ONCOLYTICS TODAY

EMPOWERING THE MEDICALLY INTEGRATED ONCOLOGY PHARMACY PRACTICE | FALL 2023

ONCOLOGY FACES A HOST OF RISING CHALLENGES

. . . AND WE MUST CONTINUE TO EDUCATE AND ADVOCATE FOR NEEDED CHANGE TO SOLVE THEM

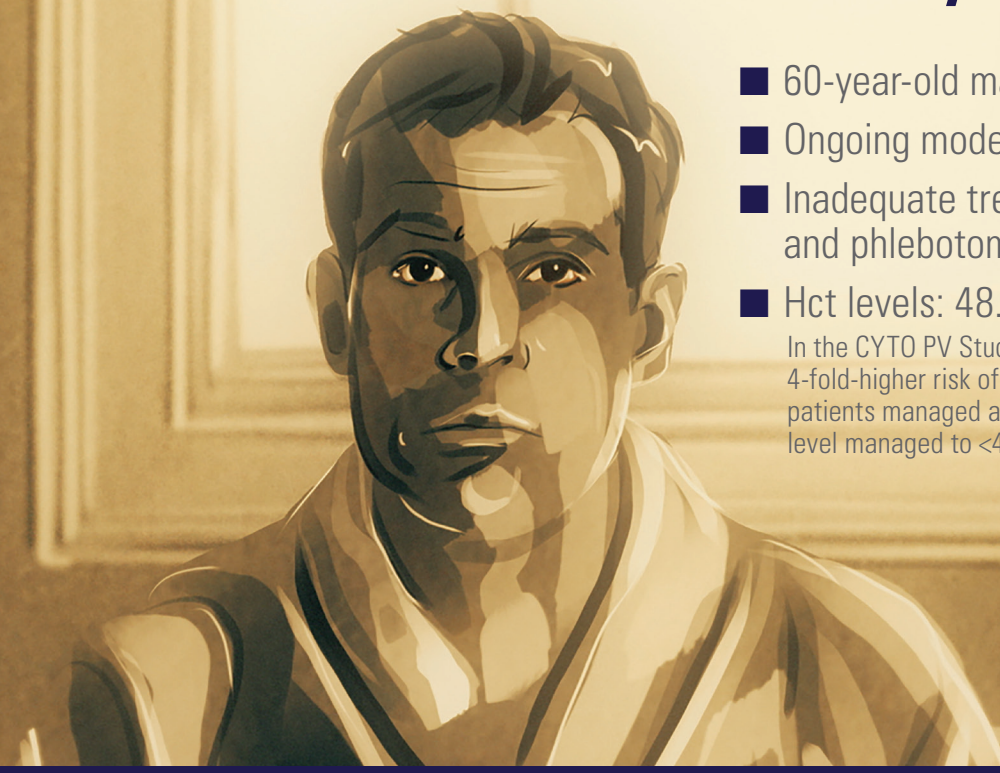
COVERAGE BEGINS ON PAGE 55

NCODA

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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Incyte

NCODA Cost Avoidance and Waste Tracker

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

How it works:

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

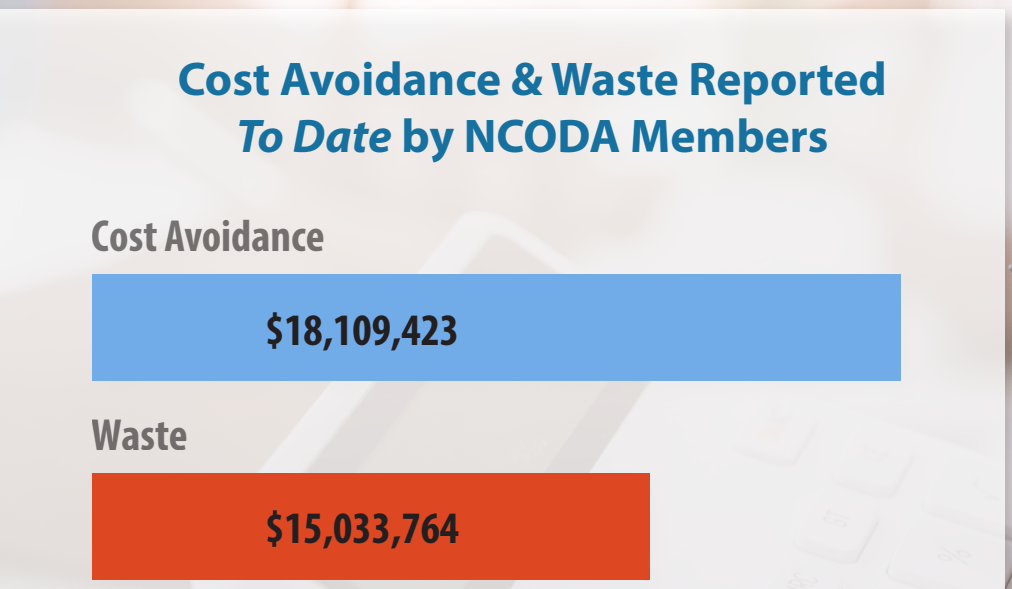
Waste: Whenever a patient brings in medication that was not used at all, *record the waste.*

How to use the data:

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

Help Us Create Change and Accountability for Healthcare Spending Nationwide!

