayo Clinic recommends cryoprecipitate repletion when fibrinogen levels are <100 mg/dL.[4] ISTH recommends utilizing cryoprecipitate in bleeding-predominant disseminated intravascular coagulation (DIC).[4]

Replacement of fibrinogen with cryoprecipitate is rare in pediatric patients, where the incidence of complications is lower. Due to limited data and a lack of guideline recommendations, institution-specific guidelines and expert opinions have been utilized to support the use of AT III to lower the risk of thrombosis.[4]

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In 2019, Emory Healthcare/Winship Care Center implemented a protocol for toxicity management and prevention associated with pegaspargase treatment for patients with ALL. Depending on the protocol, we utilize pegaspargase 2,000-2,500 IU/m^2, which is capped at 3,750 units per dose.

During induction therapy, patients were placed on anticoagulation with low molecular weight heparin for VTE prophylaxis. The protocol specifies routine monitoring and replacement of AT III during induction as there is a higher risk of thrombosis during this phase of treatment.[8] AT III levels were monitored twice weekly in order to calculate the antithrombin dose.

Thromboprophylaxis with AT III replacement occurred when AT levels were <30%. AT III replacement was also incorporated when levels were <60% in the setting of acute thrombosis.[9] Threshold amounts were selected based on previous institutional guideline recommendations.[4] Furthermore, cryoprecipitate was administered for fibrinogen deficiency <70 mg/dL to reduce risk of bleeding.

Few studies have explored the potential benefits of AT III replacement and definitive recommendations to support target thresholds for AT III and other coagulation factors are lacking.[3]

Therefore, the aim of this study was to compare the incidence of VTE in patients with ALL treated with pegaspargase before and after implementation of an AT III monitoring and replacement protocol using an institutional historical control of patients treated on similar Adolescent and Young Adult Medicine (AYA) or "pediatric-inspired" induction chemotherapy regimens.

METHODS

This was a single-center, retrospective study of adult patients with Philadelphia chromosome negative ALL receiving pegaspargase during induction therapy. The study was conducted at a single large referral center between January 1, 2016 and July 17, 2021. The study protocol was reviewed and approved by the Institutional Review Board.

The study included patients 18 years or older with ALL receiving AYA regimens containing pegaspargase (on clinical trial according to CALGB 10403, AALL0434, A041501). Patients were excluded if they did not receive pegaspargase during induction therapy or if they received pegaspargase containing regimens other than the AYA regimens (e.g., MOAD, EWALL-PH-01).

The two-cohort design of this study

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included a historical control group before implementation of the AT III replacement protocol and a study group following implementation of the AT III replacement protocol.

The primary outcome studied was the overall incidence of VTE during ALL induction chemotherapy with pegaspargase before and after the implementation of AT III replacement and monitoring.

The secondary outcomes included incidence of major/minor bleeding, incidence of VTE after induction, incidence of CNS thrombosis after induction, dose and amount of AT III administered, number of AT III doses administered per patient, and incidence of cryoprecipitate replacement.

Major bleeding was defined as symptomatic bleeding located in critical areas such as intracranial, intraspinal, intraocular, retroperitoneal, intraabdominal, or pulmonary bleeds.[10] Minor bleeding was defined as any reported bleeds that were not classified as a major bleed.[10]

Venous thromboembolism was defined as a lower or upper extremity deep vein thrombosis (DVT) or pulmonary embolism (PE).[11]

CNS thrombosis was defined as a cerebral thrombosis, ischemia or stroke.[11]

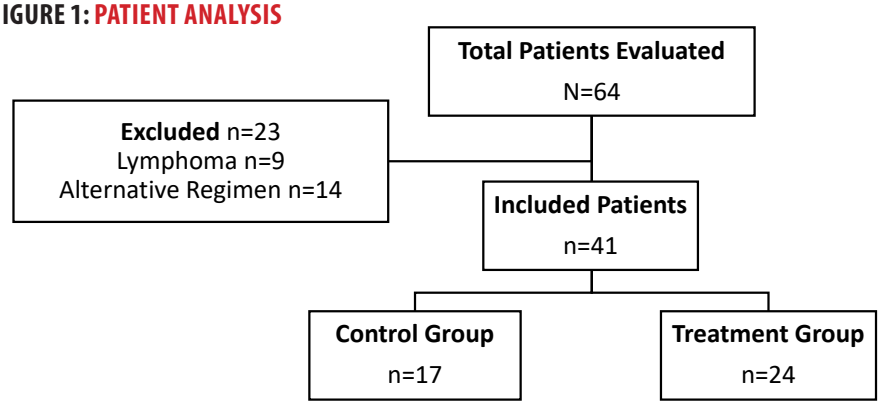
Continuous variables were summarized using mean, median, standard deviation, interquartile range, and minimum/maximum. Categorical variables were summarized with frequencies and percentages. The 95% confidence intervals were provided for estimated rates of events of interest, such as major/minor bleeding and VTE.

Chi-squared tests were utilized to compare rates of events of interest, such as major/minor bleeding and VTE between patient characteristics such as treatment group, sex, race, and age group. ANOVA was utilized to compare continuous variables between patient characteristics.

Statistical analysis was conducted using SAS 9.4 (SAS Institute Inc., Cary, North Carolina) and SAS macros developed by Biostatistics and Shared Resource at Winship Cancer Institute. Statistical significance was assessed at the 0.05 level.

All tests were two-sided, unless otherwise noted.

FIGURE 1: PATIENT ANALYSIS



Sixty-four patients were reviewed, and 41 patients met inclusion criteria. Of the total evaluated patients: 23 were excluded, nine had a diagnosis of lymphoma and 14 were on an alternative pegaspargase-containing regimen. Seventeen patients were included in the historical control group and 24 patients in the treatment group.

TABLE 1: BASELINE CHARACTERISTICS

CHARACTERISTICS	CONTROL GROUP (n=17)	TREATMENT GROUP (n=24)	p-value
Race, n (%)			
Caucasian	8 (47.1)	13 (54.2)	
African American	4 (23.5)	6 (25)	0.711
Hispanic	4 (23.5)	3 (12.5)	
Asian	1 (5.9)	2 (8.3)	
Male, n (%)	16 (66.7)	10 (58.8)	0.607
Age (years), median (IQR)	23 (20-26)	25.5 (21-32)	0.225
Weight (kg), median (IQR)	83.2 (71-91)	76.8 (70-100)	0.711
Oncology Diagnosis, n (%)			
B cell ALL	13 (76.5)	14 (58.3)	0.134
T cell ALL	4 (23.5)	10 (41.7)	
Pegaspargase Regimen, n (%)			
CALGB 10403	16 (94.1)	16 (66.7)	0.149
A041501	1 (5.9)	5 (20.8)	
AALL0434	0 (0)	3 (12.5)	
VTE history prior to treatment, n (%)	0 (0)	5 (20.8)	
DVT		3 (12.5)	0.065
PE		1 (4.2)	
Both DVT and PE		1 (4.2)	

RESULTS

Sixty-four patients were reviewed, and 41 patients met inclusion criteria. Of the total evaluated patients, 23 patients were excluded; nine patients had a diagnosis of lymphoma (diffuse large B-cell lymphoma, non-Hodgkin's lymphoma, and T-cell lymphoma) and 14 patients were on an alternative pegaspargase-containing regimen (MOAD and EWALL). Seventeen patients were included in the historical control group and 24 patients in the treatment group (**Figure 1**).

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Baseline Characteristics: The demographic data was similar between the two groups. The patient population was 63.4% male and 48.8% Caucasian with a median age of 24 years. The median weight was similar between the two groups.

Most patients had an oncology diagnosis of B-lymphoblastic leukemia and were receiving the CALGB 10403 pegaspargase-containing regimen. VTE history prior to ALL diagnosis and treatment was notable in 20.8% of patients within the treatment group and 0% in the pre-protocol group, however this was not statistically significant (p=0.065).

A full analysis of the baseline characteristics is available in **Table 1**.

Primary Outcome: There was no statistically significant difference in the overall incidence of thrombosis between the two cohorts.

The historical control group had five events (29.4%) of thrombosis versus four events (16.7%) in the treatment group (p=0.45). DVT occurred in one patient (5.9%) in the historical control group versus two patients in the treatment group (8.3%), however this was not statistically significant (p=0.5).

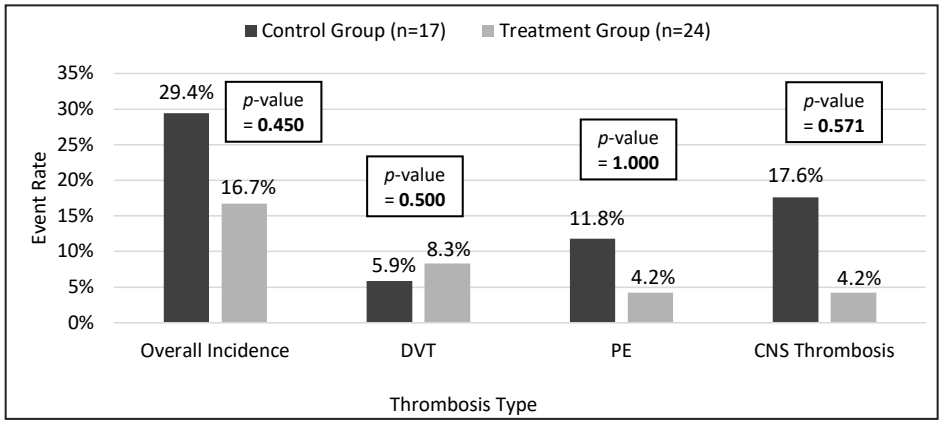
The historical control group had two incidences (11.8%) of PE while the treatment group had one incidence (4.2%). CNS thrombosis occurred in three patients (17.6%) in the historical control group compared to one patient (4.2%) in the treatment group. The full analysis of the various sites of thrombosis can be found in **Figure 2**.

Secondary Outcomes: Major bleeding occurred more frequently in the historical control group at 11.8% versus 0% in the treatment group, however this was not statistically significant (p=0.166).

In the treatment group, at least one dose of AT III was given to 11 patients and at least one dose of cryoprecipitate was administered to 15 patients. Thirteen patients in the treatment group did not require AT III or cryoprecipitate replacement based on protocol threshold values.

The full analysis of the secondary outcomes can be found in **Table 3**.

FIGURE 2: INCIDENCE OF THROMBOSIS



The historical control group had five events (29.4%) of thrombosis versus four events (16.7%) in the treatment group (p=0.45). DVT occurred in one patient (5.9%) in the historical control group versus two patients in the treatment group (8.3%). The historical control group had two incidences (11.8%) of PE while the treatment group had one incidence (4.2%). CNS thrombosis occurred in three patients (17.6%) in the historical control group compared to one patient (4.2%) in the treatment group.

TABLE 3: SECONDARY OUTCOMES

OUTCOME MEASURES	CONTROL GROUP (n=17)	TREATMENT GROUP (n=24)	p-value
Bleeding, n (%)			
Major	2 (11.8)	0 (0)	0.166
Minor	2 (11.8)	5 (20.8)	0.679
AT3 Doses, median ± SD (range)	0 ± 0.24 (0-1)	0 ± 2.69 (0-10)	0.012
Received at least one dose, n (%)	1 (5.9)	11 (45.8)	0.006
Cryoprecipitate Doses, median ± SD (range)	0 ± 1.18 (0-4)	1 ± 2.22 (0-10)	0.053
Received at least one dose, n (%)	4 (23.5)	15 (62.5)	0.014

POST-PROTOCOL GROUP SUMMARY

All 24 patients in the treatment group had AT III levels monitored appropriately according to our institutional guidelines.

Of the 24 patients, 11 patients required replacement therapy based on AT III levels. Of the 11 patients, nine patients received the correct dose(s) of AT III per protocol. There was deviation in the protocol due to a delay in replacement therapy for the first patient while the protocol was not completely followed as written for the second patient. All 24 patients also received correct monitoring of fibrinogen levels in the treatment group.

Of the 24 patients, 15 patients required replacement therapy with cryoprecipitate based on fibrinogen levels. All 15 patients received the correct dose(s) of cryoprecipitate per protocol.

DISCUSSION

This study was a retrospective pilot study used to investigate the safety and feasibility of AT III monitoring and replacement.

Thrombotic events can be life-threatening, prolong hospital stays and have a negative impact on remission rates and overall survival.[2] Thus, efforts to minimize thrombotic risk in this patient population are critical. In addition to improved morbidity and mortality, there is a $15,000 estimated cost per hospital-acquired VTE.[12]

The results of this study add to the body

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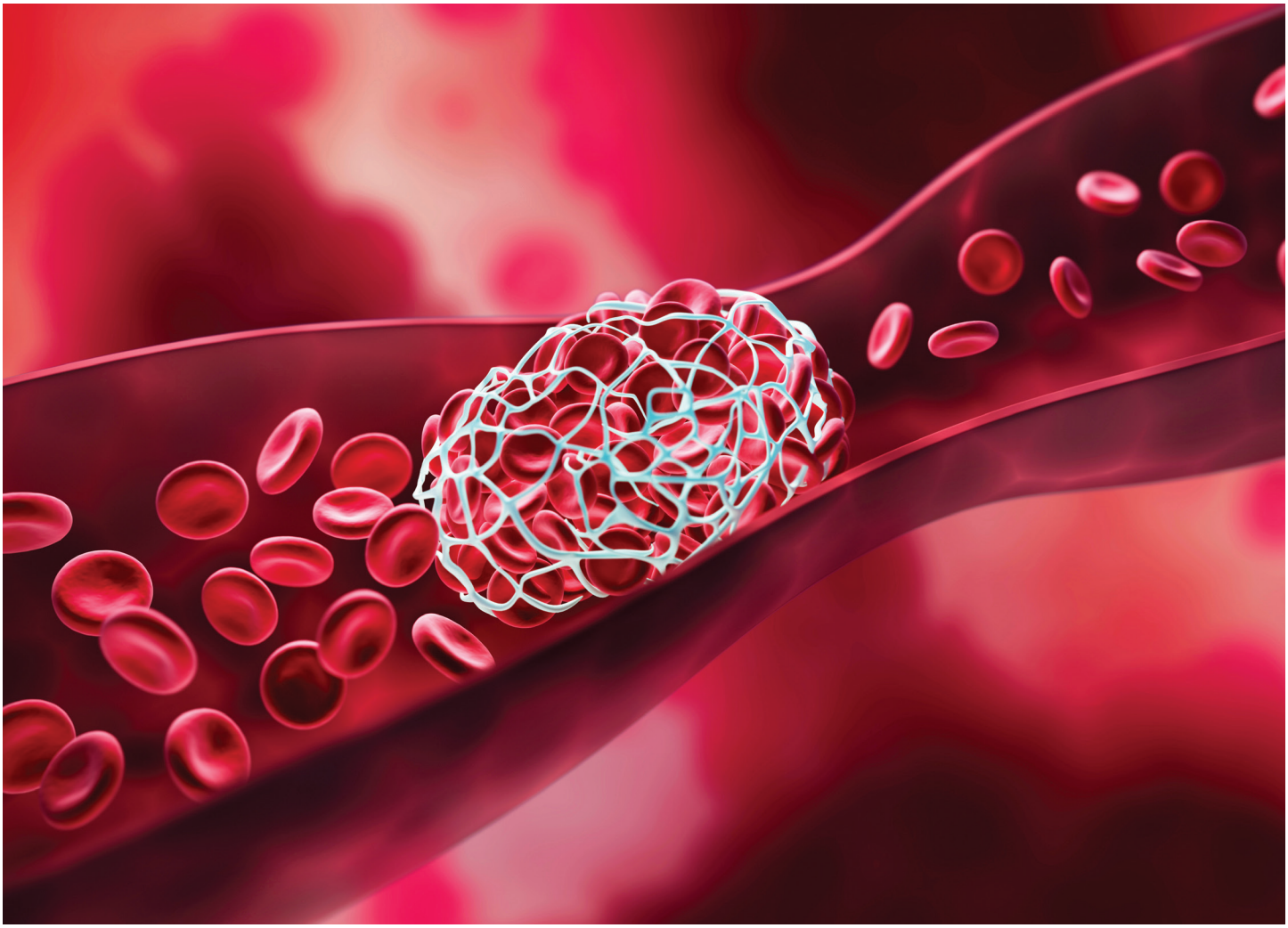

This computer-generated image depicts a thrombotic event, with a blood clot blocking a blood vessel. Symptoms include pain and swelling in one leg, chest pain, or numbness on one side of the body. Complications of thrombosis can be life-threatening, such as a stroke or heart attack.

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of literature as there is limited evidence to support the use of preemptive AT III replacement with pegaspargase induction therapy. Retrospective studies have observed overall improvements in coagulation parameters while reducing the occurrence of life-threatening thrombosis, which were found to be statistically significant.[3]

While previous studies found a statistically significant decrease in the rate of thrombosis, the small sample size of this study may have limited the ability to detect a difference between the two groups.

The CAPELAL study was a retrospective study that included 214 patients who were treated with L-asparaginase for ALL or lymphoblastic lymphoma.[8] Antithrombin replacement was provided to patients when AT III levels were <60%. The rate of thrombosis was lower for patients who received antithrombin replacement (4/83, 4.8%) compared to those who did not (16/131, 12.2%; p=0.04).[8]

In contrast, Chen, et al showed there was no statistically significant decrease in thrombotic events for patients with ALL that received pegaspargase.[13]

This was a smaller study compared to CAPELAL (N=75). The incidence of VTE was observed at 17% (8/47) for the replacement group versus 11% for the control group (3/28; p=0.52).[13]

Farrell, et al found a reduction in thrombosis occurrence for patients who received AT III replacement therapy (0/30 v 5/15; p<0.001). Antithrombin replacement was provided to patients when AT III levels were <70%.

Determination of the optimal AT III replacement threshold is an important component of the supportive care strategy in this patient population.

Conflicting results and differing AT III replacement thresholds have challenged the standardization of AT III replacement protocols.

There were a few limitations to this study. This study was not powered to detect a difference in the incidence of TE before and after the implementation of the AT III replacement protocol. Therefore, this may have influenced the results of the primary

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outcome showing no difference between the two cohorts.

Furthermore, the design of the study as a single-large referral center, retrospective, observational study limits application to outside centers and creates selection bias.

From a cost-effectiveness standpoint, the estimated cost for a course of antithrombin repletion is between $12,000 and $35,000 depending on the specific AYA regimen used.[3]

Based upon our review of the literature and consideration of healthcare costs, our institution utilizes an AT III threshold of <30% for thromboprophylaxis.

CONCLUSION

Thrombosis is a common toxicity associated with pegaspargase therapy and an important consideration during the induction phase of therapy.[3] Efforts to minimize thrombosis risk are paramount given increased morbidity and mortality with VTE during this period.

This study demonstrates the feasibility of AT III monitoring and replacement at our institution. From a patient safety perspective, replacement was well-tolerated and was not associated with increased risk of bleeding or thrombosis. A reduction in the incidence of VTE could minimize both delays in therapy and duration of hospitalizations.

Our pilot study was conducted in order to analyze the feasibility of performing a large-scale main trial. Prospective studies adequately powered to detect a benefit of thromboprophylaxis are necessary.

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This study demonstrates the feasibility of AT3 monitoring and replacement at our institution. From a patient safety perspective, replacement was well-tolerated and was not associated with increased risk of bleeding or thrombosis. A reduction in the incidence of VTE could minimize both delays in therapy and duration of hospitalizations.

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CANCER TREATMENT & REPRODUCTION

NEW OPTIONS MAY HELP PRESERVE FERTILITY IN CANCER PATIENTS

By Alexandra Minnihan, MD, & Alice Rhoton-Vlasak, MD

The treatment of cancer in reproductive age patients has been shown to have varying short- and long-term effects on fertility through impact on gonadal tissue or the hypothalamic-pituitary axis.

Alongside increasing survivorship in children and young adults to reproductive age, research on the impact of treatment on future fertility and outcome data in fertility preservation is continually evolving.

This review provides an update on fertility preservation options and outcomes.

Alexandra Minnihan

Alice Rhoton-Vlasak

ADVANCES IN ONCO-FERTILITY

Recent advances have prompted international updates in onco-fertility. The most recent recommendations from the American Society of Clinical Oncology and committee opinion released by the American Society for Reproductive Medicine were in 2018 and 2019, respectively. Updated French guidelines were presented in 2021.[1-3]

Also in 2021, the European Union funded a project with the International Late Effects of Childhood Cancer Guideline Harmonization Group, titled PanCareLIFE, to propose evidence-based clinical practice guidelines for both female and male childhood, adolescent and young adult cancer. The study included an additional review devoted to communication and ethical considerations in counseling on fertility preservation.[4-6]

Those therapies highlighted to have the most significant impact on fertility

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include alkylating agents of any dose, ovarian radiotherapy at a dose greater than 5 Gy, and cranial radiotherapy impacting the hypothalamus or the pituitary at doses greater than or equal to 30 Gy.[7]

A risk of premature ovarian insufficiency has also been documented following hematopoietic stem cell transplantation and reduced fertility suggested following unilateral oophorectomy.[8]

For women or transgender men approaching gonadotoxic cancer therapy, first-line fertility preservation remains embryo and oocyte cryopreservation with utilization of in vitro fertilization for future pregnancies.[1] Meta analysis of 34 studies from the United States and Europe reported a live birth rate of 41% for embryo and 32% for oocyte cryopreservation.[9]

Advances in ovarian stimulation to include cycle-day independent protocols have ameliorated a primary concern of onco-fertility, the delay of treatment initiation. In addition, the use of aromatase inhibitor stimulation protocols and assisted reproductive technology have not been shown to increase cancer recurrence rate, relapse rate or impact overall survival rates in estrogen-sensitive breast and gynecologic cancers.[10]

While embryo or oocyte cryopreservation can circumvent the impact of gonadotoxic therapies, another approach is protective adjunct therapies, most studied of which is ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa) to reduce chemotherapy-induced ovarian insufficiency.

In 2018, a systemic review provided evidence on the safety and efficacy of temporary ovarian suppression with GnRHa during chemotherapy in the early breast cancer population. Within that review, the three largest studies provided data on post-treatment pregnancy rates consistent with the literature at 7.9% with statistically significant higher pregnancy numbers in those treated with GnRHa (37 v 20; IRR, 1.83; 95% CI, 1.06 to 3.15; P = 0.030).[11]

The field of onco-fertility continues to evolve as data on the short- and long-term effects of cancer therapy is presented and grow in parallel to increasing interest and awareness of fertility preservation in patients and families approaching the treatment of cancer.

OVARIAN TISSUE CRYOPRESERVATION

In prepubertal females and those not clinically stable to undergo retrieval procedures or not advised to delay cancer treatment, ovarian tissue cryopreservation can be performed immediately without need for ovarian stimulation and is no longer considered an experimental technique as of 2019.

Longitudinal studies following patients treated with orthotopic or heterotopic ovarian tissue transplantation have shown this method restores ovarian endocrine function approximately 12-20 weeks after transplantation and last for up to seven to eight years. Systematic reviews suggest a pregnancy rate of 23%-37%, following IVF and spontaneous pregnancy, post-ovarian tissue cryopreservation.[5,9,12,13]

As of 2023, ovarian tissue transplantation has been associated with more than 200 live births.[14,15] To address risks of tumor cell contamination in cryopreserved tissue specifically for those with hematologic malignancies, there is growing research in the field of in vitro maturation of follicles from different states of maturation and the development of artificial scaffolding and ovaries.[15-17]

Initiation of radiation therapy may be preceded by laparoscopic ovarian transposition. However, studies show that radiation scatter – which may displace ovaries from the radiological field – leads to variable success rates from 16% to 100%.[18] For that reason, optimal location of transposition should be mapped with radiation oncology.

Depending on location of transposition, future fertility preservation attempts may be impacted by altering access to ovaries for oocyte retrieval. This procedure, along with other fertility-sparing surgical managements of malignancy — such as cone knife conization, trachelectomy, simple hysterectomy or unilateral or bilateral salpingo-oophorectomy with use of donated oocytes in cervical, endometrial and ovarian cancer respectively — are accumulating data on risk of cancer recurrence and pregnancy outcomes due to patient interest and election of fertility preservation.[19,20]

SPERM CRYOPRESERVATION

For postpubertal males approaching gonadotoxic therapy or radiation, sperm cryopreservation is effective and should be initiated prior to treatment.

Clinical status or malignancy type may occasionally impact certain semen parameters at the time of collection. However, low sperm count, and morphologic abnormalities can be addressed with the use of intracytoplasmic sperm injection and IVF.

In the absence of spontaneous arousal and ejaculatory functions, PDE-5 inhibitors, vibration and electroejaculation have been shown to stimulate arousal and ejaculation respectively for induced collection.

In those males unable to collect via masturbation or who have insufficient sperm count to cryopreserve, surgical testicular sperm retrieval may be performed in the outpatient setting or coordinated with procedures under anesthesia.

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For prepubertal males, testicular tissue cryopreservation remains experimental offered primarily under research protocols. However, ongoing research in mouse models shows testicular tissue cryopreservation to be significantly superior to testicular cell suspension in outcomes of number of viable cells post-thaw and donor-derived mouse births.[21]

Other research avenues include testicular tissue engraftment, autotransplantation of spermatogonial stem cells and in vitro maturation of spermatogonial stem cells to spermatozoa. Post-gonadotoxic therapy or radiotherapy, the risk of genetically damaged sperm remains.

In conclusion, the field of onco-fertility continues to evolve as data on the short- and long-term effects of cancer therapy is presented and grows in parallel to increasing interest and awareness of fertility preservation in patients and families approaching the treatment of cancer.

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GO BEYOND THE SCIENCE

THEIR FIGHT, OUR MISSION

Pioneering Together for a Cancer-Free Tomorrow

Together, we boldly create a future where all patients, regardless of circumstances, can access medicines that are precisely right for them.

Patient-Centered Care

- **20% of rural residents live >60 miles from a medical oncologist**, creating a barrier to treatment[1]
- **Self-care for cancer patients proves difficult**, particularly within safety-net environments, due to reduced health literacy and various other barriers[2]

Equitable Care

- Black women are **41% more likely to die** of breast cancer than white women[3]
- Only about **5% to 15% of US clinical trial participants are Black or Latino**, yet non-white people are predicted to make up the majority of the US population by the year 2045[4-7]

Precision Medicine

- **1 in 3** patients with advanced non–small cell lung cancer **did not receive next-generation sequencing (NGS) testing**[8]
- White patients with NSCLC **received timely NGS testing at higher rates** (~8%) compared to Black or Latinx patients[9,10]

How might we boldly impact patient care together?
Learn more about our initiatives at **genentechoncology.com**

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Copay Accumulators

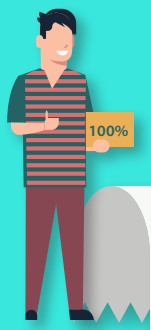
what to know & what's the difference?

Without accumulator programs

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

Your Deductible

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



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

RECEIPT

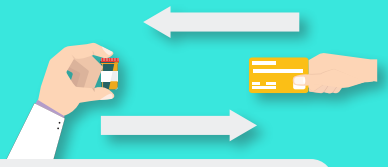
Prescription Drug Cost	$2,000.00
Manufacturer Coupon Value	-$1,995.00
Your Total at the Counter	$5.00

$2,000.00
Annual Deductible

$0.00
Remaining Deductible After Coupon*

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

With accumulator programs



Patients can still use their coupon cards but ...

Your Deductible

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

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

RECEIPT

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

$2,000.00
Annual Deductible

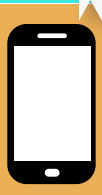
$1,995.00
Remaining Deductible After Coupon*

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

VS.

An example of what happens at the pharmacy counter

NCODA



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

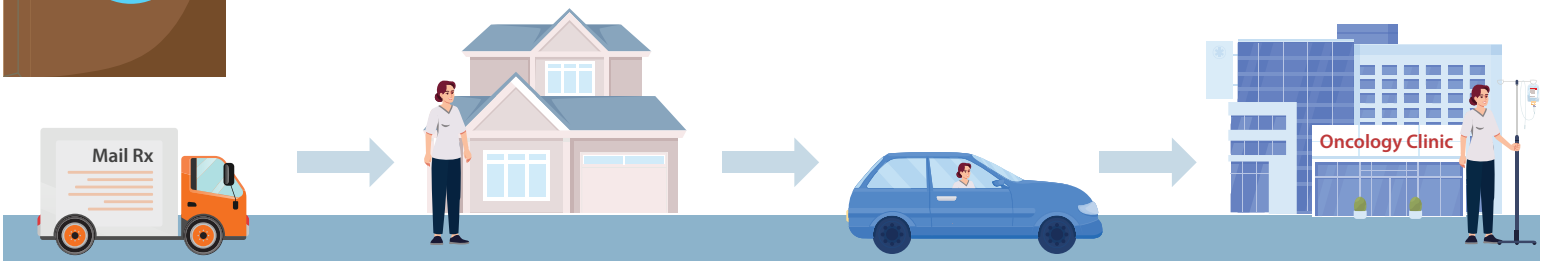
PHARMACY "BAGGING" OVERVIEW

NCODA
PASSION FOR PATIENTS

Bagging is the process by which medication is delivered from a pharmacy to the clinic for administration.

1 Brown Bagging

External mail-order pharmacy sends medication directly to a patient.
The patient then takes the medication to the clinic for administration.



PROS

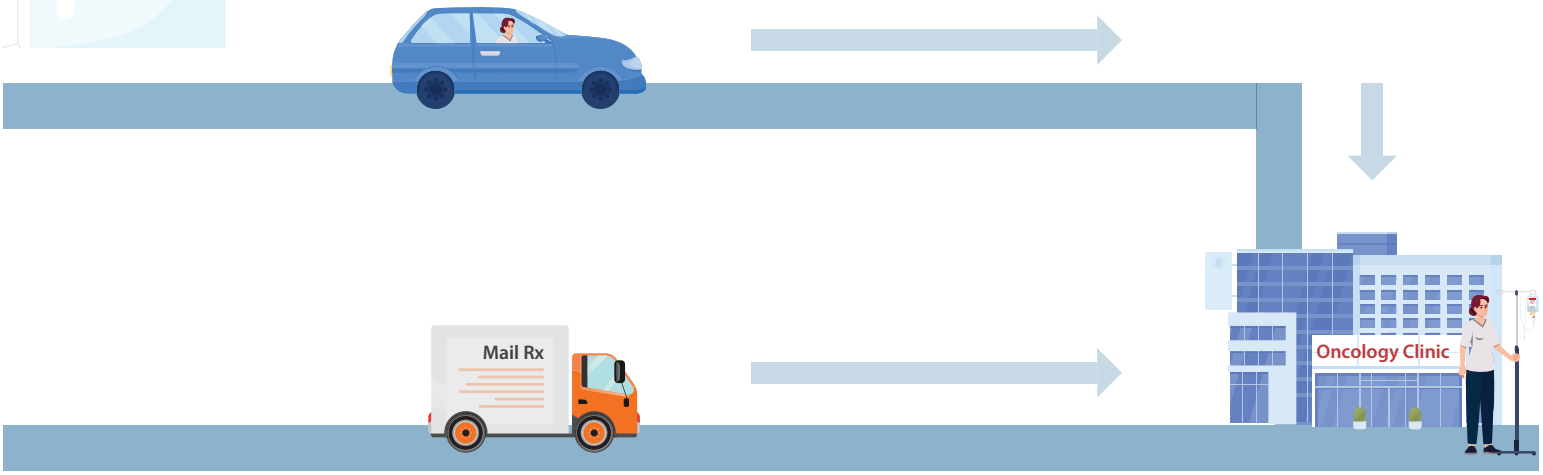
- Cost-savings for insurance companies
- Theoretically, lower risk of treatment delay as patient receives medication before appointment

CONS

- Shipping delays
- Improper storage and handling

2 White Bagging

External mail-order pharmacy delivers medication directly to the clinic where it is administered to a patient.



PROS

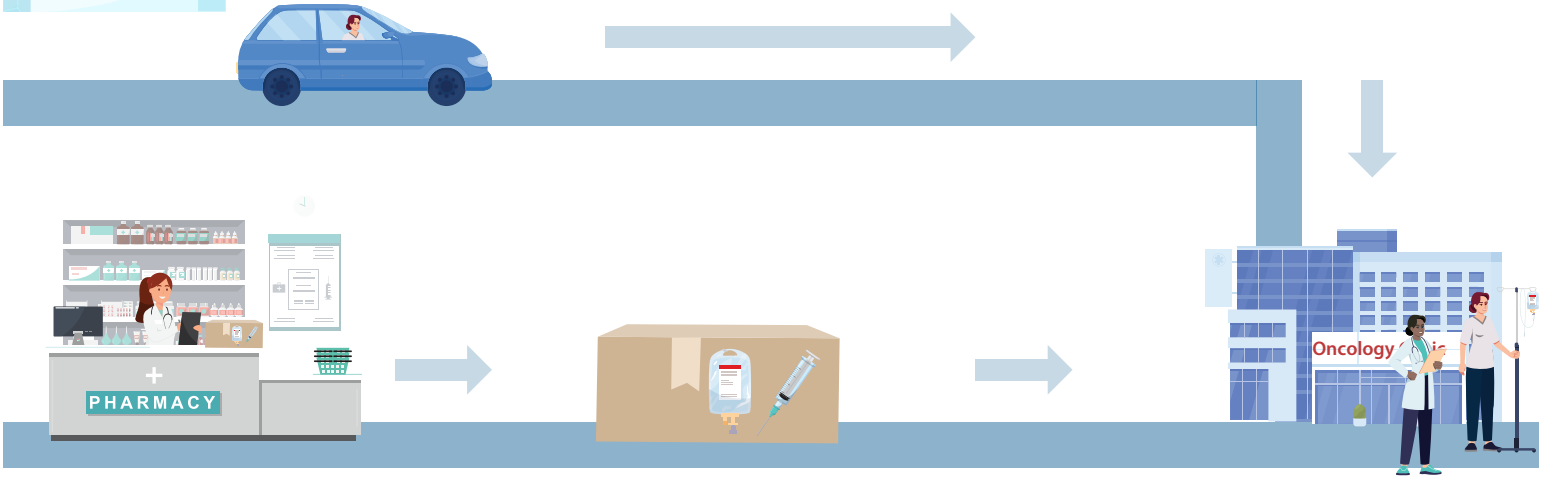
- Cost-savings for insurance companies
- No responsibility for patient regarding medication storage and handling

CONS

- Requires significant medication coordination
- Inability to individualize treatment (instead of clinic; cannot tailor treatment at point of care)

3 Clear Bagging

Clinic's internal pharmacy delivers medication directly to the location where it is administered to a patient.



- Internal pharmacy is in control of delivery
- Clinic will have proper storage and handling facilities before appointment

PROS

CONS

- Potential for increased DIR fees
- More focus on a streamlined internal workflow is needed
- Insurance company restrictions/mandates

4 Gold Bagging

The same process as clear bagging, but with more comprehensive, patient-centered care.

- Same pros as clear bagging with enhanced coordination of patient-care

PROS

CONS

- Same cons as clear bagging
- More time and resources needed for coordinated care

Looking for more information and to get connected?
Scan QR code or email contact@ncoda.org

Take back your PBM takebacks: Best practices for overcoming audit challenges

Casey Foster, MBA, Sr. Manager, Medically Integrated Dispensing Solutions, Cardinal Health
Andrea Hughes, CPhT-Adv, National Account Manager, Medically Integrated Dispensing Solutions, Cardinal Health
Briar Watercutter, CPhT & Certified ACHC Consultant, National Account Manager, Medically Integrated Dispensing Solutions, Cardinal Health

Most oncology practices will, at some point, be subject to a third-party audit. These audits occur on at least an annual basis, and some can even occur monthly or weekly. Unfortunately, the high cost of oncologic therapies means that failure to properly document claims or comply with an audit can lead to steep financial penalties, ranging from a few thousand dollars to hundreds of thousands of dollars in takebacks.