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



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

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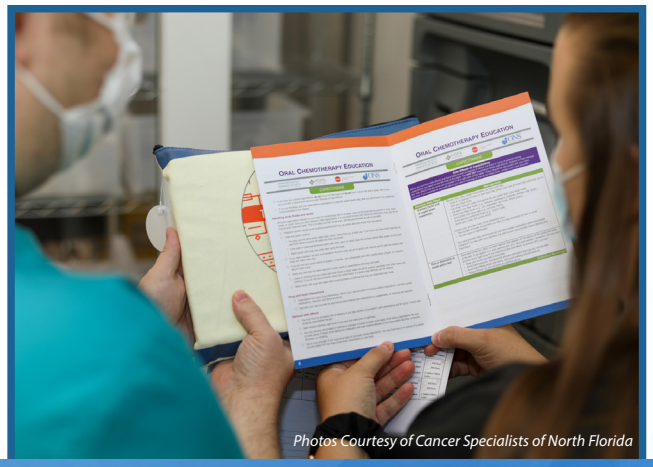

Photos Courtesy of Cancer Specialists of North Florida

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- Neratinib
- Pacritinib
- Regorafenib
- Temozolomide
- Tivozanib

To Order Kits, Scan QR Code Or Visit:
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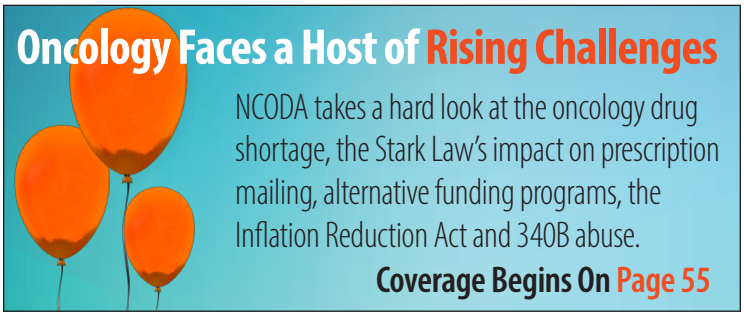
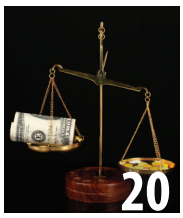


REGULAR SECTIONS

FEATURED ARTICLES



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NCODA

PROFESSIONAL STUDENT ORGANIZATION

Empowering The Future Generation of Oncology Leaders

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

PSO BENEFITS

- First professional student organization for students interested in oncology/association management/industy/leadership
- Opportunities to attend NCODA international meetings
- Create educational materials to help impact cancer care
- International publishing opportunities ***(ForumRewind, SummitRewind, Inspire & Oncolytics Today publications)***
- Increased networking opportunities with oncology clinical and industry professionals, and key opinion leaders
- Oncology clinical practice experience and mentorship
- Healthcare advocacy and policy experience

LOCATIONS OF ESTABLISHED PSO CHAPTERS

> Being a part of the NCODA Professional Student Organization community is such a remarkable experience. Together, we keep each other updated and informed on current clinical oncology practices, while also providing opportunities that aid in developing leadership skills.
>
> **- Jonathan Rivera**
> PharmD Candidate | Class of 2023
> *University of North Texas Health Science Center*

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

FALL 2023 ISSUE FOCUSES ON THE RISING CHALLENGES ONCOLOGY FACES

Welcome to the Fall 2023 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 fifth year, strives to explore 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

CHALLENGES ON THE HORIZON

In this issue, we highlight some of the economic and political issues that are impacting both our patients and our practices.

▲ **Karen Hagerty**, MD, looks at the current shortages in chemotherapy drugs such as cisplatin and carboplatin, and discusses what can be done about it.

▲ Pharmacy directors **Neal Dave**, PharmD, **Kyle Kitchen**, PharmD, MBA, and **Eric Soong**, PharmD, review the prescription mailing prohibition announced in the Stark Law FAQ on May 19, 2023, and its impact on medically integrated practices.

▲ PAN Foundation executive **Amy Niles**, MBA, explains how Alternative Funding Programs exclude specialty medications from coverage and force patients to search for their own funding.

▲ Legal expert **Govind Persad**, PhD, JD, takes a look at the Inflation Reduction Act and its implications for oncology care.

▲ Healthcare attorney **Thomas Johnson**, JD, explores how lack of transparency, oversight and accountability allows some healthcare providers to abuse the 340B safety net and the underprivileged patients that it was designed to protect.

Our special report on **Rising Challenges in Oncology** begins on **Page 55**.

ALSO IN THIS ISSUE

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

NCODA content includes reports from the Nursing Committee, highlights of the 2023 Oncology Institute and a primer for Oncology Pharmacy Technician Certification.

In other articles in Fall 2023 issue:

▲ **Nina Lathia**, RPh, PhD, MSc, BScPhm, outlines four key question to ask when critically appraising oncology clinical trials on **Page 8**;

▲ **Yen Nien (Jason) Hou**, PharmD, DipIOM, LAC and **Jyothirmai Gubili**, MS, discuss the emerging role of integrative therapies in cancer care on **Page 11**;

▲ **Katie Snell**, AGNP-C, AOCNP, explores financial toxicity and the growing need for patient assistance programs on **Page 20**;

▲ **Joanna Fawzy Doran**, Esq., provides key tips for navigating health insurance denials on **Page 23**;

▲ Speaking from personal experience, **Kafilat Salawu**, DNP, FNP-C, AOCNP, BCPA, talks about the critical role of health advocates for chronically ill patients on **Page 27**;

▲ **Tom Greenlee**, PharmD, and **Kayla Hodges**, CPhT, reveal a career ladder development program designed to both train and retain technical staff on **Page 39**;

▲ **Matthew Malone**, PharmD, MBA, BCOP, provides an in-depth look at BiTE therapy, a novel class of anticancer drugs designed to redirect T cells to target cancer cells, on **Page 78**;

▲ **Stephanie Trexler**, PharmD, BCOP, reviews testing considerations and barriers for dihydropyrimidine dehydrogenase deficiency on **Page 83**;

▲ **Jing Chien**, DNP, CRNP, AOCNP, looks at current treatment modalities for chemotherapy-induced neuropathy on **Page 86**;

▲ **Hardeep Phull**, MD, reviews the dual product Opdualag™, a new treatment for advanced melanoma, on **Page 91**;

▲ **Derek Gyori**, PharmD, BCOP, and **Kirollos Hanna**, PharmD, BCPS, BCOP, outline the latest FDA oral oncolytic approvals on **Page 97**, and

▲ **Kristin Hutchinson**, PharmD, BCOP, CSP, shares lessons learned in her personal transition from healthcare provider to caretaker during her mother's cancer journey on **Page 103**.

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

4 KEY QUESTIONS TO ASK WHEN CRITICALLY APPRAISING ONCOLOGY CLINICAL TRIALS

By Nina Lathia, RPh, PhD, MSc, BScPhm

The number of oncology drugs approved by the U.S. Food and Drug Administration (FDA) increased exponentially in the decade leading up to 2020.[1]

Many of these newly approved drugs, however, did not demonstrate an improvement in overall survival.[2] Furthermore, a recent study found that one-third of drugs that have not demonstrated benefit continue to be recommended by clinical guidelines for use in patients.[3]


Nina Lathia

Given this landscape, it's imperative that clinicians approach the oncology literature with a healthy skepticism. To that end, here are four questions to ask when critically appraising oncology clinical trials:

1 Do the results of the study demonstrate both statistical significance AND clinical significance?

Statistical significance refers to the reliability of a study's results; in other words, whether the study's results are true.

Statistical significance is expressed in terms of a p-value, or probability value. The p-value indicates how likely it is that the results of a study are NOT true, and are a chance-only finding, meaning that there is no difference between the two interventions being compared.

A p-value of 0.05 is the threshold that defines statistical significance; p-values above this point denote results that are not statistically significant, while p-values below this point denote results that are statistically significant.

As an example, consider a p-value denoted as $p<0.02$; this value indicates that there is a less than 0.02 probability that the results of a study are NOT true.

Clinical significance, on the other hand, refers to the magnitude of the treatment effect, in other words, what the difference in treatment effect size is between the interventions being compared in the study.

In oncology, a minimum improvement of two to six months in overall survival is considered clinically significant, depending on the type of cancer.[4] For health-related quality of life (HRQoL), the minimal clinically important difference is defined specifically for each individual HRQoL instrument.

Users of the medical literature need to understand that a statistically significant result does not always translate into clinically meaningful benefit. Also, a statistically significant result is more likely with a large sample size.

Consider the example of a clinical trial of 569 advanced pancreatic cancer patients that was published in the *Journal of Clinical Oncology.*

This study compared erlotinib plus gemcitabine versus gemcitabine alone, and demonstrated an increase in median overall survival for the combination therapy group vs. the gemcitabine-only group (6.24 months vs. 5.91 months, $P = 0.038$). This p-value indicates the probability this finding was by chance-only is 0.038, below the p-value threshold of 0.05, meaning the result is statistically significant.

Most oncologists, however, would not consider this finding to be clinically significant, since the survival benefit in the combination therapy group was only 10 days (6.24 vs 5.91 months).[5]

To help users of the medical literature avoid conflating statistical significance with clinical significance, studies should report the estimated treatment effect size and its likely range reported as the 95% confidence interval.[6]

KEY POINT: Clinicians should make judgments related to a treatment's clinical significance based on the treatment effect size, and not simply on whether statistical significance was achieved based on a p-value.

2 Were the results of the study reported in terms of progression-free survival or overall survival?

Although overall survival (OS) is the gold-standard primary endpoint for randomized controlled trials (RCTs) in patients with metastatic solid tumors, it is being increasingly replaced with progression-free survival (PFS).

OS is an objective, easily measurable, patient-centered outcome, but its evaluation requires complex trial design, extended follow-up time, and is expensive. As such, OS has declined as the primary endpoint used in most oncology RCTs in favor of PFS, which is commonly defined as tumor growth beyond a certain threshold or death.

But, PFS is a surrogate outcome that is disease-centered, rather than patient-centered, and its evaluation is often subjective.[7,8]

For PFS to be a useful outcome, it should reliably predict changes in OS. A recent analysis of 260 RCTs in metastatic solid tumor patients, however, demonstrated that less than 40% of RCTs that reported improved PFS as the primary endpoint went on to demonstrate improved OS.

Industry-sponsored RCTs were associated with a lower likelihood of improved PFS predicting improved OS, compared to non-industry sponsored RCTs.[7]

KEY POINT: Improvements in PFS often do not translate into improvements in OS. As such, studies that report PFS as the endpoint should be interpreted with caution.

3 Are the results of the study generalizable to real-world oncology settings?

Results observed in oncology clinical trials might not be applicable in routine oncology clinical practice settings.