Failure to understand the pharmacy benefit manager (PBM) audit process before an audit occurs can result in unnecessary stress, inefficient use of staff time and frustration. The good news is that you can successfully defend your practice against audit recoveries by following these key best practices before, during and after an audit.

Before an audit

Educating yourself and your entire staff about claims submission best practices is crucial to ensuring a favorable audit down the road. Before an audit, you should:

- Familiarize yourself with the most common causes for audit recoveries to avoid making those mistakes
- Create thorough claims processing procedures that increase the likelihood of submitting claims properly on the front end and in compliance with the unique contract requirements of each individual PBM
- Maintain comprehensive, written or electronic documentation of all factors surrounding PBM claims — and ensure that documentation can be quickly accessed

During an audit

PBM audits can be conducted via fax, phone, email or regular mail, and even on-site at your practice. Regardless of the type of audit your practice faces, these best practices can increase the likelihood of a favorable outcome:

- Immediately assign a staff member to manage all aspects of the audit until it's complete
- Consider asking your pharmacy services administrative organization (PSAO) or group purchasing organization (GPO) account representative to review audit notifications and relevant documents to support an accurate response
- Provide all information requested by the auditor, and be pleasant and polite
- Ask the auditor to provide a timeline, including when you should expect to receive your audit findings

After an audit

You should expect to receive an official response from the PBM explaining that you are under no obligation to accept the accuracy of their findings. Follow these best practices to ensure the greatest likelihood of disputing takeback findings:

- Comply with the method and timeframe required by the auditor for any rebuttal of findings
- Challenge findings with supporting documentation
- Be willing to accept small claim recovery amounts so you can focus on large claim recoveries
- Keep a record of all audit recoveries

How we can help

PBM audits are an unavoidable reality. However, preparation, employee training, good recordkeeping, professionalism and accountability are essential to navigating a third-party audit and securing the optimal result for your practice. If you'd like support in ensuring you have best practices in place to avoid PBM audits — or if you'd like knowledgeable guidance to refer to when responding to one — contact our Medically Integrated Dispensing team at Cardinal Health.

Connect with our experts. Visit **cardinalhealth.com/dispensing**

How Cardinal Health helped one practice successfully dispute more than $1 million in PBM takebacks

In 2023, a West Coast practice was faced with an on-site PBM audit. Practice staff invested significant time into preparing and submitting the required documentation — but were shocked and disappointed when the PBM advised that it planned to take back nearly $1.14 million in claims. The practice immediately reached out to the **Medically Integrated Dispensing team at Cardinal Health** to request urgent assistance in disputing the audit findings.

The Cardinal Health team of experts quickly realized that most of the takebacks resulted from claims submission errors that could be quickly remedied, provided that the correct audit dispute processes were followed and that the appropriate documentation was available. These errors included missing/mismatched dates, missing or invalid patient documentation, missing signatures, unprocessed reversals, and prescriptions picked up after the allowed 14-day window. The Cardinal Health team quickly partnered with the practice to review the PBM's required documentation list, familiarize practice staff with the PBM's preferred audit rebuttal processes, teach practice staff how to sort prescription claims by the PBM's BIN number and prepare the necessary documentation to appeal the findings.

With support from Cardinal Health, the PBM reduced its takeback from nearly $1.14 million to $83,000*. Most of the claims that did not get reversed were for prescriptions picked up after the permitted 14-day window — and the practice implemented a stricter return-to-stock policy to prevent this issue from causing future audit penalties.

*Individual results may vary

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CardinalHealth™

FILLING THE DIVERSITY GAP

IN CANCER CARE

ADVANCING HEALTH EQUITY WITH CHARITABLE COPAY ASSISTANCE

By Patricia Falconer, MBA, Fred Asiedu Larbi, MBA, Samuel Sappor & Krista Zodet, MSW

An important reason to focus on elevating cancer health equity is that advances in cancer care and treatments have improved the quality of care but may not be accessible to all individuals.

Cancer health disparities are the difference in cancer measures such as cancer incidence, deaths, complications, survivorship and quality of life, screening rates and stage of diagnosis that exist among certain populations.

Well-documented cancer health disparities persist for members of racial and ethnic communities, individuals with limited English proficiency and individuals with low health literacy.[1]

Additionally, socioeconomic inequities in cancer mortality have widened over the past three decades. Racial and ethnic minorities tend to receive lower-quality healthcare than Non-Hispanic Whites.

For example, Black patients have the highest death rate and shortest survival of any racial/ethnic group in the U.S. for most cancers. (**See Figure 1**).

IMPACT OF FINANCIAL TOXICITY

Another reason to advance health equity is the opportunity to reduce financial toxicity. The same population of individuals experiencing cancer healthcare disparities

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Patricia Falconer

Fred Asiedu Larbi

Samuel Sappor

Krista Zodet

COPAY ASSISTANCE

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are also at a greater risk for financial toxicity.

Financial toxicity describes financial hardships and strain that patients experience related to the cost of treatment and care. Financial toxicity is the unintended, but not necessarily unanticipated, objective financial burden and subjective financial distress experienced by cancer patients because of their treatment costs.[2]

Objective financial burden describes the direct out-of-pocket costs for medical care and the non-medical costs such as transportation, housing, food and childcare.

Subjective financial burden results from the accumulation of the out-of-pocket expenses over the time from diagnosis, reduction of personal assets and the coping strategies used by the patients and families.

Often, guideline-adherent multidisciplinary cancer care includes surgery, oral and/or intravenous administered (systemic) therapies and radiation therapy. Of cancer patients who receive systemic therapy, radiation therapy, surgery, or who participate in a clinical trial. Twenty-two percent to 50% reported financial distress.

Financial toxicity has been linked to several clinically relevant patient outcomes such as quality of life, symptom burden, compliance and survival.

However, there are many ways that patients can get philanthropic medical aid to cover high-cost treatments.

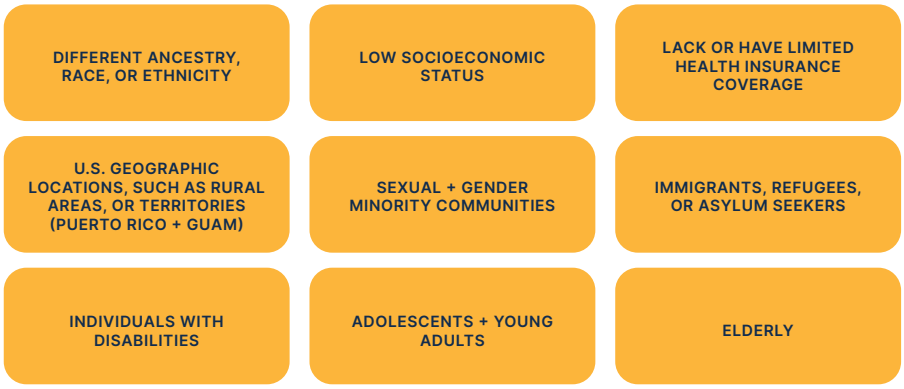
Drug manufacturers (life science companies) and charitable foundations provide financial programs for patients facing out-of-pocket costs associated with high-cost therapeutic drugs.

Charitable foundations also provide support grants to help patients pay for costs such as health insurance premiums, clinical trial participation, transportation, housing, food, utilities and childcare.

In a 2022 American Cancer Society Cancer Action Network survey of 1,241 patients across the U.S. that were treated for cancer, one-third reported that prescription drug costs were a challenge.

FIGURE 1: WHICH U.S. POPULATION GROUPS EXPERIENCE CANCER HEALTH DISPARITIES?

According to the National Cancer Institute, cancer health disparities in the U.S. are adverse differences in cancer measures such as number of new cases, number of deaths, cancer-related health complications, survivorship and quality of life after cancer treatment, screening rates, and stage at diagnosis that exist among certain population groups including:



It is important to note that some populations may carry even a higher burden of cancer because they simultaneously fall into more than one of these categories.

AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR) CANCER DISPARITIES PROGRESS REPORT 2022

In a 2022 American Cancer Society Cancer Action Network survey of 1,241 patients across the U.S. that were treated for cancer, one-third reported that prescription drug costs were a challenge.

One-fifth reported having skipped or delayed taking a prescribed medication due to difficulty paying the cost. Significantly higher rates of missed medication were reported by patients with lower income or individuals representing racial/ethnic minorities.[3]

Additionally, many hospitals and health systems provide patients access to copay assistance programs via financial navigators or financial counselors. Performance is often measured based on productivity, access and financial metrics to illustrate the economic benefit or return on investment of the program.

For example, Cleveland Clinic's Financial Navigation Program metrics include the percentage of all infusion treatment patients reached by financial navigators, copay assistance program applications filed, copay assistance program applications approved, aggregate dollars applied/dollars received, total dollar amount of approved applications for free drug, average total dollar amount per application and the time in days from patients' first positive biopsy to first treatment.[4]

Little is known about the sociodemographic characteristics of the patients receiving copay assistance or those left behind. Program metrics that measure reduction in healthcare disparities are not widely understood.

By applying the Centers for Medicare & Medicaid Services' (CMS) Framework for Health Equity to clinical outcomes reported in a published national survey and data from a national charitable foundation,

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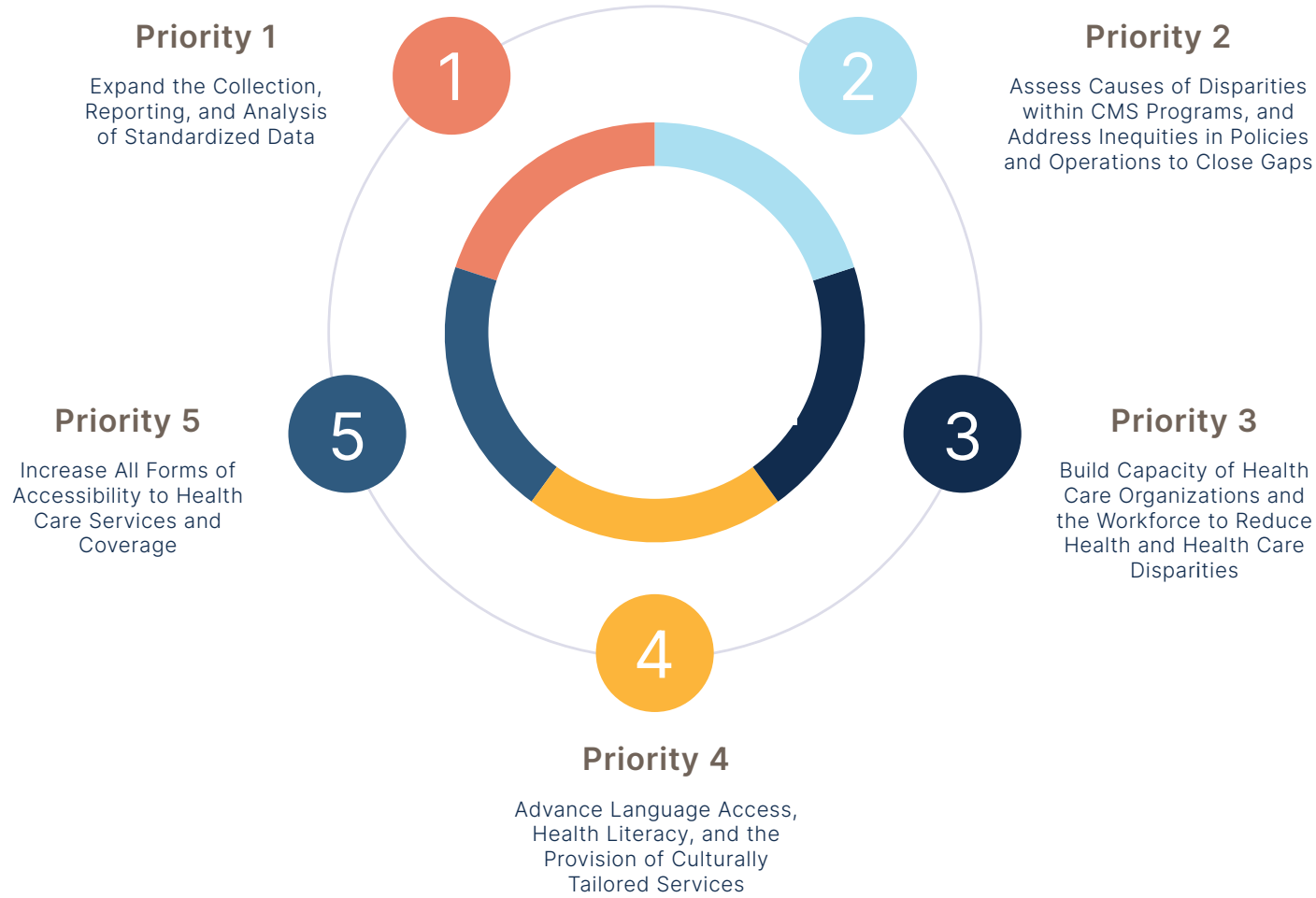
FIGURE 2: CMS FRAMEWORK FOR HEALTH EQUITY PRIORITIES



COPAY ASSISTANCE

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this paper will identify opportunities to uncover healthcare disparities as a way forward for copay assistance programs to elevate health equity.

A NEW DESIGN FOR COPAY ASSISTANCE

Copay assistance programs' current state design may not reduce healthcare disparities without a new structured approach.

The CMS Framework for Health Equity was designed to help organizations achieve health equity and reduce disparities among minority and underserved populations.[5]

Since most cancer patients are Medicare eligible and charitable foundations serve mainly Medicare recipients, this framework is a good fit.

The CMS Framework for Health Equity outlines five priorities which provide an integrated approach to build health equity into existing and new efforts by CMS and its stakeholders.

Based on the funds considered here, 92% of HealthWell's grant recipients are Medicare-eligible, age 65+. Additional sociodemographic data of copay assistance recipients will be needed based on the recommendations in this framework. **(See Figure 2)**.

HEALTHWELL FOUNDATION CROSS-SECTIONAL SURVEY AND CANCER DISEASE FUNDS

Current published research illustrates some of the sociodemographic data for cancer patients receiving copay financial assistance.

Jeffrey Peppercorn, MD, Director of Supportive Care and Survivorship for Massachusetts General Hospital Cancer Center, and authors representing organizations including Fox Chase Cancer Center, Temple University Health Systems, University of North Carolina, and University of Oklahoma conducted a national, cross-sectional survey of copay financial assistance recipients from HealthWell Foundation.

HealthWell Foundation is a leading independent nonprofit dedicated to improving access to healthcare for America's uninsured. HealthWell Foundation assists patients with copays, premiums and deductibles.[6]

A total of 1,108 recipients of copay assistance grants (financial assistance) from HealthWell Foundation were surveyed. Patients represented included:

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FIGURE 3: COMPARISON WITH HEALTHWELL FOUNDATION CANCER DISEASE FUNDS

Disease Fund Name	Solid Tumor or Hematologic Malignancy	Medicare Access Only	Primary Diagnosis	Secondary Diagnosis
Acute Myeloid Leukemia	H	Y	Y	
B-Cell Lymphoma	H	Y	Y	
Bladder Urothelia	S	Y	Y	
Bone Metastasis		Y		Y
Break Through Cancer Pain		Y		Y
Breast Cancer	S	N	Y	
Cancer-Related Behavior Health		N		Y
Carcinoid Tumors	S	N	Y	
Chemotherapy-Induced Anemia		N		Y
Chemotherapy-Induced Neutropenia		Y		Y
Chemotherapy-Induced Nausea/Vomiting		N		Y
Chronic Lymphocytic Leukemia	H	N	Y	
Chronic Myelogenous Leukemia	H	N	Y	
Colorectal Cancer	S	Y	Y	
Cutaneous T-Cell Lymphoma	H	N	Y	
Gastric Cancer	S	Y	Y	
Glioblastoma	S	N	Y	
Head & Neck Cancer	S	Y	Y	
Hepatocellular (Liver)	S	Y	Y	
Hodgkins Lymphoma	H	N	Y	
Mantle Cell Lymphoma	H	N	Y	
Melanoma (Skin)	S	N	Y	
Multiple Myeloma	H	Y	Y	
Myelodysplastic Syndrome	H	Y	Y	
Non-Hodgkins Lymphoma	H	Y	Y	
Non-Small Cell Lung Cancer	S	N	Y	
Ovarian	S	Y	Y	
Pancreatic	S	Y	Y	
Prostate	S	Y	Y	
Renal Cell (Kidney)	S	Y	Y	
Small Cell Lung Cancer	S	Y	Y	
Waldenstrom's Macroglobulinemia	H		Y	

COPAY ASSISTANCE

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▲ More than 20 different cancer types (30% solid tumors and 70% hematologic malignancies);

▲ An average age of 72 years old;

▲ 60% were male;

▲ 88% were non-Hispanic white;

▲ 55% were college-educated;

▲ 67% had an annual income less than $60,000; and

▲ 96% had Medicare coverage, of which;

- 53% had traditional fee for service Medicare;
- 58% had Medicare Part A and Part B with supplemental insurance; and
- 43% had a Medicare Advantage plan.

The primary outcome of interest was patient self-reported financial distress using the Comprehensive Score for Financial Toxicity (COST).

Secondary outcomes included measures of out-of-pocket spending, perspectives on copay assistance, healthcare access and costs, and the impact of financial burden on healthcare utilization.

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COPAY ASSISTANCE

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The survey revealed:

56% reported mild and 27% reported moderate/severe financial toxicity. Traditional fee-for-service Medicare insurance was significantly associated with greater financial distress.

18% reported skipping medical services due to cost.

17% reported delays in starting therapy due to cost with over one in four patients experiencing delays beyond four weeks.

54% reported spending greater than $500 per month on healthcare, with 39% spending greater than 10% of their household income.

24% believed they would not have received treatment without financial assistance.

73% reported a decrease in financial concerns because of receiving patient copay assistance.

Published research data alone will not identify health disparities and elevate health equity as research participants may not represent all patient populations.

The findings from the cross-sectional survey were compared to the sociodemographic data of grant recipients of HealthWell Foundation's cancer disease funds for 2021 and 2022.

HealthWell Foundation has 39 cancer (oncologic/hematologic malignancies) disease funds of which 33 are defined by primary diagnoses and six are by secondary (supportive care) diagnoses.

Of the primary cancer disease funds, one-third are for patients with hematologic malignancies and two-thirds for solid tumors.

Forty-six percent of the cancer disease funds are available to Medicare insured patients only. (**See Figure 3**).

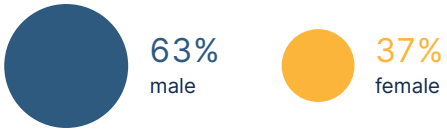
The number of approved grants for cancer patients in 2021 was 68,677, which decreased 5% to 65,243 in 2022. The total dollar value of grants paid was $352,000,000 in 2021 and decreased 8% to $324,000,000 in 2022. The average grant amount paid was $5,125 in 2021 and $4,968 in 2022.

While all disease fund recipient locations were different, the most common top three states where grant recipients resided were Florida, Texas and California.

Ninety-nine percent of the grant types were copay assistance and 1% were health insurance premiums.

For 2021 and 2022 combined, the age distribution of the grant recipients was 92% age 65+, 7% age 50-64 and 1% age 35-49; 0% age under 35 and 63% were male, 37% female (**See Figure 4**).

FIGURE 4: 2021-2022 DISTRIBUTION OF HEALTHWELL GRANT RECIPIENTS



Family income for grant recipients across all funds was reported as a percentage of the Federal Poverty Level (% FPL). Eligibility for most programs requires family income to be below 400% to 500% FPL.

For example, in 2021, the largest percentage of grant recipients (21%) family income measured at 150% to 200% FPL, the second-largest (19.7%) at 100% to 150% FPL and third-largest (17.2%) at 200% to 250% FPL (**See Figure 5**).

In the current state, HealthWell does not capture grant applicants' sociodemographic data such as educational level attained, race, ethnicity, preferred language, sexual orientation, gender identification, disability status or other social determinants of health (SDoH).

PATIENT ACCESS TO HEALTHWELL'S DISEASE-BASED PROGRAMS

Accurate referral data is essential to determine potential healthcare disparities. Data from 2021 and 2022 was

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FIGURE 5: 2021 FEDERAL POVERTY LEVEL DISTRIBUTION — ALL HEALTHWELL FUNDS

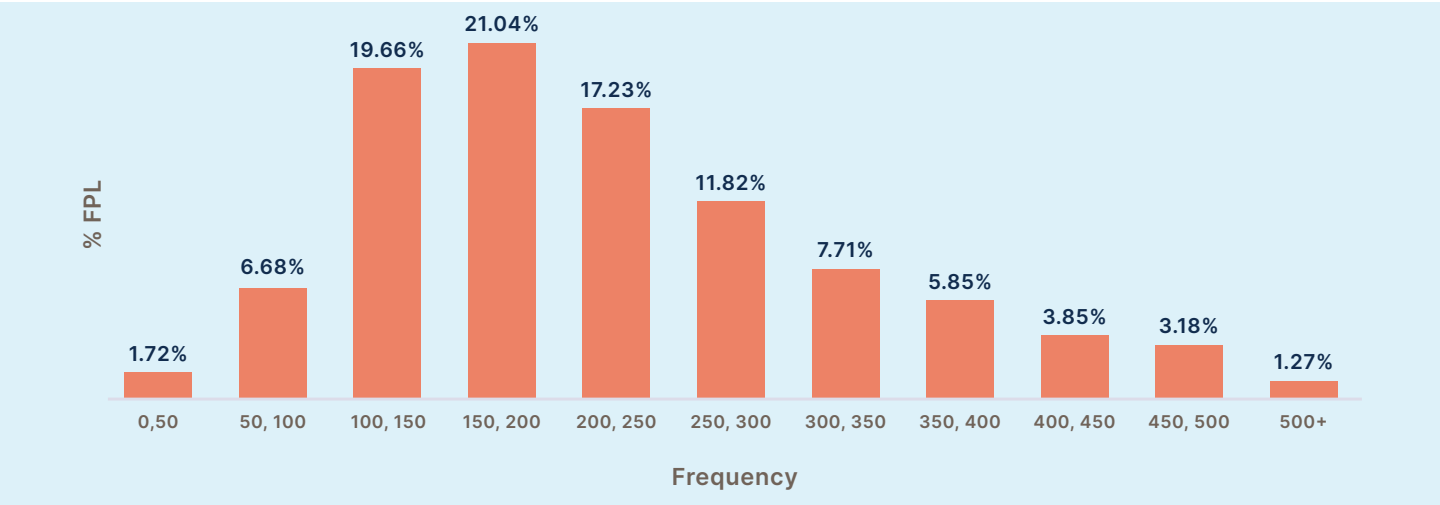

FIGURE 6: REFERRAL SOURCES FOR HEALTHWELL FOUNDATION

Referral Sources	2021	%	2022	%
Another Copay Foundation (Patient Assistance Program)	5,076	8.26%	4,765	7.96%
Case Manager/Social Worker	2,807	4.57%	2,272	3.80%
Disease-Specific Nonprofit/Patient Support Organization	1,738	2.83%	1,152	1.92%
Financial Counselor	722	1.18%	716	1.20%
Media/Social Media	158	0.26%	140	0.23%
Other (Including Blanks, Not Applicable, Not Provided and Unsure)	8,152	13.27%	7,485	12.50%
Patient/Family Member/Caregiver	1,673	2.72%	2,179	3.64%
Pharmacy	18,384	29.93%	17,091	28.55%
Private Insurer (e.g., BCBS, United)	725	1.18%	546	0.91%
Provider/Physician/Nurse/Advocate	14,822	24.13%	16,279	27.20%
Public Insurer (Medicare, Medicaid)	378	0.62%	377	0.63%
Reimbursement Support Line/Manufacturer	5,534	9.01%	5,710	9.54%
Website/Web Search	1,247	2.03%	1,146	1.91%
Total	**61,416**		**59,858**	
Grant Enrollment by Provider (Portal)				
Provider Portal	124,074		123,710	
Grand Total	**185,490**		**183,568**	

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reviewed to determine how patients access HealthWell's copay assistance programs.

In 2021 and 2022, more than two-thirds of patients — 124,074 and 123,710 patients respectively — were referred to HealthWell via their portal, where applications were completed on the patients' behalf effectively reducing barriers to access.

For 2021 and 2022, the remaining one-third of patients — 61,416 and 59,858 respectively — were directed to the HealthWell website or hotline number to self-enroll.

For example, in 2022 the largest referral sources for patients' self-enrollment were pharmacies (17,091), providers, nurses, and advocates (16,279), other (7,485), drug manufacturer reimbursement support line (5,710) and copay assistance program sponsored by another foundation (4,765).

Percentages for each referral source do not match the HealthWell website data as the "Referral Source, Other" does not include blanks, not applicable, unsure, not provided (**See Figure 6**).

LANGUAGE BARRIERS

Language can be a barrier to accessing copay assistance programs. Language contributes to patients' health literacy level, which impacts self-enrollment ability via the hotline and the website.

In current state, the HealthWell website content is available in English. For Spanish-speaking individuals, there is an Espanol tab in the home webpage and Solcitar tab in the application section which displays the instructions and application in Spanish.

A small number of patients requested translation services when using the HealthWell hotline — 270 in 2021 and 222 in 2022.

When patients requested interpreter services, Spanish was used 96% of the time for phone encounters (**See Figures 7A and 7B**).

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FIGURE 7A: LANGUAGE USED WHILE APPLYING FOR A GRANT THROUGH THE HEALTHWELL FOUNDATION HOTLINE

Language Used	2021	2022
Spanish	238	190
Other Languages	32	32

FIGURE 7B: RANKING OF LANGUAGES USED WHEN PATIENTS WERE CONNECTED TO HEALTHWELL'S THIRD-PARTY LANGUAGE LINE

Language	Use of Language Line (#)	Use of Language Line (%)
Spanish	1,670	95.7%
Korean	13	0.74%
Mandarin	10	0.57%
Vietnamese	8	0.46%
Cantonese	6	0.34%
Russian	6	0.34%

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OPPORTUNITY TO LINK GRANTS TO PREVALENT DISEASES FOR RACIAL/ETHNIC MINORITIES

The value of philanthropic donations contributed to each HealthWell disease-based fund determines the total dollars available per year and the number of approved grants per fund. The average grant paid amount is determined by the actual paid awards by year.

Currently, life science companies are the largest donor source.

As we apply the CMS Framework for Health equity to copay assistance programs, expanding the number of diagnosis-based funds and increasing the total value of diagnosis-based funds using cancer prevalence for racial and ethnic minorities as the criteria will expand access for more patients and families.

To reduce healthcare disparities, disease-based funds for patient populations with the highest incidence of cancer would have the highest total grant amounts.

The 2022 total grant amount, approved number of grants and average grant amount per patient for each diagnosis-based fund were compared to new cancer cases and the National Cancer Institute (NCI) five-year survival rates for overall population. The NCI five-year survival rate is the percentage indicating the proportion of people with a particular cancer diagnosis that are likely to be alive after five years.

Besides the prostate cancer disease-based fund, the amount of funds

available do not match the diseases with the highest prevalence for all populations and specifically for Black and Hispanic men and women.

The breast cancer disease-based fund at $7.9 million is surprisingly small given that breast cancer has a 90.3% five-year survival rate and is the most prevalent cancer in women across all populations.

For Black and Hispanic women, breast cancer has a higher prevalence, but significantly greater mortality when compared to White women.

The three disease-based funds with the largest total grant value distributed in 2022 were prostate cancer at $47 million, kidney cancer at $45 million and leukemia at $27.4 million.

Only the prostate cancer disease-based fund represents the top three cancers by incidence (breast, prostate and lung) or the top five cancers with the highest five-year survival rates (thyroid, prostate, melanoma, breast and uterine).

A greater gap is illustrated when we compare diagnosis-based funds with the top-ranked cancer incidence for Black and Hispanic men and women.

For Black men, prostate, lung and colorectal cancers are the top three in terms of incidence, with only the prostate cancer fund being one of the largest disease-based funds.

Despite being the second- and third-most prevalent cancer for Black men, the lung and colorectal cancer disease-based funds were small, with lung at $4.7 million and colorectal cancer at $600,000.

There were no available funds for uterine cancer and thyroid cancer diagnosis-based funds, even though these diagnoses represented the second and third most prevalent cancers for Hispanic women.

Data representing these gaps would be useful to identify new philanthropic sources and health equity grants for oversubscribed and missing disease-based funds (**See Figure 8**).

LOOKING THROUGH A NEW LENS

Advancing health equity presents a compelling reason to look at data collection and analysis through a new lens. Given social drivers affecting cancer outcomes and program elements of copay assistance, the additional data for consideration would be race, ethnicity, preferred language, gender identity, sexual orientation, disability and education level.

Collecting data on race, ethnicity

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FIGURE 8: TOP-RANKED CANCER PREVALENCE AMONG BLACK AND NON-WHITE HISPANIC MEN AND WOMEN

Cancer Type	New Cancer Prevalence- all population	Top-ranked diagnosed cancer type- Black Men	Top-ranked diagnosed cancer type- Black Women	Top-ranked diagnosed cancer type- Hispanic Men	Top-ranked diagnosed cancer type- Hispanic Women	New Cases 2021	%	NCI 5-year Survival	2022 Total Grant	2022 Approved Grants	2022 Avg Grant
Breast	1		1		1	284,200	14.8%	90.3%	$ 7.9 M	1,764	$4,525
Prostate	2	1		1		248,530	13.1%	97.5%	$ 47 M	14,306	$3,291
Lung	3	2	2	3		235,760	12.4%	21.7%	$ 4.7 M	1,900	$2,498
Colorectal	4	3	3	2	2	149,500	7.9%	64.7%	$ .6 M	279	$2,132
Melanoma	5					106,110	5.6%	93.3%	$ 4.1 M	651	$6,371
Bladder	6					83,730	4.4%	77.1%	$ 0 M	484	$1,754
NHL	7					81,560	4.3%	73.2%	$ 0 M	0	$-
Kidney	8					76,080	4.0%	75.6%	$ 45 M	7,949	$6,054
Endometrial (uterine)	9				2	66,570	3.5%	81.1%	$ 0 M	0	$-
Leukemia (all types)	10					61,090	3.2%	65.0%	$ 27.4 M	5,767	$4,967
Pancreatic	11					60,430	3.2%	10.8%	$ 0.71 M	467	$1,522
Thyroid	12				3	44,280	2.3%	98.3%	$ 0 M	0	$-
Liver	13					42,230	2.2%	20.3%	$ 0 M	0	$-

AMERICAN CANCER SOCIETY CANCER FACTS & FIGURES 2021

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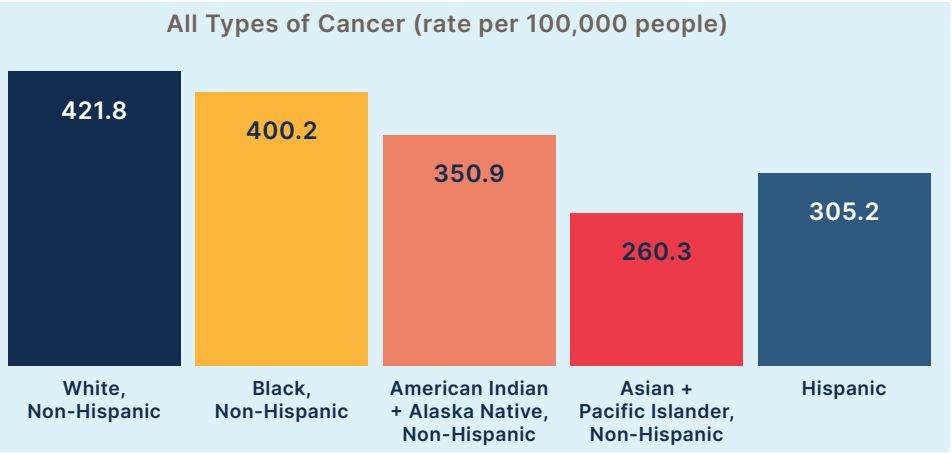
and preferred language for individuals applying for copay assistance is a crucial step to identify potential disparities and determine how to address them.

When we compare the race and ethnicity composition of the participants in the "national survey of financial burdens and experience among patients with cancer receiving charitable copay assistance" to the rate of new cancers in the U.S. by race and ethnicity, we see significant differences.

First, the national survey included a small number of total grant recipients, 1,108, when compared to the total number of patients with approved HealthWell cancer grants, more than 133,000 a year in 2021 and 2022.

Secondly, 88% of survey participants were Non-Hispanic White individuals, which is much higher than the 2020 rate per 100,000 people of new cancers for Non-Hispanic White men and women.[7] This suggests that Non-Hispanic White survey participants were disproportionately represented (**See Figure 9**).

FIGURE 9: RATE OF NEW CANCERS BY RACE AND ETHNICITY, BOTH SEXES



USCS DATA VISUALIZATIONS —CENTERS FOR DISEASE CONTROL AND PREVENTION

IMPACTS OF LOW HEALTH LITERACY

Health literacy is defined by the U.S. Department of Health & Human Services (HHS) as the degree to which individuals understand and use health related information and services.[8] Individuals who do not speak English at home, immigrants and individuals with lower levels of education are at a higher risk for having limited English language skills and low literacy.

Having limited English proficiency can be a barrier to accessing healthcare services and limited literacy is a barrier to accessing health information.

Research demonstrates that limited language skills and low literacy are associated with worse health outcomes.[9]

One in six (16%) cancer survivors report low health literacy.[10] The prevalence of low health literacy was higher among Hispanic and Black cancer survivors and among those with lower educational attainment and household income.

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Given that the impact of English proficiency and low health literacy on outcomes, the percentage of time that patients asked for a language interpreter service when using the HealthWell telephone hotline was compared with the percentage of individuals in the U.S. that speak English as their primary language. The use of the interpreter service was less than 0.5%.

In 2019, 21.6% of the U.S. population older than five years spoke a language other than English at home. This significant difference in percentages could suggest barriers to accessing copay assistance programs for non-English speaking patients.

Applying for a copay assistance grant requires patients to have a certain level of language skills and health literacy. The complexity of enrollment is mitigated when healthcare providers complete the enrollment process on behalf of patients using HealthWell's provider portal.

In 2021 and 2022, the two largest referral sources of patients to the HealthWell hotline were from pharmacists/pharmacy technicians, 30%, and providers/physicians/nurses/advocates, 24%.

Historically, HealthWell has found that patients prefer to talk through the enrollment process with a specialist via the hotline. In fact, one-third of the total grant applicants self-enrolled via the hotline.

In addition to the patient portal, HealthWell supports robust and continuously enhanced provider and pharmacy portals; increased use of the HealthWell portals by non-patient advocates like providers and pharmacies would support greater access to copay assistance with lower health literacy.

CONCLUSION

To implement best practices aligned with the CMS Framework for Health Equity, data collection for copay assistance grant applicants should include additional standardized data such as race, ethnicity, preferred language, gender identity, sexual orientation and disability status.

As we strive to ensure inclusive resources, charitable foundations will need to provide linguistically and culturally appropriate access to programs.

Future analysis needs to include a review of patients who applied for a copay assistance grant but were not eligible to identify if health disparities exist.

Establishing processes and timing for obtaining additional data will be essential to ensure that the data requests do not create unintended enrollment barriers.

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ABOUT ATLAS HEALTH AND THE HEALTHWELL FOUNDATION

Atlas Health automates patient financial assistance to improve access, affordability, outcomes and health equity for vulnerable populations. Through intelligent matching and patient-friendly digital enrollment to thousands of patient financial assistance programs, healthcare organizations can improve patient outcomes, advance health equity, reduce the total cost of care and improve the patient experience. Learn more at Atlas.Health.