The greatest clinical barrier to participation in oncology clinical trials is narrow eligibility criteria. While trials need to balance the competing objectives

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4 QUESTIONS

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of demonstrating a consistent treatment effect and enrolling a representative sample of patients for whom the treatment will be used, they are often criticized for having eligibility criteria that are too narrow, limiting their generalizability.

Performance status (PS) is one of the most common inclusion/exclusion criteria in cancer clinical trials. Many trials exclude patients with low-functioning PS, resulting in important differences between trial participants and general oncology populations with the disease.[9]

Additionally, clinical trials represent the ideal circumstances in which an intervention should be used and don't reflect many of the factors that determine the real-world effectiveness of a cancer therapy.

These could include toxicity and comorbidity burden, patient and physician motivation, protocol-enforced surveillance, treatment access issues such as cost, and other factors that could potentially lead to early discontinuation of treatments in real-world settings.[10]

KEY POINT: Applying data from oncology clinical trials to real-world settings is complex because of the differences between these settings. When translating clinical trial outcomes to routine practice, clinicians should consider whether the extent of these differences could influence the real-world effectiveness of cancer therapies.[10]

4 Have patient preferences been adequately considered?

Oncology patients are often faced with complex treatment decisions in which they have to consider the effectiveness, safety, quality of life, and costs associated with various treatment choices.[11]

Many patients faced with a shortened life span may not wish to incur the side effects, financial burdens, and time commitments associated with receiving therapies that provide only modest survival gains. These considerations may be most relevant to people with advanced cancer who must make treatment decisions in the context of limited time.[12]

"Financial toxicity" is the term coined to describe the financial burdens of cancer treatment, which have been linked to several clinically relevant patient outcomes, including HRQoL, symptom burden, adherence, and, most recently, survival.[13]

Another aspect of cancer care that has been receiving attention more recently is "time toxicity," which is time spent in coordinating care and in frequent visits to a healthcare facility (including travel and wait times), seeking urgent/emergent care for side effects, hospitalization, and follow-up tests.[14]

KEY POINT: Many oncology clinical trials do not systematically evaluate patient preferences. When applying the results of these trials to patient treatment decisions, clinicians should systematically consider patient preferences using techniques such as shared decision-making.[11]

These four questions provide a practical framework for clinicians to critically appraise the results of oncology trials in a systematic and objective way. This practice will help to ensure that cancer patients receive evidence-based therapies that have the greatest likelihood of improving their health outcomes.

▲ **Nina Lathia**, RPh, PhD, MSc, BScPhm, is a pharmacist, health economist and independent consultant. She resides in Toronto, Ontario.

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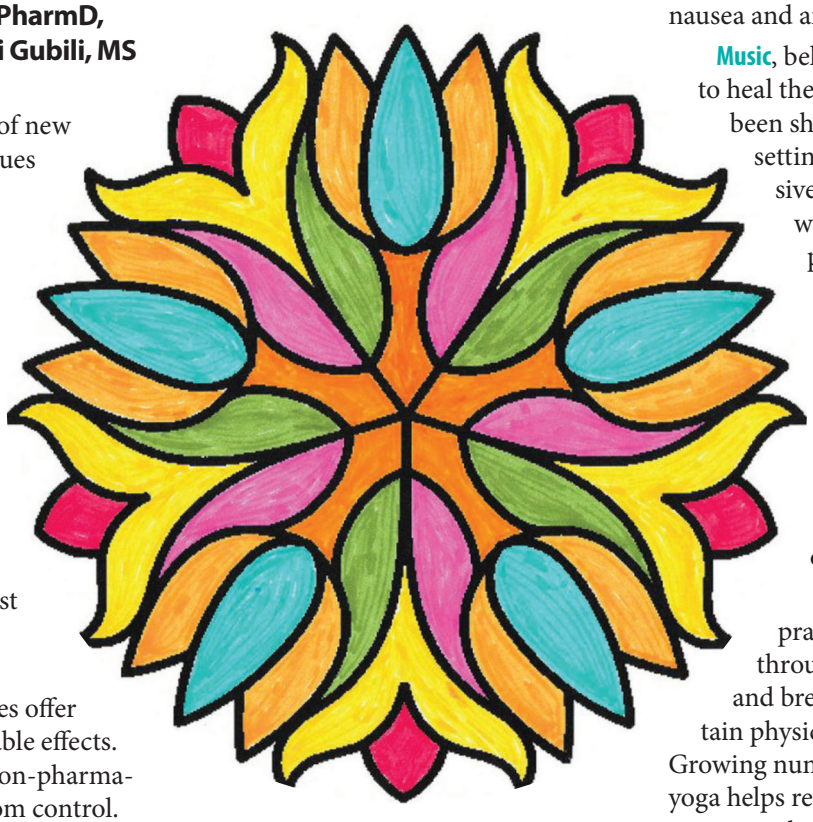
MIND AND BODY: THE EMERGING ROLE OF INTEGRATIVE THERAPIES IN CANCER CARE

By Yen Nien (Jason) Hou, PharmD, DiplOM, LAc & Jyothirmai Gubili, MS



Even as the number of new cancer cases continues to rise worldwide,[1] survival rates have improved due to advances in early detection and treatments.

However, many survivors endure symptoms that have a significant negative impact on their quality of life. These include pain, fatigue, anxiety, depression and cognitive impairment, which can persist for years following cancer treatments.

Conventional approaches offer relief but can cause undesirable effects. Increasingly, patients seek non-pharmacological options for symptom control.

An evidence-informed and patient-centered field, integrative oncology uses mind-body therapies, lifestyle modifications and natural products along with standard cancer care to improve patients' quality of life. It allows patients and their families to be active participants in their own care from prevention through treatment and survivorship.

Mind-body therapies include provider-dependent offerings such as acupuncture, massage and music therapies, movement practices such as yoga, as well as contemplative practices such as meditation.

Acupuncture is an integral component of traditional Chinese medicine, involving stimulation of predetermined body points using thin needles, sometimes along with heat (moxibustion) or electricity (electroacupuncture) for

Yen Nien (Jason) Hou

Jyothirmai Gubili

therapeutic effect. Several large trials reported it to be effective against cancer pain, fatigue and hot flashes, as well as beneficial in managing chemo-induced nausea and vomiting, and xerostomia.[2,3] Acupuncture is generally safe in oncology settings and well-tolerated.[4,5]

Massage is a centuries-old technique that involves manipulation of muscles and soft tissues of the body. It increases circulation, promotes relaxation and has been shown to reduce pain, fatigue, nausea and anxiety.[6,7]

Music, believed since ancient times to heal the mind and body, also has been shown valuable in oncology settings. Patients may listen (passive participation), play or even write their own music (active participation) with guidance from a professionally trained music therapist. Studies have shown that music helps promote relaxation and has a positive impact on pain, fatigue and mood disturbances including anxiety and depression.[8-10]

Yoga, an ancient Indian practice, involves moving through postures, meditation and breathing exercises to attain physical and emotional health. Growing number of studies indicate that yoga helps reduce stress and anxiety and improves sleep as well as quality of life in both newly diagnosed patients and survivors.[11,12]

Meditation, practiced for millennia in many traditions around the world, is defined as "a wakeful hypo-metabolic physiologic state" in which the practitioner is relaxed but alert and focused. Common goals of meditative practices include physical relaxation, inner calmness and improved vitality and coping. Several studies reported that mindfulness and other forms of meditation affect significant reductions in anxiety, stress, depression, pain, fatigue, insomnia and vasomotor symptoms.[13,14]

ONCOLOGY GUIDELINES

Given the growing evidence base, the National Comprehensive Cancer Network (NCCN) and the Society for Integrative Oncology (SIO) guidelines — endorsed

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New NCCN and SIO guidelines now endorse acupuncture, music therapy, massage therapy and meditation as a part of cancer therapy.

INTEGRATIVE THERAPY

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by the American Society of Clinical Oncology (ASCO) — recommend:

▲ **Acupuncture** for cancer pain, fatigue and hot flashes;

▲ **Music therapy** for anxiety, stress reduction, depression and mood disorders;

▲ **Massage therapy** for depression and mood disorders;

▲ **Yoga** for anxiety, stress reduction, depression, mood disturbance and improved quality of life; and

▲ **Meditation** for anxiety, stress reduction, depression, mood disturbance and improved quality of life.[15-17]

Further, a newly released joint SIO-ASCO guideline recommends:

▲ **Acupuncture** for aromatase inhibitor-related joint pain, musculoskeletal pain and general cancer pain;

▲ **Massage therapy** for patients with pain during palliative or hospice care; and

▲ **Hypnosis** for patients undergoing painful procedures, such as large core breast biopsies and tumor embolization or radiofrequency ablation.[18]

Although research is limited, factors such as physical activity, diet, sleep hygiene and stress management also have been shown to impact several health measures that include lifetime risk of developing or dying from cancer.[19]

NATURAL PRODUCTS

Cancer patients increasingly use herbs and natural products for symptom control. However, clinical data on such products are limited.

Other concerns include poor quality control and the potential for herbal interactions with chemotherapy, radiotherapy, anticoagulants, immunosuppressants and hormonal therapies.

Also, many providers lack the knowledge to have useful discussions with their patients about herbal use.

Despite the proliferation of websites providing information on dietary supplements, it can be overwhelming to find a reliable source.

To address this issue, the Integrative Medicine Service at Memorial Sloan Kettering Cancer Center (MSKCC) has created and maintains a free website, ***About Herbs*** **(www.mskcc.org/aboutherbs)** along with free Apps available for both Android and iOS devices.

About Herbs provides unbiased, evidence-based information on 292 and growing entries on herbs, vitamins, minerals, other dietary supplements, and unproven anticancer treatments. Each entry, with healthcare professional and consumer versions, is regularly updated with the latest research findings.

For more information on ***About Herbs***, scan the QR code above.

The Integrative Medicine Service at MSKCC also demonstrated the feasibility of incorporating herbal medicines into an academic oncology setting through its novel herbal program, developed in collaboration with the Pharmacy department.

Following careful consultations, Integrative Medicine providers offered their patients quality-controlled traditional Chinese medicine (TCM) formulas with evidence of safety and preliminary efficacy for common cancer symptoms such as pain, diarrhea, constipation, fatigue and anxiety.[20] Patient satisfaction with the program was high with few adverse effects.

WHAT PHARMACISTS NEED TO KNOW

Available evidence suggests that integrative therapies are safe and effective treatment options in cancer populations. A majority of the NCI-designated centers offer them for cancer symptom management.[21]

Looking ahead, rigorous research is needed to expand the evidence base and clinical guidelines, to educate oncology providers and to inform healthcare policy. A broader integration of these modalities will enhance comprehensive cancer care.