The HealthWell Foundation is a leading independent nonprofit dedicated to improving access to healthcare for America's underinsured. When health insurance is not enough, we fill the gap by assisting with copays, premiums, deductibles and out-of-pocket expenses. In 2022, we awarded more than $896 million in grants through our Disease Funds, and since 2004 we have helped more than 822,000 patients afford essential treatments and medications. HealthWell is recognized as one of America's most efficient charities — 100% of every dollar donated goes directly to patient grants and services. Learn more at HealthWellfoundation.org.

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KINDRED DIVERSITY:

COMMUNICATING ACROSS ECLECTIC HEALTHCARE TEAMS TO EFFECT CHANGE

By Joni L. Watson, DNP, MBA, RN, OCN

Ineffective healthcare communication is costly — to patients, healthcare team members and myriad industry organizations.

While the literature is unclear on cumulative financial waste, a 2009 study found that miscommunication in all U.S. acute care settings alone costs $12 billion annually.[1] In simplest terms, this is like one organization losing $1 million every day for nearly 33 years.

Joni Watson

It is baffling that the U.S. healthcare industry loses so much money annually — and more when considering all non-acute care settings — due to poor communication between teams, organizations and patients.

Healthcare is a complex adaptive system characterized by dynamic, highly networked, interdependent, heterogeneous agents (e.g., team members, care delivery organizations, payors, etc.) nested within other complex adaptive systems (e.g., supply chain, government, etc.) continually experiencing external and internal tensions and pressures.

As these agents and systems interact, they develop new relationships and behaviors more than the sum of the individual agents and systems. As a result, despite our best predictive models, healthcare is unpredictable.[2-4]

It is no wonder that communicating within healthcare and across care teams is inherently difficult.

Interprofessional cancer care is highly collaborative, touching every department and discipline. Most healthcare and oncology professionals are accustomed to working simultaneously on various teams.

Formal healthcare leaders support more diverse and homogeneous teams than ever before. Gender, age, race, ethnicity, culture, professional discipline, socioeconomic background and political views are just a few diversity aspects that make up complex and evolving healthcare teams.[5] These differences are important, ensuring healthcare teams relate to and understand the diverse patient populations they serve.

Yet systems of inequity, lack of organizational psychological safety, and a natural pull toward team equilibrium in the face of ongoing differences and regular conflict can create homogeneous groups that overlook the needs of a diverse population.[4-8]

This pull toward sameness within teams can be visible, such as a team of a single gender or race, or invisible, such as a team with groupthink or trained by the same healthcare professionals.

VISIBLE DIVERSITY IS NOT ALWAYS ENOUGH

Visible team member diversity can contribute to invisible team diversity in thought and perspectives, but relying on visible team characteristics is not a foolproof way to ensure team thought diversity. The diversity of perspectives in teams include differences in clinical

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approaches, problem-solving strategies and research interests, which can lead to innovation and improved patient care. This diversity is hard to curate and maintain within organizations because diversity creates conflicting perspectives.[3-8]

Most leaders have been trained to eliminate conflict as it is uncomfortable. However, modern, adaptive leadership knowledge and techniques continuously work within the conflict, recognizing it as a transformative space to find win-win solutions via "both/and" thinking rather than single perspectives.[4,9]

This is easier said than done, though, as any leader facing the daily onslaught of healthcare industry pressures and team member personalities can attest.

With intention, leaders can communicate well in and across eclectic teams by understanding team composition, avoiding stereotyping and reframing differences, leveraging team diversity by fostering an inclusive and psychologically safe work environment and focusing on continual communication training.

UNDERSTAND TEAM COMPOSITION

With five generations in today's workforce, more than 250 distinct healthcare professions within the industry[5,10] and America's beautiful melting pot population, teams formally and informally develop into unique amalgams. As team members join or leave teams, the team dynamics change, further reinforcing teams as complex and often unpredictable systems.[5]

The first step in understanding anything is to assess or identify. While it may sound simple, many leaders do not take the time to honestly know and understand team members — their strengths, opportunities, passions, educational and experiential backgrounds, hobbies and more. Healthcare prides itself on holistic care, yet we often overlook holistic relationships in work, missing critical pieces of people's lives that can contribute to workplace transformation.

For example, a colleague who is a master gardener may be a prime representative to serve on a healthcare greening initiative. Or a team member's previous non-healthcare career experience could provide a completely different perspective on a new issue. Or a brand-new colleague graduate team member may indicate a strong pulse on a current trend's evidence.

Only through identifying the differences in the team can the leader, organization, and team truly appreciate the diversity and acknowledge potential friction and transformation points.[5]

AVOID STEREOTYPING, REFRAME DIFFERENCES

Whether acknowledged or not, every person has biases often created and perpetuated through erroneous information and biased feedback loops that impact decision-making. Categorizing and stereotyping individuals — leading to avoiding or outing people — is an easy trap, especially when individuals do not take the time to develop sincere relationships.

Many people feel it is easier to be in a community with like-minded people with the same habits and preferences. Generational differences often fall into this trap, and people quickly stereotype individuals within generations in today's fast-paced work environment.

For example, many people categorize Baby Boomers (born 1946-1964) as driven, resistant to change and technology-naive, while others might stereotype Millennials (born 1981-1996) as lazy, tech-savvy self-prioritizers. However, organizational behavior evidence indicates that people — even across generations — are far more alike in work behaviors and desires than they are different.[11-14]

As an evidence-based industry, we must remember this to avoid pigeonholing team members based on their differences. Rather than viewing differences with others as liabilities, view them as opportunities and assets as teams can see things from multiple perspectives.[5]

FOSTER AN INCLUSIVE WORK ENVIRONMENT

Encourage an environment where everyone acknowledges and respects individuals' strengths and preferences. Organizations and leaders can achieve this through open communication, team-building activities, diversity trainings and celebrations.[5]

The adage "Trust is gained in drops and lost in buckets" is true in fostering psychologically safe environments and teams. Leaders shape organizational culture with every decision and conversation.

When an organization or group has mutual trust and understanding, and all team members know they can speak up and share their perspectives and feedback — without fear of punishment, condescension, or other repercussions — they can offer rich dialogue to propel work and care forward.

Teams with both high conflict and high relational affinity outperform other groups as they have a deeper understanding and appreciation of each other's viewpoints, seeing these differing perspectives as curiosity leading to innovation, or contributing to problem-solving rather than creating problems.[4-6]

CONTINUAL COMMUNICATION TRAINING

Diverse healthcare teams have myriad communication styles. Healthcare has more than 250 distinct professional disciplines[10] and just as many non-licensed healthcare team member departments. In an ironic twist, almost every group received different communication training.

For example, physicians often receive succinct communication training while nurses learn a narrative communication structure and style, and pharmacists can learn a blend of these styles based on the training location and care setting.[15-16]

Looking at only three disciplines — who work arm-in-arm in work and care — it is easy to see these communication styles may combine for frustrating conversations with high-risk outcomes, especially in oncology care.

Add in body language, attitude, tone,

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differences in communication format (e.g., written and verbal), and both synchronous and a barrage of asynchronous communication platforms, "communication" begins to look more complex than we often view it in daily work.

Communication is a skill. Contrary to popular belief, communication does not get better with experience. Difficult conversations do not improve simply by walking away from them. Communication reliably improves through training — and lots of it.[5-15] It is a cumulative skill, and there are evidence-based communication training techniques such as reverse and reciprocal mentoring, team goal-setting, formal educational courses, coaching, simulations, reflective journaling and debriefs.[5]

Communication is the root of numerous problems, including many quality and safety issues that lead to poor patient outcomes and significant financial waste.[1] People and teams are complex. As long as team members are in the workplace, communication is an area for focus and development.

In conclusion, diversity in healthcare teams encompasses demographic, professional, cultural and cognitive dimensions, contributing to more effective, patient-centered care and a more comprehensive understanding of the healthcare landscape. The key to harnessing team and organizational diversity lies in effective communication.

By understanding and respecting differences, continually enhancing communication styles and techniques, and fostering an inclusive and psychologically safe culture, healthcare organizations can create vibrant, dynamic, and productive work environments.

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NEW SEASON

THE PQI PODCAST

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

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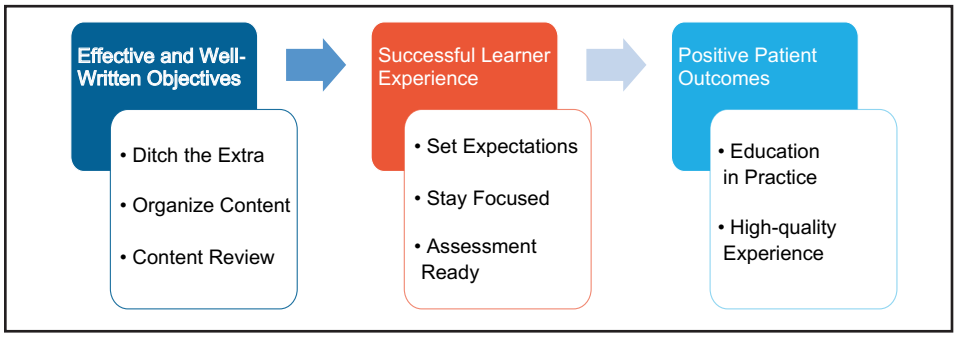
EFFECTIVE LEARNING OBJECTIVES LEAD TO POSITIVE PATIENT OUTCOMES

By Brian Sturgeon, MEd



Creating well-written learning objectives that translate to clinical practice can be a challenging task for anyone.

Taking the time to develop clear objectives that set expectations for learners will provide the foundation for high-quality learning experiences, such as presentations and continuing education (CE), which can help healthcare providers deliver a higher level of patient care.


Brian Sturgeon

When learners are aware of the intended results from participating in a learning experience, they are more likely to be engaged with the presented content and retain the information.

This article will outline the process of creating effective learning objectives, paving the way for an impactful learning experience that will ultimately lead to Positive Patient Outcomes.

EFFECTIVE AND WELL-WRITTEN OBJECTIVES

Learning objectives are the foundation of effective instruction. They should drive all content and assessment development decisions for any type of learning experience.

After writing the learning objectives, identify the key content needed to achieve them. Continuously reviewing the learning objectives throughout the entire development process will result in learning experiences that are more effective and engaging for learners.[1]

DITCH THE EXTRA: Clearly identifying the specific skills or knowledge learners should acquire during the presentation can eliminate content that is nonessential to achieving the objectives. "Ditching the Extra" ensures that learning experiences are focused and time-efficient.

▲ **ACTION:** Use your objectives to stay focused on key content and remove nonessential content that may waste precious presentation time.

ORGANIZATION CONTENT: Learning objectives help organize content in a clear and logical order. They provide a framework for arranging content. When learning objectives are used to outline the presentation, learners can better understand and follow along with the content. Objectives should aid in the development of the content outline, not the other way around.[2]

▲ **ACTION:** Place learning objectives in the same order you will present them to learners. This will help learners use the objectives as an outline and track progress as you move through content.

CONTENT REVIEW: Objectives should guide a comprehensive review of all presentations and materials. Remember that objectives are flexible, and rewriting them can decrease the chance of significant gaps in content or uncovered objectives. If the review cannot identify the content for a particular objective, additional content may be needed, or the objective may need to be removed/rewritten.

By using objectives to guide the review process, only the most essential material will make its way into the presentation, which will help ensure that the content is accurate and relevant.

▲ **ACTION:** Ask your content reviewer to use the learning objectives to drive their review and ensure all content falls under at least one of the objectives. The results may require you to "Ditch the Extra" and remove/rewrite some of your objectives.

SUCCESSFUL LEARNER EXPERIENCE

Well-crafted learning objectives not only help create an outline of the content for the presenter, but also create a roadmap to success for learners, helping them stay engaged and motivated, and providing a sense of accomplishment. A successful and positive learning experience for your learners starts when they understand what they will achieve by the end of the presentation.[3]

SET EXPECTATIONS: Learning objectives should be clearly written in a way so learners know what they can expect to achieve by the end of the presentation, ensuring they are not disappointed or frustrated from not receiving the promised information. Learners should be able to read the objectives beforehand, make the decision to attend, and know they will be taking away a new skill that will contribute to their professional goals and present to their patients or colleagues.

CONTINUED ON NEXT PAGE

LEARNING OBJECTIVES

CONTINUED FROM PREVIOUS PAGE

▲ **ACTION:** Reflect on where your learners are now and the knowledge they possess before attending your presentation. Write your objectives using language that will be understood BEFORE attending the experience. Learners should not need to complete the learning experience to be able to understand what the objectives are stating.

STAY FOCUSED: Reviewing objectives with learners will guide the learning process by keeping them focused during a learning experience. When learners know what they are expected to learn, they are more likely to pay attention and engage with the material. Learning objectives can empower learners to self-assess their progress and identify areas needing additional support.

▲ **ACTION:** Take a few extra moments to review the objectives with learners at the start of your presentation. Don't just simply read them word for word off the side. Giving them a true overview of what you will achieve together will help your learners stay focused and engaged till the very end.

ASSESSMENT READY: Help learners be successful in retaining the presented information and understand how they will be assessed. If your content is for CE credit, make sure that all questions from your assessment fall under at least one of your objectives and distribute questions evenly across all objectives. Using objectives to create assessment questions will help ensure learners are not caught off guard and have a more positive experience.

▲ **ACTION:** If your learning experience requires some form of assessment, strive to have an equal distribution of questions from all objectives and provide learners with adequate time to ask for clarification before the final assessment.

POSITIVE PATIENT OUTCOMES

Overall, skillfully written objectives contribute to enhanced experiences for learners and patients. By helping learners develop the knowledge and skills they need to be successful, good learning objectives can lead to better-prepared, more confident, and more satisfied learners. Ultimately, improving patient experiences and health outcomes when these skills are put into practice.

EDUCATION IN PRACTICE: When learners have completed a learning experience and feel they have mastered the learning objectives, they will put their newly acquired skills into practice. On the contrary, when learners are not confident they have mastered the content, they are less likely to put new skills into practice or share what they have learned with colleagues.

Investing the time to develop learning objectives will create a more effective and efficient environment. This investment will pay off in the long run by producing positive educational outcomes that may improve the quality of care.

▲ **ACTION:** During the conclusion of your presentation, tell your learners where to start. Provide them with that first step and tell them how to get started tomorrow! Give them something to take with them out the door or provide a list of resources on where to find more information.

HIGH-QUALITY EXPERIENCE: While many things go into making an excellent presentation, it all starts with high-quality learning objectives. When learners have a positive experience from a learning activity, they are more likely to come back in the future because they will undoubtedly learn valuable skills and knowledge to improve their practice and provide better care for their patients.[3]

A high-quality learning experience does more than list facts on a screen for a learner to memorize. It conveys information and critical thinking that allow learners to apply their newly acquired knowledge, so they are better equipped to make sound decisions about patient care.

▲ **ACTION:** Ask for feedback and take it to heart. Asking simple questions in a post-survey such as "Did you enjoy the presentation?" will not help you better the content. Ask thought-provoking questions that can lead to improvement in the future. Did you receive the information you expected? How likely are you to put this information into practice? Is there any information on this topic you think should have been discussed but was not?

OBJECTIVE WRITING TIPS

1 **REFLECT ON YOUR END GOAL:** Before you even begin the objective writing process, reflect on how your learners and their patients will be affected by your learning experience.

Next, take a moment to write down some open-ended questions to give yourself a sense of your final vision. Some example questions are:

- *What new skills or concepts will my learners take away from this learning experience?*
- *How will these skills and concepts positively affect patients?*
- *If my learners only take away one thing, what do I want it to be?*
- *What should my learners know before and after my presentation, and how will I close this gap in knowledge?*

2 **USE THE "ABCD METHOD" FOR OBJECTIVE WRITING**: This simple technique will help you construct clear and concise learning objectives.[4]

- **Audience:** Who is the target audience? Pharmacists? Pharmacy technicians? Reference your audience.
- **Behavior:** What is the action your learners should be able to perform at the end of your presentation? Take a page from Benjamin Bloom's Bloom's Taxonomy (e.g., "Pharmacists will be able to determine ... ").
- **Condition:** What are the conditions or constraints in which the learners will be expected to perform the tasks (e.g., By the end of the presentation)?
- **Degree:** How will the behavior be performed (e.g., the differences in adverse event profiles for the CDK4/6 inhibitors currently approved by the FDA)?

Once all four parts of the objective have been identified, put them together to create a new concise objective:

CONTINUED ON NEXT PAGE

LEARNING OBJECTIVES

CONTINUED FROM PREVIOUS PAGE

"By the end of the presentation, pharmacists will be able to determine the differences in adverse event profiles for FDA-approved CDK4/6 inhibitors."

3 **SET REALISTIC EXPECTATIONS:** Do not overpromise and underdeliver. A learning objective describes what learners should be able to do upon completing the educational activity. Sometimes, you only have an hour when you would love to have three. You might not change the world in an hour, but you can get started.

The objective "Create workflow processes to improve patient monitoring" may be unsuitable for an hour-long presentation. Will your learners truly create a workflow process in their time with you? A better alternative might be "Review workflow strategies that help improve patient monitoring."

WHERE TO GET STARTED

Just as in presentations, articles can provide learners with some information on how they can get started today. Here are a few ways you can start writing more effective outcomes today.

ACTION ITEMS: This article provided eight Action items that can help improve your next presentation. Some of which you may already do. Do not get overwhelmed by trying to incorporate these all at once. Start small and continue to improve over time.

▲ Identify two to three action items that will be easiest for you to implement right away.

▲ Integrate these action items into your next presentation.

▲ After a successful presentation, implement another action.

REVIEW OBJECTIVES OF PAST PRESENTATIONS: Reflect on past presentations and analyze the effectiveness of your learning objectives.
Consider the following questions:

▲ Did your objectives utilize appropriate Bloom's Taxonomy verbs?

Writing effective learning objectives is the first step in a trickle-down effect that leads to high-quality care for patients.

▲ Did you provide adequate resources for learners to "Get Started" after the presentation? If not, what could you have provided?

▲ Did your objectives provide a clear roadmap for learners?

How can you further refine these objectives for future presentations?

NCODA RESOURCES

Explore the NCODA University Program Overview tab for several for several resources that will help you become an objective writing master and learn more about other learning strategies.