As pharmacy practice evolves to address the growing needs of patients living with cancer, pharmacists are required to actively participate as team members within emerging collaborative care and integrated health systems.[22]

The challenge is to train the next

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INTEGRATIVE THERAPY

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generation of pharmacists to ensure they are well-rounded for providing comprehensive care in a patient-centered setting, involving shared decision-making with the patient, as well as effectively communicating with integrative medicine providers, oncologists and other pharmacists.[23]

To ensure proper use of integrative modalities, it is also important to guide patients to seek licensed practitioners experienced in working with cancer populations.

▲ **Yen Nien (Jason) Hou**, PharmD, DipI. OM, LAc is Manager of the About Herbs website. **Jyothirmai Gubili**, MS, is an Editor. Both are employed at Integrative Medicine Service, Memorial Sloan Kettering Cancer Center in New York.

The challenge is to train the next generation of pharmacists to ensure they're well-rounded for providing comprehensive care in a patient-centered setting, involving shared decision-making with the patient, as well as effectively communicating with integrative medicine providers, oncologists and other pharmacists.

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LOOKING TO THE FUTURE: THE ROLE OF THE NURSE IN ORAL ONCOLYTIC MONITORING

By Suzanne Hinman, RN, OCN

Oral oncolytics have as much potential for toxicity as antineoplastic medications that are administered intravenously (IV).

Yet, oral medications have the added challenge of ensuring that the patient is adhering appropriately to their regimen when taking their treatment at home.

Suzanne Hinman

In oncology clinics and hospitals, the role of the infusion nurse administering IV treatments is well-defined and tightly regulated. In contrast, the role of the oncology nurse caring for patients taking oral anticancer medications (OAMs) currently lacks clear definition and standardized workflows.

The NCODA Nursing Community hosted a workshop during the 2023 Spring Forum to address the challenges of developing OAM monitoring workflows and the role of this specialized nurse.

Workshop panelists included Mary Anderson, BSN, RN, OCN, NCODA; Dallas Lawry, DNP, FNP-C, OCN, University of California, San Diego; and Suzanne Hinman, RN, OCN, Smilow Care Center-Yale New Haven Health.

This article will provide an overview of the workshop, ensuing discussions and potential solutions brought forth by the panelists and attendees of the program.

The goals of the session were to:

- Identify barriers that keep nurses from performing their roles and responsibilities in adequately monitoring patients taking OAMs;
- Describe the consequences of inadequate OAM monitoring;
- Illustrate effective nurse-driven OAM monitoring programs;
- Describe the role and responsibilities of the Oncology Nurse; and
- Develop strategies to create workflows specifically for nurses to improve patient monitoring.

CHALLENGES

Prior to administering an IV anticancer infusion, the oncology nurse performs multiple safety checks. This may include a review of the patient's vital signs, bloodwork, test results (such as EKG or echocardiogram), a physical assessment and the verification of the appropriate physician's orders with a pharmacist and a second nurse.

Continual assessment and monitoring are just as vital clinical management practices for patients taking OAMs, but the role of the nurse is harder to define when the patient is self-administering their treatment at home. There is a lack of existing standardized protocols and nursing workflows for OAM monitoring.

Perhaps most notably, the dedicated OAM nursing role has yet to be fully integrated into oncology care. The slow integration of OAM nursing is due in part to lack of reimbursement, lack of buy-in for the role by administration and co-workers, and lack of definition of the role.

Historically, oncology nurses care for patients that are present in the clinic for labs or infusion (chemotherapy/immunotherapy). With nurses prioritizing the needs of these patients, the equally important responsibilities and needs of patients taking OAMs are being overshadowed.

CONSEQUENCES OF INADEQUATE OAM MONITORING

Based on their extensive experience, the panelists identified some specific touch-points in the process of starting and following patients on OAM. Without a dedicated OAM nurse, patients have the potential to fall through the cracks at multiple touchpoints:

Examples of this include:

- The physician enters a treatment plan in the EMR, but does not sign the orders, so the prescription never reaches the pharmacy.
- The patient receives their new medication and starts it without notifying anyone. Consequently, this patient is not scheduled for a two-week laboratory visit.

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OAM MONITORING

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▲ The patient experiences side effects and self-discontinues or holds their medication without notifying the oncology team.

▲ The patient experiences significant side effects but continues to take their medication.

▲ The patient misunderstands how to take their medication (example: patient takes OAM four times per day instead of four tablets once per day).

There are multiple reasons why patients may not adhere to their OAM treatment plan and nonadherence can have severe negative effects on the outcome of the treatment. Studies show that the consequences of inadequate monitoring of patients taking OAMs include increased costs, increased utilization of emergency healthcare services, increased hospital admissions and unmanaged, potentially toxic side effects.

HOW DOES A NURSE'S INVOLVEMENT IN OAM MONITORING MAKE A DIFFERENCE?

The following questions were posed to the workshop participants:

▲ What are the specific benefits of having oncology nurses track OAM patients?

▲ Why does a nurse need to own this role (versus other members of a healthcare team)?

▲ How does the oncology nurse provide value to the practice by tracking OAM?

Benefits of the Nurse Involvement

Participants agreed that ongoing patient assessment is a fundamental and essential part of the nursing process. Nurses are trained to perform physical and emotional assessments at every patient point of contact.

During the patient assessment, the nurse identifies potential barriers that may prevent the patient from remaining adherent to their OAM. Physical assessment is vital to determine whether a symptom is a new side effect or a more chronic concern.

Support of the patients and their family is also an important part of the nursing process. The nurse identifies gaps in the patient's and caregiver's knowledge and provides education at every visit. The nurse is instrumental in providing proactive adherence strategies, ongoing symptom management and continuous education that is tailored to each unique patient and their caregivers.

A key result of this nursing process is the development of the patient-nurse relationship. Because of this relationship, the nurse becomes a trusted point of contact for the patient.

The first step in managing side effects of an OAM is having patients call to report them, and patients are more likely to call the nurse they know and trust. In addition, regular communication with the patient improves patient satisfaction and outcomes.

Workshop participants agreed that nursing involvement in the OAM process reduces delays in care through proactive outreach communication to the pharmacy, insurance companies and manufacturer patient assistance programs (PAP).

Why nurses need to own this role

Abnormal lab results indicate a potential developing toxicity. However, if the patient does not have their blood work drawn, there are no results to review. It is often the nurse that keeps a finger on the pulse on the patient's laboratory and monitoring protocols, thus making sure the visits are appropriately scheduled

Members of the NCODA Nursing Community gathered for a photo at the 2023 NCODA International Spring Forum in Indianapolis, Indiana.

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OAM MONITORING

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and completed. Early identification and management of adverse events can reduce emergency department visits and hospital admissions.

Nursing interventions specific to OAM that can potentially reduce the risk of a serious adverse event include:

▲ Individualized proactive outreach to the patient based on previously identified adherence barriers, preexisting risk factors and treatment complexity rather than a "one size fits all" monitoring schedule; and

▲ Confirmation that the patient maintains their monitoring (laboratory, cardiac assessment) schedule; and

▲ Performing a physical and psychosocial assessment at each clinic visit.

How tracking OAM adds value to the practice

The value an oncology nurse adds to the practice when tracking OAMs includes:

▲ Identification of concerns and solutions upstream in the process ;

▲ Appropriate and ongoing monitoring that keeps the patients from falling through the cracks during the multiple touch points in the process of obtaining their OAM and their follow-up; and

▲ Interprofessional communication and collaboration.

SOLUTIONS

Audience participants shared common themes and strategies that have been effective in improving OAM monitoring in their own practices. Examples included identification of gaps in workflows, collaboration with nursing leadership and creation of an interdisciplinary task force to improve the processes.

Collaboration with the Information Technology (IT) department is also important in the development or adjustment of flowsheets to include the nursing process. OAM workflows that are currently used by the participants include:

▲ Excel spreadsheets to track OAM patients throughout their treatment;

▲ NCODA tracking sheets;

▲ EMR reports of patients actively taking OAMs; and

▲ EMR Best Practice notifications of new orders.

ORAL ONCOLOGY NURSE NAVIGATORS PROMOTE PROACTIVE PATIENT-CENTERED CARE

Participants also discussed workflows and technologies they are currently using to track patients and whether these justified the need for a dedicated role of an Oral Oncolytic Nurse Navigator (OONN). The consensus is that the current reactive approach in OAM nursing care results in a poor utilization of time and resources, unsafe practices, delays in care and poor treatment outcomes.

Utilization of an OONN is a more proactive approach to OAM monitoring that can reduce healthcare costs and improve patient outcomes. The deployment of the OONN role, along with an efficient protocol, will allow patients to be managed and triaged at the nursing level.

This is essential as adhering to regimens, attending scheduled laboratory appointments, reporting adverse side effects and attending provider follow-up visits are key elements in proactive workflows for OAM monitoring.

IMPLICATIONS FOR THE FUTURE

Currently, discussions within the NCODA Nursing Community reveal that there are many oncology nurses around the country who are independently focusing on OAM management without the support of their administrators.

The NCODA Nursing Community will continue to further define, standardize and promote the OONN role.

This will validate and legitimize the role of the nurse in oral oncolytic management and ultimately achieve a higher standard of care for cancer patients on OAMs.

▲ **Suzanne Hinman**, RN, OCN, retired in 2023 from the Smilow Cancer Hospital Care Center in Torrington, Connecticut. She is an active member of NCODA's Nursing Community.

THE NCODA NURSING COMMUNITY IS COMMITTED TO EMPOWERING MIP NURSES

The NCODA Nursing Community is comprised of more than 800 oncology nurses dedicated to elevating nurses as a vital part of the Medically Integrated Oncology Practice.

We will achieve this through innovation of tools and resources that empower nurses to provide the best care possible, so patients receive the maximum benefit from their treatment.

In addition to a robust and growing library of resources developed by and for nurses, the NCODA Nursing Community gathers virtually once a month.

These interactive webinars allow the opportunity to support frontline nurses in their daily patient care by providing educational learning opportunities, sharing best practices and presenting solutions to challenges in patient care.