Resources include:

▲ **Objective Writing Crash Course:** This interactive course provides a comprehensive overview of objective writing principles and best practices outlined in this article.

▲ **Articles:** Review this and future articles offering practical tips and insights on effective learning strategies.

▲ **ABCD Worksheet**: Utilize this valuable tool to structure and refine your learning objectives.

▲ **Bloom's Taxonomy Graphic**: This visual guide provides a clear and concise reference for Bloom's Taxonomy verbs and their corresponding classification.

CONCLUSION

Learning objectives are the foundation of effective instruction. They should be the first step in creating any learning experience and drive all content and assessment development decisions.

Well-crafted learning objectives will provide a clear roadmap for both learners and presenters, ensuring that everyone is on the same page about what needs to be learned and how it will be assessed.

After writing objectives for your learning experience, identify the key content needed to achieve them. Continuously reviewing the learning objectives throughout the entire development process will result in learning experiences that are more effective and engaging for learners.

Remember that learning objectives are not set in stone. If you are struggling to find the content that will fulfill the objectives, rewire them to meet the needs of your learners and presentation.

Writing effective learning objectives is the first step in a trickle-down effect that leads to high-quality care for patients.

By helping learners develop the knowledge and skills they need to be successful, good learning objectives can lead to better-prepared, more confident, and more satisfied learners.

These learning experiences make a real difference in the lives of learners who put this information into practice for their patients.

▲ **Brian Sturgeon**, MEd, is Associate Manager of Instructional Design at NCODA in Indianapolis, Indiana.

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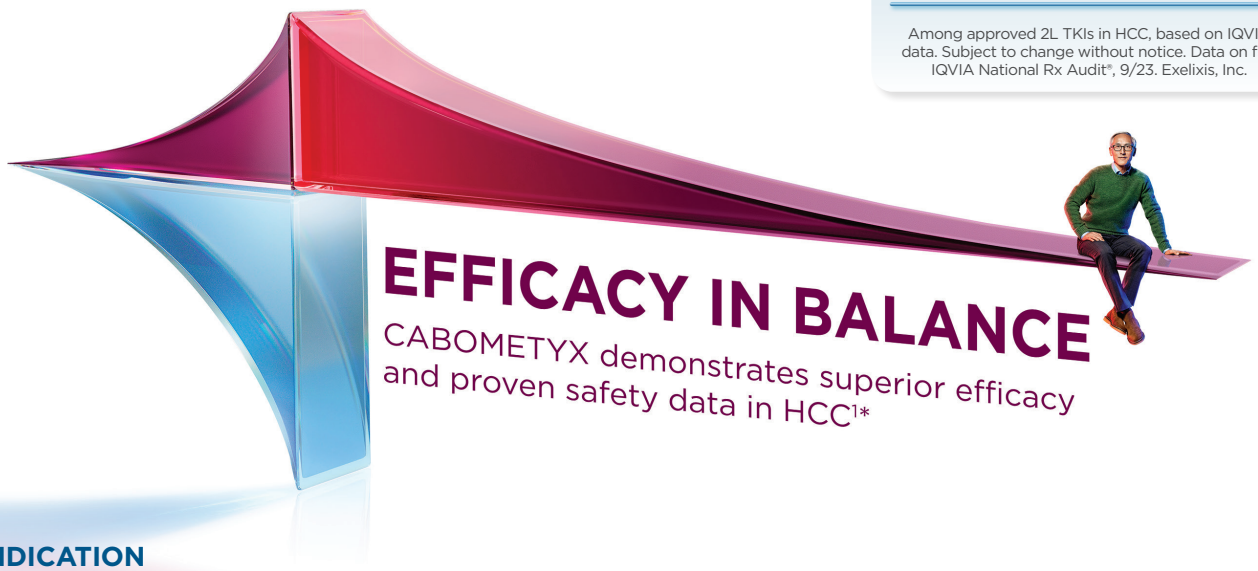
HCC

#1 TKI
PRESCRIBED IN 2L HCC

Among approved 2L TKIs in HCC, based on IQVIA data. Subject to change without notice. Data on file. IQVIA National Rx Audit®, 9/23. Exelixis, Inc.



EFFICACY IN BALANCE

CABOMETYX demonstrates superior efficacy and proven safety data in HCC[1]*

INDICATION

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

*CABOMETYX vs placebo in post–sorafenib-treated patients.[1]

Primary endpoint median OS results: 10.2 months (n=470) vs 8.0 months (n=237); HR=0.76 (95% CI: 0.63-0.92; *P*=0.0049). Secondary endpoint median PFS results: 5.2 months (n=470) vs 1.9 months (n=237); HR=0.44 (95% CI: 0.36-0.52; *P*<0.0001).[1]

2L=second-line; CI=confidence interval; HR=hazard ratio; ITT=intent to treat; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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.

Please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.

OS and PFS results

Superior OS and PFS in the treatment of 2L HCC[1]

- **Primary endpoint:** Median OS was 10.2 months with CABOMETYX (n=470) vs 8.0 months with placebo (n=237) in the ITT population of patients who received at least one prior therapy (HR=0.76; 95% CI: 0.63-0.92; *P*=0.0049)
- **Secondary endpoint:** Median PFS was 5.2 months with CABOMETYX (n=470) vs 1.9 months with placebo (n=237) in the ITT population of patients who received at least one prior therapy (HR=0.44; 95% CI: 0.36-0.52; *P*<0.0001)

In a prespecified exploratory subgroup analysis of patients who received only one prior systemic therapy

CABOMETYX exceeded 11 months median OS and 5 months median PFS in the second-line[2-4]

Subgroup analysis: Median OS (second-line)[2,3†]

11.4 MONTHS CABOMETYX (n=335) vs **7.7** MONTHS placebo (n=174)

26% reduction in risk

HR=0.74 (95% CI: 0.59-0.92)

Subgroup analysis: Median PFS (second-line)[2,4†]

5.5 MONTHS CABOMETYX (n=335) vs **1.9** MONTHS placebo (n=174)

57% reduction in risk

HR=0.43 (95% CI: 0.35-0.52)

†No statistical procedure was employed for controlling type 1 error. Results should be considered hypothesis generating.[2]

CELESTIAL STUDY DESIGN: CELESTIAL was a randomized (2:1), double-blind, phase 3 trial of CABOMETYX vs placebo in 707 HCC patients (Child-Pugh A). All patients received prior sorafenib and 27% of patients received more than one prior systemic regimen. The starting dose for CABOMETYX was 60 mg, administered orally once daily.[1,2]

The only phase 3 trial of a TKI in HCC that enrolled patients previously treated with VEGF inhibitors (707/707) and immune checkpoint inhibitors (17/707)[2,5]

NCCN CATEGORY 1 RECOMMENDATION[6]

National Comprehensive Cancer Network® (NCCN®)

Cabozantinib (CABOMETYX) is recommended as a Category 1 subsequent-line treatment option for HCC[‡]

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. NCCN Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

‡**For certain patients with Child-Pugh Class A liver function only, following disease progression on first-line systemic treatment.**

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, and constipation.

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.

Discover more at **CABOMETYXHCP.COM/HCC**

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc. **2.** Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54-63. **3.** Data on file. Overall survival; Presented at: ASCO Gastrointestinal Cancers Symposium; January 18-20, 2018; San Francisco, CA. Exelixis, Inc. **4.** Data on file. Progression-free survival. Presented at: ASCO Gastrointestinal Cancers Symposium; January 18-20, 2018; San Francisco, CA. Exelixis, Inc. **5.** Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma [supplementary appendix]. *N Engl J Med*. 2018;379(1):54-63. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatocellular Carcinoma V.2.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed January 24, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org.

CABOMETYX® (cabozantinib) tablets

60 mg | 40 mg | 20 mg

CABOMETYX® (cabozantinib) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

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

1 INDICATIONS AND USAGE

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

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

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

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Renal Cell Carcinoma

METEOR

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

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

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

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

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

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

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

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

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

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

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

CABOSUN

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

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

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

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

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

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

CHECKMATE-9ER

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

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

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

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

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

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

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

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

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

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

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

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

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

[h] Includes primary hypothyroidism.

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

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis

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

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

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

Hepatocellular Carcinoma

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

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

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

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

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

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

[2] NCI CTCAE Version 4.0

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

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

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

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

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

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

Differentiated Thyroid Cancer

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

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

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

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

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

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

[2] NCI CTCAE Version 5.0

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

[4] Includes the following terms: fatigue, asthenia

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

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

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

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

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

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

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CABOMETYX

Strong CYP3A4 Inhibitors

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

Strong CYP3A Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

Infertility

Females and Males

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

8.4 Pediatric Use

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

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

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

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

Juvenile Animal Toxicity Data

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

8.5 Geriatric Use

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

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Embryo-fetal toxicity:

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

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

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

Important administration information

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

This brief summary is based on the CABOMETYX Prescribing Information

Revision 10/2023

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FOOD AND DRUG ADMINISTRATION ANNOUNCES THE APPROVAL OF 15 NEW ORAL ONCOLYTICS


Derek Gyori


Kirollos Hanna

By Derek Gyori, PharmD, BCOP, & Kirollos Hanna, PharmD, BCPS, BCOP

The U.S. Food and Drug Administration (FDA) approved 15 oral oncology agents from Q4 2023 through Q1 2024 through February 16. In the chart below and on the following five pages, the asterisk (*) represents a new indication for a previously approved therapy.

Further information can be found on the FDA website and/or in the medication-specific prescribing information.

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Bosutinib (BOSULIF®)[1-3]	9/26/2023*	• **Newly Diagnosed Pediatric CML:** 300mg/m2 orally once daily • **Resistant or Intolerant Pediatric CML:** 400 mg/m2 orally once daily	**BCHILD** Multicenter, nonrandomized, open label study **Newly Diagnosed** • n=21 • MCyR: 76.2% (95% CI: 52.8-91.8) • CcyR: 71.4% (95% CI: 47.8-88.7) • MMR: 28.6% (95% CI: 11.3-52.3) **Resistant or Intolerant** • n=21 • MCyR: 82.1% (95% CI: 63.1-93.9) • CcyR: 78.6% (95% CI: 59, 91.7) • MMR: 50% (95% CI: 30.6-69.4)	• **≥20%:** diarrhea, abdominal pain, vomiting, nausea, rash, fatigue, hepatic dysfunction, headache, pyrexia, decreased appetite and constipation • **Lab Abnormalities ≥45%:** increased creatinine, increased alanine aminotransferase or aspartate aminotransferase, decreased white blood cell count and decreased platelet count	• Approval is for patients 1 year and older • Take with food • In pediatric trials, 55% of patients had nausea or vomiting; fluid replacement and antiemetics should be utilized for management • Available as 50mg and 100mg capsules and 100mg, 400mg and 500mg tablets • Capsules can be opened and mixed into applesauce or yogurt
Encorafenib (BRAFTOVI®) & **Binimetinib** (MEKTOVI®)[1 4-6]	10/11/2023*	• **Metastatic NSCLC with BRAF V600 E mutation:** Encorafenib 450mg orally once daily and Binimetinib 45mg orally twice daily	**PHAROS** Open-label, multicenter, single-arm study **Treatment-Naïve** • n=59 • ORR: 5% (95% CI: 62-85) • DoR: not estimable (NE) (95% CI: 23.1-NE) **Previously Treated** • n=39 • ORR: 46% (95% CI: 30-63) • DoR: 16.7 months (95% CI: 7.4, NE)	• **≥25%:** fatigue, nausea, diarrhea, musculoskeletal pain, vomiting, abdominal pain, visual impairment, constipation, dyspnea, rash and cough	• Encorafenib can be taken with or without food • Encorafenib is available as 75mg capsules • Correct hypokalemia and hypomagnesemia prior to treatment initiation • Binimetinib can be taken with or without food • Binimetinib is associated with moderate/high emetic potential • Binimetinib is available as 15mg tablets

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Entrectinib (ROZLYTREK®)[1,7-8]	10/20/2023*	• **Pediatric patients older than one month with solid tumors with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation:** Dosing for pediatric patients is dependent on age and BSA *Refer to package insert for dosing instructions*	**STARTRK-NG or TAPISTRY** Multicenter, single-arm clinical trials • n=33 • ORR: 70% (95% CI: 51- 84) • DoR: 25.4 months (95% CI: 14.3-NE) *Most common cancers were primary central nervous system tumors and infantile fibrosarcoma	**≥ 20%:** Pyrexia, constipation, increased weight, vomiting, diarrhea, nausea, cough, fatigue, pain in extremity, skeletal fracture, decreased appetite, headache, abdominal pain, urinary tract infection, upper respiratory tract infection and nasal congestion	• Administer with or without food • Available as 100mg and 200mg capsules; 50mg packets
Ivosidenib (TIBSOVO®)[1,9-10]	10/24/2023*	• **Relapsed or refractory MDS with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation:** 500mg once daily; continue until disease progression or unacceptable toxicity	**AG120-C-001** Open-label, single-arm, multicenter trial • n=18 • CR Rate: 38.9% (95% CI: 17.3-64.3) • CR Duration: NE (Range 1.9-80.8+ months) 6 (67%) of 9 patients who were transfusion-dependent became RBC and platelet transfusion-independent during any 56-day post-baseline period	• **Most common:** diarrhea, constipation, mucositis, and nausea, arthralgia, fatigue, cough, myalgia and rash • May cause QTc prolongation	• BBW: Differentiation Syndrome • Administer at same time each day, w/wo food (do not administer with high-fat meal) • Available as 250mg tablets In patients without disease progression or unacceptable toxicity, continue for a minimum of six months to allow time for clinical response
Fruquintinib (FRUZAQLA®)[1,11-13]	11/8/2023	• **Refractory metastatic colorectal cancer:** 5mg once daily on days 1 to 21 of each 28-day cycle; continue until disease progression or unacceptable toxicity	**FRESCO-2** International, multicenter, randomized, double-blind, placebo-controlled trial • N=691 • Median OS: fruquintinib 7.4 months (95% CI: 6.7-8.2) vs placebo 4.8 months (95% CI: 4.0-5.8) (HR 0.66 [95% CI: 0.55-0.80] p-value < 0.001) **FRESCO** Multicenter, placebo-controlled trial conducted in China • N=416 • Median OS: fruquintinib 9.3 months (95% CI: 8.2-10.5) vs placebo 6.6 months (95% CI: 5.9-8.1)	**≥20%:** hypertension, palmar-plantar erythrodysesthesia, proteinuria, dysphonia, abdominal pain, diarrhea and asthenia	• Administer with or without food at approximately the same time each day • Available as 1mg and 5 mg capsules • Do not initiate unless BP is adequately controlled • Temporarily withhold for ≥2 weeks prior to major surgery; do not resume for ≥2 weeks after major surgery and until adequate wound healing has occurred

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Repotrectinib (AUGTYRO™)[1,14-15]	11/15/2023	• **Locally advanced or metastatic ROS-1 Positive NSCLC:** 160mg once daily for 14 days, then increase dose to 160mg twice daily; continue until disease progression or unacceptable toxicity	**TRIDENT-1** Global, multicenter, single-arm, open-label, multi-cohort clinical trial • n= 71 ROS1 TKI-naïve patients • ORR: 79% (95% CI: 68-88) • DoR: 4.1 months (95% CI: 25.6-NE) • n=56 who received prior ROS1 TKI therapy • ORR: 38% (95% CI: 25-52) • DoR: 14.8 months (95% CI: 7.6-NE)	**>20%:** dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, ataxia, fatigue, cognitive disorders and muscular weakness	• Administer with or without food at approximately the same time each day • Available as 40mg capsules • Patients are at risk for experiencing CNS toxicity while being treated with repotrectinib (ataxia, cognitive disorders, dizziness, mood disorders and sleep disturbances)
Capivasertib (Truqap™)[1,16-17]	11/16/2023	• **HR+ HER2- locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations:** 400mg twice daily for four consecutive days, followed by three days off (administer capivasertib on days 1 to 4 of each week) in combination with fulvestrant; continue until disease progression or unacceptable toxicity	**CAPItello-291** Randomized, double-blind, placebo-controlled, multicenter trial **Tumors with PIK3CA/AKT1/PTEN-alterations** • n=289 • mPFS: 7.3 months (95% CI: 5.5-9.0) in the capivasertib-fulvestrant group vs. 3.1 months (95% CI: 2.0-3.7) in the placebo-fulvestrant group • (HR 0.50 [95% CI: 0.38, 0.65] p-value< 0.0001)	**≥20%:** diarrhea, cutaneous adverse reactions, increased random glucose, decreased lymphocytes, decreased hemoglobin, increased fasting glucose, nausea, fatigue, decreased leukocytes, increased triglycerides, decreased neutrophils, increased creatinine, vomiting and stomatitis	• Administer with or without food, approximately every 12 hours on scheduled days • Available as 160mg and 200mg tablets • For pre- and peri-menopausal patients, also administer a luteinizing hormone-releasing hormone (LHRH) agonist; may consider administering an LHRH agonist for males
Enzalutamide (XTANDI®)[1,18-19]	11/17/2023*	• **Non-metastatic castration-sensitive prostate cancer with biochemical recurrence:** 160mg daily; continue until disease progression or unacceptable toxicity	**EMBARK** Randomized, controlled clinical trial **MFS Enzalutamide plus Leuprolide**: • (HR 0.42; 95% CI: 0.30-0.61; p-value<0.0001) **MFS Enzalutamide monotherapy:** • (HR 0.63; 95% CI: 0.46-0.87; p-value = 0.0049) **OS data was immature at time of MFS analysis*	• **Enzalutamide plus leuprolide ≥ 20%:** hot flush, musculoskeletal pain, fatigue, fall and hemorrhage • **Enzalutamide monotherapy ≥ 20%:** fatigue, gynecomastia, musculoskeletal pain, breast tenderness, hot flush and hemorrhage	• Administer at the same time each day, either with or without food • Available as 40mg capsules or 40mg and 80mg tablets

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Nirogacestat (OGSIVEO™)[1,20-21]	11/27/2023	• **Desmoid Tumor:** 150mg administered orally twice daily until disease progression or unacceptable toxicity	**DeFi** International, multicenter, randomized, double-blind, placebo-controlled trial • N= 142 • PFS: NR in the nirogacestat arm vs. 15.1 months (95% CI: 8.4-NR) in the placebo arm • (HR 0.31 [95% CI: 0.15-0.55] p-value=<0.001) • ORR: 41% (95% CI: 29.8-53.8) in the nirogacestat arm vs 8% (95% CI: 3.1-17.3) in the placebo arm (p=<0.001)	**Most common:** diarrhea, ovarian toxicity, rash, nausea, fatigue, stomatitis, headache, abdominal pain, cough, alopecia, upper respiratory tract infection and dyspnea	• Administer with or without food • Available as 50mg tablets • Severe electrolyte abnormalities including hypophosphatemia and hypokalemia may occur • Diarrhea, including severe cases can occur (median onset nine-day [range: 2-434 days])
Pirtobrutinib (Jaypirca®)[1, 22-23]	12/1/2023*	• **CLL/SLL:** 200mg orally once daily until disease progression or unacceptable toxicity	**BRUIN** Open-label, international, single-arm, multicohort trial • N=317 • ORR: 73.3% (95% CI: 67.3-78.7) • PFS: 19.6 months (95% CI: 16.9-22.1) • DoR: 16.5 months (range: 0.2 - 39.9)	**≥ 20%:** fatigue, bruising, cough, musculoskeletal pain, COVID-19, diarrhea, pneumonia, abdominal pain, dyspnea, hemorrhage, edema, nausea, pyrexia and headache **Grade 3 or 4 laboratory abnormalities > 10%:** decreased neutrophil counts, anemia and decreased platelet counts **Serious infections occurred** in 32% of patients, including fatal infections in 10% of patients	• Administer with or without food at approximately the same time each day • Available as 50mg and 100mg tablets • Consider the benefit versus risks of withholding pirtobrutinib for three to seven days prior to and after surgery (depending upon the type of surgery and risk of bleeding) • Consider prophylaxis (including vaccinations and antimicrobial prophylaxis) in patients who are at increased risk for infections, including opportunistic infections
Eflornithine (IWILFIN™)[1,24-25]	12/13/2023	• **Adult and Pediatric High-Risk Neuroblastoma:** Dosing is based on BSA • BSA> 1.5 m2: 768mg twice daily • 0.75 to 1.5 m2: 576mg twice daily • Continue until disease recurrence, unacceptable toxicity, or a maximum of two years	**Study ANBL0032** Multi-center, open label, non-randomized trial with two cohorts **Study 3b Cohort** • N=105 • EFS: HR 0.48 (95% CI: 0.27-0.85) • OS: HR 0.32 (95% CI: 0.15-0.70)	**≥5%:** otitis media, diarrhea, cough, sinusitis, pneumonia, upper respiratory tract infection, conjunctivitis, vomiting, pyrexia, allergic rhinitis, decreased neutrophils, increased ALT, increased AST, hearing loss, skin infection and urinary tract infection	• Administer with or without food • Available as 192mg tablets • Recalculate the BSA dose every three months during treatment

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Belzutifan (WELIREG™)[1,26-27]	12/14/2023*	• **Advanced Renal Cell Carcinoma:** 120mg once daily; continue until disease progression or unacceptable toxicity	**LITESPARK-005** Open-label, randomized, head-to-head trial • N=746 • PFS: 5.6 months (95% CI: 3.9-7.0) in the belzutifan arm vs. 5.6 months (95% CI: 4.8-5.8) in the everolimus arm • HR 0.75 [(95% CI: 0.63, 0.90); 1-sided p-value=0.0008] • OS: Immature at analysis	• **≥25%:** decreased hemoglobin, fatigue, musculoskeletal pain, increased creatinine, decreased lymphocytes, increased alanine aminotransferase, decreased sodium, increased potassium and increased aspartate aminotransferase	• Administer at the same time each day, with or without food • Available as 40mg tablets • Exposure to belzutifan during pregnancy can cause embryo-fetal harm; verify pregnancy status prior to initiation
Erdafitinib (BALVERSA®)[1,28-29]	1/18/2024	• **Locally advanced or metastatic urothelial carcinoma:** 8mg once daily; assess serum phosphate after 14 to 21 days, if serum phosphate is <9 mg/dL (and no ocular disorders or ≥ grade 2 toxicity), increase dose to 9mg once daily based on tolerability; continue until disease progression or unacceptable toxicity occurs	**Study BLC3001 Cohort 1** Randomized, open-label • N=266 • OS: 2.1 months (95% CI: 10.3-16.4) for erdafitinib vs 7.8 months (95% CI: 6.5, 11.1) for chemotherapy (HR 0.64 [95% CI: 0.47, 0.88]; p-value=0.005) • PFS: 5.6 months (95% CI: 4.4-5.7) for erdafitinib and 2.7 months (95% CI: 1.8-3.7) for chemotherapy (HR 0.58 [95% CI: 0.44, 0.78]; p-value=0.0002) • ORR: 35.3% (95% CI: 27.3-43.9) for erdafitinib and 8.5% (95% CI: 4.3-14.6) for chemotherapy (p-value<0.001)	• **>20%:** increased phosphate, nail disorders, diarrhea, stomatitis, increased alkaline phosphatase, decreased hemoglobin, increased alanine aminotransferase, increased aspartate aminotransferase, decreased sodium, increased creatinine, dry mouth, decreased phosphate, palmar-plantar erythrodysesthesia syndrome, dysgeusia, fatigue, dry skin, constipation, decreased appetite, increased calcium, alopecia, dry eye, increased potassium and decreased weight	• Administer with or without food • Available as 3mg, 4mg and 5mg tablets • Restrict phosphate intake to 600mg to 800mg daily. Avoid concomitant use with agents that may alter serum phosphate levels before the initial (days 14 to 21) dose increase period • Patients should receive dry eye prophylaxis with ocular demulcents as needed
Tepotinib (TEPMETKO®)[1,30-31]	2/15/2024	• **Metastatic non–small cell lung cancer with MET exon 14 skipping mutation:** 450mg once daily; continue until disease progression or unacceptable toxicity	**VISION** Multicenter, non-randomized, open-label, multicohort study **Treatment-Naïve** • n=164 • ORR: 57% (95% CI: 49- 65) with 40% of responders having a DOR ≥12 months **Previously Treated** • N=149 • ORR: 45% (95% CI: 37-53) with 36% of responders having a DOR	• **≥20%:** edema, nausea, fatigue, musculoskeletal pain, diarrhea, dyspnea, decreased appetite and rash	• Administer with food at approximately the same time each day • Available as 225mg tablets

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Osimertinib (TAGRISSO®)[1,32-33]	2/16/2024*	• **Locally advanced or metastatic non-small cell lung cancer whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations (with platinum-based chemotherapy):** 80mg orally once daily	**FLAURA 2** Open-label, randomized trial • PFS: 25.5 months (95% CI: 24.7-NE for osimertinib with platinum-based chemotherapy and 16.7 months (95% CI: 14.1- 21.3) for osimertinib monotherapy • OS results were immature at analysis	• **≥ 20%:** leukopenia, thrombocytopenia, neutropenia, lymphopenia, rash, diarrhea, stomatitis, nail toxicity, dry skin and increased blood creatinine	• Administer with or without food • Available as 40mg and 80mg tablets

Abbreviations: MCyR = major cytogenetic response, CCyR = complete cytogenetic response, MMR = major molecular response, ORR = objective response rate, DoR = duration of response, MDS = myelodysplastic syndrome, BBW = Black Box Warning, OS = overall survival, HR = Hazard Ratio, MFS = metastasis-free survival, PFS = progression-free survival, CLL = chronic lymphocytic leukemia, SLL = small lymphocytic lymphoma, EFS = event-free survival

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CALQUENCE®

acalabrutinib 100 mg tablets

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Important Product Information

CALQUENCE is a prescription oral treatment for adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). May cause serious side effects including: serious infections, bleeding problems, decrease in blood cell count, new cancers, and heart rhythm problems. Some may lead to death. Tell your doctor if you experience infections such as flu-like symptoms; unexpected bleeding such as blood in your stool or urine; or heart rhythm problems such as fast or irregular heartbeat. Use sun protection when outside.

Please read Brief Summary of Prescribing Information on adjacent page.

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

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PATIENT INFORMATION
CALQUENCE® (KAL-kwens) (acalabrutinib) tablets

CALQUENCE®
acalabrutinib 100 mg tablets

What is CALQUENCE?

- CALQUENCE is a prescription medicine used to treat adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

It is not known if CALQUENCE is safe and effective in children.

Before taking CALQUENCE, tell your healthcare provider about all of your medical conditions, including if you:

- have had recent surgery or plan to have surgery. Your healthcare provider may stop CALQUENCE for any planned medical, surgical, or dental procedure.
- have bleeding problems.
- have or had heart rhythm problems.
- have an infection.
- have or had liver problems, including hepatitis B virus (HBV) infection.
- are pregnant or plan to become pregnant. CALQUENCE may harm your unborn baby and cause problems during childbirth (dystocia).
  - If you are able to become pregnant, your healthcare provider may do a pregnancy test before you start treatment with CALQUENCE
  - Females who are able to become pregnant should use effective birth control (contraception) during treatment with CALQUENCE and for 1 week after the last dose of CALQUENCE
- are breastfeeding or plan to breastfeed. It is not known if CALQUENCE passes into your breast milk. Do not breastfeed during treatment with CALQUENCE and for 2 weeks after your last dose of CALQUENCE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking CALQUENCE with certain other medications may affect how CALQUENCE works and can cause side effects. Especially tell your healthcare provider if you take a blood thinner medicine.

How should I take CALQUENCE?

- Take CALQUENCE exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking CALQUENCE unless your healthcare provider tells you to.
- Your healthcare provider may tell you to decrease your dose, temporarily stop, or completely stop taking CALQUENCE if you develop certain side effects.

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- Take CALQUENCE 2 times a day (about 12 hours apart).
- Take CALQUENCE with or without food.
- Swallow CALQUENCE tablets whole with a glass of water. Do not chew, crush, dissolve, or cut tablets.
- If you miss a dose of CALQUENCE, take it as soon as you remember. If it is more than 3 hours past your usual dosing time, skip the missed dose and take your next dose of CALQUENCE at your regularly scheduled time. Do not take an extra dose to make up for a missed dose.

What are the possible side effects of CALQUENCE?

CALQUENCE may cause serious side effects, including:

- **Serious infections** can happen during treatment with CALQUENCE and may lead to death. Your healthcare provider may prescribe certain medicines if you have an increased risk of getting infections. Tell your healthcare provider right away if you have any signs or symptoms of an infection, including fever, chills, or flu-like symptoms.
- **Bleeding problems (hemorrhage)** can happen during treatment with CALQUENCE and can be serious and may lead to death. Your risk of bleeding may increase if you are also taking a blood thinner medicine. Tell your healthcare provider if you have any signs or symptoms of bleeding, including blood in your stools or black stools (looks like tar), pink or brown urine, unexpected bleeding or bleeding that is severe or you cannot control, vomit blood or vomit that looks like coffee grounds, cough up blood or blood clots, dizziness, weakness, confusion, changes in your speech, headache that lasts a long time, or bruising or red or purple skin marks.
- **Decrease in blood cell counts.** Decreased blood counts (white blood cells, platelets, and red blood cells) are common with CALQUENCE, but can also be severe. Your healthcare provider should do blood tests to check your blood counts regularly during treatment with CALQUENCE.
- **Second primary cancers.** New cancers have happened in people during treatment with CALQUENCE, including cancers of the skin or other organs. Your healthcare provider will check you for skin cancers during treatment with CALQUENCE. Use sun protection when you are outside in sunlight.

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- **Heart rhythm problems (atrial fibrillation and atrial flutter)** have happened in people treated with CALQUENCE. Tell your healthcare provider if you have any of the following signs or symptoms: fast or irregular heartbeat, dizziness, feeling faint, chest discomfort, or shortness of breath.

The most common side effects of CALQUENCE include headache, diarrhea, muscle and joint pain, upper respiratory tract infection, and bruising.

These are not all the possible side effects of CALQUENCE. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please see full Prescribing Information, including Patient Information.

How should I store CALQUENCE?

- Store CALQUENCE at room temperature between 68°F to 77°F (20°C to 25°C).

Keep CALQUENCE and all medicines out of the reach of children.

General information about the safe and effective use of CALQUENCE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use CALQUENCE for a condition for which it was not prescribed. Do not give CALQUENCE to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about CALQUENCE that is written for health professionals.

What are the ingredients in CALQUENCE?

Active ingredient: acalabrutinib

Inactive ingredients:

Tablet core: low-substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate.

Tablet coating: copovidone, ferric oxide yellow, ferric oxide red, hypromellose, medium-chain triglycerides, polyethylene glycol 3350, purified water, and titanium dioxide.

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For more information,
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CALQUENCE® (KAL-kwens) (acalabrutinib) tablets

CALQUENCE®
acalabrutinib 100 mg tablets

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Author-veterinary oncologist Renee Alsarraf enjoys some outdoor time with her boxer, Dusty, in 2020. Alsarraf credits Dusty for helping with her recovery from metastatic endometrial carcinoma.

MEDICAL CARE IS GOING TO THE DOGS

OUR FURRY FRIENDS CAN TEACH US A LOT ABOUT ENDURING CANCER WITH GRACE AND HUMANITY

By Renee Alsarraf, DVM, DACVIM (Onc)

Tyrosine kinase drugs, alkylating agents, platinol compounds, vinca drugs, checkpoint inhibitors … the list goes on. Veterinary oncology often uses the same or similar chemotherapeutics given to human patients. But while we treat the same cancers using these medications, the process is often different.

As a veterinary oncologist, I have been treating animals with cancer for more than 30 years. I've treated dogs, cats, birds, ferrets and rabbits with both chemo and radiation.

In general, they have much fewer side effects than people exhibit. Typically, only 15% of dogs and 10% of cats will have gastrointestinal upset (vomiting, diarrhea, inappetence). In part, this is because veterinary oncologists use lower doses than used in people, often as our intent is to obtain a remission and not a cure.

Cats and most dogs will not lose their fur with chemotherapy. This is due to the fact that their fur remains in a telogen phase, or resting phase, where it does not grow. Some breeds will have

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DOGS

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more hair-like qualities, with their fur residing in the anagen phase, or continued growth phase. These breeds (poodles, Bichon Frise, etc.) can be good for those families with allergies.

Even with surgery, animals tend to heal much quicker. After an ovariohysterectomy, though a dog is supposed to be kept quiet, she often will run after a squirrel in the back yard the next day. People? A woman often walks hunched over, slowly and in pain, and is instructed not to drive for a period of time.

It was no small irony when I was diagnosed with what I like to call the c-word … or cancer, specifically metastatic endometrial carcinoma.

After battling it for my patients day in and day out, I underwent radical surgery, 25 fractions of intensity-modulated radiation therapy and months of chemotherapy.

My furry, slobbering animal patients understood my struggle in ways that surprised even me and ultimately helped me heal. They were my cancer recovery role models and set the bar higher for me.

The silver lining that stemmed from this journey were the lessons that I learned from our four-legged friends. While animals biologically seem to fare better than people medically, I feel that they possess innate qualities that further improve not only their healing but their lives.

Having had a front-row seat to the enormous power that the human-animal bond plays in our lives, I believe dogs are not just wonderful companions but that they can serve as incredible guides to humans who are struggling … and we all struggle at times.

Despite the emotional topic of cancer in animals, the profession has lifted me up. I have gotten to not sit in front of pet parents, but to sit next to them, learn about their struggles, see how families rely on their dog, get what they need and let their dog be their guide.

My furry, slobbering animal patients understood my struggle in ways that surprised me and ultimately helped me heal.

INSIGHT #1:

WITH DOGS, THERE IS NO JUDGEMENT

Plain and simple, dogs meet us where we're at. We all have periods in our lives where it's hard to face another person, where we might be embarrassed by a misstep or by something we've said. But our furry friends never judge us. Sure, dogs experience a wide array of feelings — happiness, sadness, excitement, fear — but their gazes are never judgmental.

I know my dog looked at me adoringly despite my straggly chemo hair plastered to my head, and the pajamas that I was wearing for four straight days. I was a whole person in his eyes, which gave me courage and strength to battle on. He saw me for me.

Dogs possess this magical ability to see us for who we are more than any one person can see us. It is human nature for people to judge each other, but we're all better off if we don't. Instead of knocking us down, dogs make us feel seen, make us feel loved. To be loved unconditionally, without judgement, is the best feeling around.

And I think if we could impart more of that to ourselves, we'd all be better off. I have this voice inside my head and sometimes she can be rather nasty to me. Dogs don't have that. There is no twisted, harsh critic in them. Let's have dogs remind us to quiet that voice within us.

INSIGHT #2:

THE BENEFITS OF BEING A PACK ANIMAL

Dogs are pack animals. In the wild, dogs survive because they exist in a pack. Each has a role within the group. But they function better because they are together. They help each other obtain food, they rely on each other for safety, they lay on each other for warmth and security — it's as if dogs are their own weighted blankets.

Instead, we go to the mall to buy a weighted blanket. Weighted blankets are supposed to help with improving sleep, providing more restful sleep and reducing anxiety. They reportedly comfort autistic children. But dogs have cornered the market on relieving stress. Having my pooch lie alongside me or on me is the best therapy around.

Dogs have genetically evolved to be a part of our pack. Thousands of years ago, they lived in the periphery of our existence, picking meat off bones that we discarded. But with time, they evolved to work and live alongside us — helping us to hunt, and helping to keep both us and our livestock safe. And now, canines are emotionally fully integrated into our daily lives.

I've treated canines that aid police in search and rescue. The sum of this team's work far exceeds what the two individuals can accomplish alone. They are better together. They are better in their pack. Taking this concept out a little further — we people are better off as a pack rather than as individuals acting alone. We are designed to be connected — which promotes joy, love and feelings of being securely attached to each other. Social isolation significantly increases a person's risk of premature death and risks of dementia.

Sadly, we saw this at the height of the COVID-19 pandemic. Being away from our pack, especially for the aged population, is not good for us mentally or physically. Dogs show us that working and living together improves all our lives.

INSIGHT #3:

DOGS PRACTICE MINDFULNESS

Sometimes it is really hard to live in

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DOGS

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the moment, especially when that moment is really hard to take. We lose sight of maintaining mindfulness. Yet our furry friends always live in the moment. They neither fret about what might happen in the future nor do they stew about what happened in the past.

Using my dog patients as my guides, I realize the four-legged among us don't worry. Our furry friends face life and each obstacle head-on. They don't fret before chemo; they don't get upset after chemotherapy is done. They don't think "Will I get sick?" or "How sick is sick?"

Dogs don't waste their energy on the negative. And that helps their healing process. When we have a positive outlook, it lowers our levels of pain, contributes to a greater resistance to illness, benefits our cardiovascular health and makes us more resilient.

INSIGHT #4:

DOGS CELEBRATE IMPERFECTIONS

People often feel whole in the presence of animals. Dogs don't care if our hair is a bit gray or if we have gained Covid weight. And as dogs age, they sometimes develop lumps, fatty lipomas and warts, even become gray around their muzzle. Yet we love our dogs just the same. We don't extend the same love to ourselves. With dogs, we can be who we really are with them. No false pretense, no insecurities.

For me, losing my hair was a big deal. My medical team saw bald as the norm, one of those necessary losses. But I realized for me it was more than vanity — I was trying to control the uncontrollable. And hair does grow back. Dogs embrace these imperfections, live in the moment.

Franny, an older bloodhound with gastric mast cell disease, enjoyed life despite her wrinkles, her endless drool and weight gain of 50 pounds during her chemotherapy! She lumbered when she walked.

While our four-legged friends battle the same diseases, the same cancers with the same or similar drugs, they handle such crises much differently. Placed in our lives at different times, filling our needs without question, dogs are here to mirror for us how best to live.

Yet when I was sick, I had a pity party for myself for gaining weight from treatment-related lymphedema. I battled so hard to stay alive, yet wasted time by being unhappy with so-called imperfections. We should celebrate ourselves and each other despite the dents we get along the way.

INSIGHT #5:

DOGS MODEL WHAT A BEST FRIEND SHOULD BE!

Steadfast, loving, loyal, protective, unbridled companions with unconditional love — these are coveted qualties in good friends. Dogs possess all these attributes and more. Our lives are so much better with them by our sides. In fact, the word "pet" seems inadequate. They're special beings. We're not their owners, we're their partners in life.

The human-animal bond is a mutual relationship based on trust. Friends trust each other. Though we are responsible for them, they feel they are 100% responsible for us.

Daisy, an older cocker spaniel with lymphoma, comes to her veterinary appointments sporting a blue dress as the Disney Princess Elsa from "Frozen." The family's daughter loved Disney princesses, so her parents would dress up this easy-going spaniel.

Their daughter, Kathy, is a special-needs girl who was adopted by the family when she was only a baby.

Kathy is held up in her wheelchair with safety belts. She cannot eat by mouth nor talk. She has very limited use of her arms and hands — and cannot dress herself, let alone costume a dog. Daisy never leaves the side of her wheelchair. She is her constant companion. Though the girl is unable to speak, Daisy seems to know exactly what she is saying and brings such happiness to Kathy.

In addition to the girl's special needs, Kathy also has uncontrolled seizures. With no training whatsoever, Daisy became a seizure-alert dog, warning the family just before Kathy goes into an epileptic episode. The irony is that Daisy also has epilepsy. Thankfully, Daisy's seizures were able to be well-controlled with medications. She is the ultimate friend.

I believe that dogs possess a sixth sense to understand us at a much deeper level, more than we even understand ourselves. For those who are not familiar with the Disney movie "Frozen," the main character, Elsa, is able to manipulate snow and ice to create a better, more magical world. How interesting that Daisy, often dressed like Elsa, was able to do the exact same thing for her family.

While our four-legged friends battle the same diseases, the same cancers with the same or similar drugs, they handle such crises much differently. Placed in our lives at different times, filling our needs without question, dogs are here to mirror for us how best to live.

I am grateful to have experienced a few of my own dogs in my lifetime. I have learned from them all. Lessons I needed along the way.

▲ **Renee Alsarraf**, DVM, DACVIM (Onc), is a Senior Veterinarian at The Schwarzman Animal Medical Center in New York, New York. She is also the author of *Sit, Stay, Heal: What Dogs Can Teach Us About Living Well* (HarperCollins Publishers).

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A FITNESS ICON'S NOISY COMEBACK FROM CANCER

FITZ KOEHLER UTILIZED DIET AND EXERCISE TO OVERCOME 15 MONTHS OF EXHAUSTIVE TREATMENT

By TaMar Hicks, PharmD

Cancer treatment can take a dire physical toll, often preventing patients from performing the simplest things in life.

So, what happens when your purpose in life is to promote fitness and push others to start moving, but you receive such detrimental news yourself?

You adapt and keep going.

Fitz Koehler, MSESS, President of Fitzness.com, is a fitness icon who specializes in motivating others to get active. The Florida resident's mission is to add 10 years of life to everyone she meets by encouraging them to eat wisely and exercise.

She also spreads joy and inspiration across the country as a professional race announcer, motivating runners at the starting line and welcoming them back like champions at the finish.

Yet her own marathon with cancer is an inspiration in itself.

Seven weeks after a crystal-clear mammogram, Koehler felt an itch after she got out of the shower. A lump had formed within that short time. She was diagnosed with stage 2B breast cancer.

The cancer was spreading rapidly through multiple lymph nodes. Koehler, of Gainesville, had to be treated immediately and aggressively. She received radiation, a lumpectomy with 13 lymph nodes removed, and 15 months of chemotherapy treatment (she refers to it as "mean chemo," because the side effects hit her hard).

In the first five months of her 15-month treatment, Koehler received the TCHP chemotherapy regimen consisting of docetaxel, carboplatin, trastuzumab and

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Fitness professional Fitz Koehler underwent 15 months of exhaustive chemotherapy after being diagnosed with stage 2B breast cancer in 2019. Once her cancer was in remission, she diligently trained to get her strength back. A year later, she ran the Boston Marathon.

COMEBACK

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pertuzumab. She lost her hair and fingernails, her eyes changed colors and her vision became blurry. In her last 10 months of chemotherapy, she continued trastuzumab and lost a lot of weight because she had a hard time eating.

The journey was difficult for her and her family, but she remained steadfast. Koehler, who earned a Master of Science in Exercise and Sports Sciences at the University of Florida, used her knowledge to stay physically active and weaponize nutrition.

The moment Koehler was released to lift weights after healing from surgery, she went to the gym. But when she sat down at a weight machine, she realized she had lost 80% of her strength and could lift close to nothing.

As this moment sank in, Koehler began to empower herself. She knew she could bounce back because she was confident in her abilities as a fitness expert. She designed a comeback program with baby steps that allowed her to get stronger.

Koehler knew the power of fitness and how it would allow her to feel confident and strong throughout the process,

During 15 months of exhaustive chemotherapy, Koehler lost all her hair and 80% of her strength. She used her fitness knowledge to remain active and weaponize nutrition.

and upon finishing her treatment, she ran two races within a month.

A year later, she was running in the Boston Marathon.

Many cancer patients are not fitness experts. They do not have the knowledge that will help them stay active throughout treatment. These patients will have their weight fluctuate and lack strength, balance and stamina. Many are defeated mentally, not knowing where to start.

Koehler wants to change that. The self-described "bossy fitness pro," mindful that inactivity can be detrimental during treatment, encourages patients to take baby step toward physical well-being.

In her own journey, Koehler had had to premedicate with diphenhydramine before every round of chemotherapy. The sedative effects caused her to push her chemotherapy treatments to the early afternoons so she could exercise beforehand after she realized she didn't have the energy after treatment. This minor change made a big difference in her active lifestyle.

Now, Koehler's journey has taken her to new heights. She focuses on spreading her messages via television, radio, magazines and public appearances. She also wrote a book, "Your Healthy Cancer Comeback: Sick to Strong" (Fitness Books), a comprehensive guidebook for cancer patients and survivors eager to maintain and regain strength, stamina, vibrancy, athleticism and health.

Koehler also has a companion book, "The Healthy Cancer Comeback Journal," that allows patients to follow prompts and track their oncology experiences, thoughts and feelings.

Her books are easy to read and understand, making them suitable for all oncology patients. Topics include nutrition, exercise, sleep and supplemental care during chemotherapy, radiation and surgery.

She even takes it a step further to help patients post-treatment. Koehler wants patients to commit to exercise and pursue it on the day of diagnosis, if not

"Push yourself to have an athletic adventure. Because nothing brings to light how short life is and how precious our days are than when someone looks at you and says, 'Hey, I'm so sorry, you have cancer.'"

Fitz Koehler
Fitness Professional

sooner. Once you've finished care, she encourages you to move forward.

Koehler is a positive force in the oncology field, and we should take note of her prowess.

"Push yourself to have an athletic adventure," she says, "Because nothing brings to light how short life is and how precious our days are than when someone looks at you and says, 'Hey, I'm so sorry, you have cancer.'"

▲ **TaMar Hicks**, PharmD, is an Oncology, Advocacy, Health Policy & Equity Fellow at NCODA. He lives in Houston, Texas with his family.

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FILLING THE HEALTHCARE EQUITY GAP

ADVANCING HEALTH EQUITY WITH CHARITABLE COPAY ASSISTANCE

By Patricia Falconer, MBA, Fred Asiedu Larbi, MBA, Samuel Sappor & Krista Zodet, MSW

An important reason to focus on elevating cancer health equity is that advances in cancer care and treatments have improved the quality of care but may not be accessible to all individuals.

Cancer health disparities are the difference in cancer measures such as cancer incidence, deaths, complications, survivorship and quality of life, screening rates and stage of diagnosis that exist among certain populations.

Well-documented cancer health disparities persist for members of racial and ethnic communities, individuals with limited English proficiency and individuals with low health literacy.[1]

Additionally, socioeconomic inequities in cancer mortality have widened over the past three decades. Racial and ethnic minorities tend to receive lower quality healthcare than Non-Hispanic Whites.

For example, Black patients have the highest death rate and shortest survival of any racial/ethnic group in the U.S. for most cancers. (See Figure 1).

IMPACT OF FINANCIAL TOXICITY

Another reason to advance health equity is the opportunity to reduce financial toxicity. The same population of individuals experiencing cancer healthcare disparities

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FILLING THE HEALTHCARE EQUITY GAP

COPAY ASSISTANCE

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are also at a greater risk for financial toxicity.

Financial toxicity describes financial hardships and strain that patients experience related to the cost of treatment and care. Financial toxicity is the unintended, but not necessarily unanticipated, objective financial burden and subjective financial distress experienced by cancer patients because of their treatment costs.[1]

Objective financial burden describes the direct out-of-pocket costs for medical care and the non-medical costs such as transportation, housing, food and childcare.

Subjective financial burden results from the accumulation of the out-of-pocket expenses over the time from diagnosis, reduction of personal assets and the coping strategies used by the patients and families.

Often, guideline-adherent multidisciplinary cancer care includes surgery, oral and/or intravenous administered (systemic) therapies and radiation therapy. Of cancer patients who receive systemic therapy, radiation therapy, surgery, or who participate in a clinical trial, Twenty-two percent to 50% reported financial distress.

Financial toxicity has been linked to several clinically relevant patient outcomes such as quality of life, symptom burden, compliance and survival.

However, there are many ways that patients can get philanthropic medical aid to cover high-cost treatments.

Drug manufacturers (life science companies) and charitable foundations provide financial programs for patients facing out-of-pocket costs associated with high-cost therapeutic drugs.

Charitable foundations also provide support grants to help patients pay for costs such as health insurance premiums, clinical trial participation, transportation, housing, food, utilities and childcare.

In a 2022 American Cancer Society Cancer Action Network survey of 1,241 patients across the U.S. that were treated for cancer, one-third reported that prescription drug costs were a challenge.

One-fifth reported having skipped or delayed taking a prescribed medication due to difficulty paying the cost. Significantly higher rates of missed medication were reported by patients with lower income or individuals representing racial/ethnic minorities.[1]

Additionally, many hospitals and health systems provide patients access to copay assistance programs via financial navigators or financial counselors. Performance is often measured based on productivity, access and financial metrics to illustrate the economic benefit or return on investment of the program.

For example, Cleveland Clinic's Financial Navigation Program metrics include the percentage of all infusion treatment patients reached by financial navigators, copay assistance program applications filed, copay assistance program applications approved, aggregate dollars applied/dollars recovered, total dollar amount of approved applications for free drug, average total dollar amount per application and the time in days from patients' first positive biopsy to first treatment.[4]

Little is known about the sociodemographic characteristics of the patients receiving copay assistance or those left behind. Program metrics that measure reduction in healthcare disparities are not widely understood.

By applying the Centers for Medicare & Medicaid Services' (CMS) Framework for Health Equity to clinical outcomes reported in a published national survey and data from a national charitable foundation,

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FIGURE 1: WHICH U.S. POPULATION GROUPS EXPERIENCE CANCER HEALTH DISPARITIES?

According to the National Cancer Institute, cancer health disparities in the U.S. are adverse differences in cancer measures such as number of new cases, number of deaths, cancer-related health complications, survivorship and quality of life after cancer treatment, screening rates, and stage at diagnosis that exist among certain population groups including:

- DIFFERENT ANCESTRY, RACE, OR ETHNICITY
- LOW SOCIOECONOMIC STATUS
- LACK OR HAVE LIMITED HEALTHCARE INSURANCE COVERAGE
- U.S. GEOGRAPHIC LOCATIONS, SUCH AS RURAL AREAS, OR TERRITORIES (PUERTO RICO + GUAM)
- SEXUAL + GENDER MINORITY COMMUNITIES
- IMMIGRANTS, REFUGEES OR ASYLUM SEEKERS
- INDIVIDUALS WITH DISABILITIES
- ADOLESCENTS + YOUNG ADULTS
- ELDERLY

It is important to note that some populations may carry even a higher burden of cancer because they simultaneously fall into more than one of these categories.

AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR) CANCER DISPARITIES PROGRESS REPORT 2022

In a 2022 American Cancer Society Cancer Action Network survey of 1,241 patients across the U.S. that were treated for cancer, one-third reported that prescription drug costs were a challenge.

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AS NCODA'S MEMBERSHIP HAS GROWN, SO TOO HAVE OUR INITIATIVES AND SUPPORT TEAM

It's no secret that NCODA has undergone and continues to undergo phenomenal growth as an association.

So far in 2024, we've expanded to more than 9,500 members worldwide, a substantial increase since last year.

Because of this dramatic evolution, NCODA as an organization also has grown, both to stay connected with our membership and to offer an array of new initiatives for the oncology community.


Michael Reff

We've come a long way from our grassroots beginning.

As an oncology pharmacist, I had become increasingly concerned about the fast-emerging field of oral oncolytics, and the lack of standards, best practices and education in patient management regarding their use.

Back then, I — along with several passionate, forward-thinking colleagues — began trying to convince others in the industry of the need to standardize dispensing practices of oral chemotherapy drugs.

We were passionate about charting our own course, and not letting others chart it for us. We envisioned an organization that was both proactive and cooperative, where both internal and external stakeholders could participate in something larger than themselves.

And from that vision, NCODA was created in 2015.

From the beginning our focus was on education, both for healthcare professionals and for patients. Development of two of NCODA's core initiatives — the **Oral Chemotherapy Education (OCE)** library and **Positive Quality Interventions (PQIs)** — began around that time.

But it soon became clear that we'd need a dedicated staff to help fulfill our Mission. So, in May 2017, NCODA hired its first full-time employee. A second staff member was hired later that fall.

We worked out of a small one-room office in downtown Cazenovia, New York, in the same building we still occupy now, essentially an old Victorian-style house.

In early 2018, I left my full-time role as an oncology pharmacist in a community cancer center in Syracuse, New York, so I could commit myself full-time to NCODA. Things really began to take off at that point.

Four more team members were hired that year. We began developing plans to take our PQIs to the next level by showing how practices benefited from them in real life. **PQI In Action** grew out of that endeavor.

Our previous office space had a fireplace, and above the mantle we used to post sticky notes with ideas for NCODA goals and initiatives. It started out as a handful of reminders, but eventually the chimney became plastered in a pastel waterfall of green, yellow and pink sticky notes.

One of the early notes simply said: "Newsletter." Later that year, we started working on a small newsletter, but by the time it was launched in the summer of 2019, it had evolved into ***Oncolytics Today,*** the publication that you're reading right now.

With all of its notes, I'm surprised our idea board didn't turn into a fire hazard. However, that issue slowly resolved itself. Every time we reached a goal or launched an initiative, we'd remove the relevant sticky note. Eventually the chimney was cleared of our initial ideas, yet new plans continued to flow.

The year 2019 also saw the launch of NCODA's **Treatment Support Kit (TSKs)** initiative, plus the addition of another four staff members.

NCODA's staff expansion continued at a steady pace from 2020 through 2023, when 22 more staff members were brought on board. We currently employ 32 people across the United States and Canada.

The additional staffing has allowed NCODA to evolve from a simple grassroots organization into a more patient-centered structure that focuses on all facets of oncology patient care.

Along the way we've launched an array of new initiatives, include **Intravenous Cancer Treatment Education (IVE)** sheets, the **ASCO/NCODA Medically Integrated Dispensing Standards**, **NCODA University**, the **NCODA Center of Excellence Medically Integrated Pharmacy Accreditation Program** the **Oncology Pharmacy Technician Association**, the **Professional Student Organization**, and much more.

Yet despite all of our organizational changes, one thing at NCODA has never changed: our Mission to empower the medically integrated oncology team to deliver positive, patient-centered outcomes by providing leadership, expertise, quality standards and best practices.

Michael J. Reff, RPh, MBA
Executive Director & Founder | NCODA

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