LEADERSHIP TEAM

Membership Engagement/ Scholarship: Dallas Lawry, DNP, FNP-C, AOCNP, Advanced Nurse Practitioner | UC San Diego

Education: Amanda McCauley, BSN, RN, OCN, Assistant Nurse Manager | Norton Cancer Institute; April Hallatt, BSN, RN, OCN, Oncology Nurse Navigator | IU Health Ball Memorial Cancer Center

Resource Tools/ Initiatives: Dawn Landolph, MPA, BSN, RN, ONC, Associate Director of Specialty Pharmacy Nursing Services | Florida Cancer Specialists & Research Institute

Oral Oncolytic Nurse Navigator initiatives: Elizabeth Bettencourt, MSN, BSN, RN, OCN, Oral Oncolytic Nurse Navigator | Palo Alto Medical Foundation/Sutter Health; Suzanne Hinman, RN, OCN, Practice Nurse (retired) | Smilow Cancer Hospital, Torrington Care Center

NCODA SCHOLARSHIP PROVIDES OPPORTUNITY FOR APPLICANT TO ATTEND ONS CONGRESS

By Dallas Lawry, DNP, FNP-C, AOCNP

Since its beginning as a grassroots organization of 20 oncology nurses in 1973, the Oncology Nursing Society (ONS) has been the foundation of education, scholarship and evidence-based practice for oncology nurses.

NCODA began much the same way, but started in the oncology pharmacy sphere as a response to the dramatic increase of oral oncolytic and targeted therapies. As NCODA began to grow, it continued to strongly promote a Mission that is "patient-centered and always collaborative."

Dallas Lawry

This interdisciplinary collaboration that is so unique to NCODA made it natural for NCODA and ONS to become strong partners in patient advocacy and nursing education, particularly in oral anticancer therapies.

With this partnership in mind, NCODA launched a new scholarship in 2022, the **NCODA Nursing Scholarship for ONS Congress**. The inaugural scholarship recipient, April Hallatt, BSN, RN, OCN, received funding to participate in the annual Oncology Nursing Society Congress.

The ONS Congress is the premier conference for the entire oncology nursing community. It covers a wide variety of topics, but has grown to include advanced practice nursing, research and publication, ethics and palliative care, and the frontier of oncology — oral anticancer medications and immunotherapy.

NCODA will now support a nurse in attending ONS Congress every year. This scholarship helps cover costs associated with registration, hotel and airfare.

The scholarship selection committee is made up of the NCODA Nursing Community Leadership team, who review applications each December.

To be considered for the scholarship, applicants must take part in initiatives that elevate their professional practice, care for oncology patients and participation in NCODA. Each initiative is worth points that are tallied at the end of the year.

The scholarship application process begins Oct. 26, 2023. You can find the application by following the QR code at right. Note: you must be signed into your NCODA account to access the page.

Scan the QR code above to apply for the **NCODA Nursing Scholarship for ONS Congress**.

Possible initiatives include:

▲ Attending monthly Nursing Community calls (via Zoom);

▲ Authoring a Positive Quality Intervention (PQI) with NCODA, or participating in a "PQI in Action" within your practice;

▲ Presenting during an NCODA Nursing Community call;

▲ Utilizing NCODA nursing resources (i.e., Welcome Letter) in a quality improvement project at your practice;

▲ Writing an article for NCODA's publication *Oncolytics Today;*

▲ Becoming a member in one of the four NCODA Nursing Community's Sub-committees;

▲ Attending the NCODA Spring Forum or Fall Summit and participating through a poster or presentation;

▲ Sitting on the board of your local ONS chapter; and

▲ Participating in a service activity within your local community

Hallatt, NCODA's first scholarship recipient, noted she enjoyed being active in NCODA from the beginning and participated in many of the organization's programs and events.

April Hallatt

"Little did I know that with each opportunity I participated in, I was working towards an incredible opportunity to attend the 48th Oncology Nursing Society Congress via a scholarship from NCODA," Hallatt said.

The 2023 ONS Congress was held in San Antonio, Texas, from April 26-30. This year's theme was "Rejuvenate, Refocus, and Revitalize."

"Since participating in the NCODA International Spring Forums and Fall Summits, I have dreamed of attending ONS Congress, but due to the cost associated with registration and travel, I knew it would be an event I would need to either focus on saving for personally or explore external financial assistance opportunities," Hallatt said. "When the scholarship was announced, I was so thankful for the support of NCODA for oncology nurses to participate in such an amazing event."

While attending the Congress, Hallatt said she attended sessions that pushed her professionally and empowered her to continue to grow as an oncology nurse.

▲ **Dallas Lawry**, DNP, FNP-C, AOCNP, is an Oncology and Palliative Care Nurse Practitioner at UC San Diego Health in San Diego, California. She also is an Executive Council Member of NCODA and the Membership Engagement & Scholarship Chair for the NCODA Nursing Community.

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FACING THE FINANCIAL TOXICITY OF CANCER

By Katie Snell, AGNP-C, AOCNP

In recent years, mortality rates from cancer have been declining.[1] This is due in part to the evolution of personalized cancer medicine and immunotherapy.

However, the fall in mortality is accompanied by the rising cost of cancer care. Newer targeted treatments are expensive. The cost of treating even the most common cancers has increased.[2]

Katie Snell

In a study conducted from 1998-2014, more than 40% of the 9.5 million cancer survivors aged 50 or over had exhausted their life savings and all other assets two years after diagnosis.[3]

The impact of financial toxicity associated with high out-of-pocket costs for cancer medication is widely reported.[3] Patients must choose between food and prescriptions or pay for treatment on credit cards or borrowed money.[4]

Cost is also a barrier to treatment compliance. Individuals do not pick up prescriptions due to the high price. It is also documented that patients try to make medication last longer by taking less than prescribed or not as scheduled. This can lead to poor outcomes due to underdosing.[5]

ASSISTANCE PROGRAMS

An intervention to address the financial pressure of cancer treatment is the use of medication and patient assistance programs. Medication assistance programs (MAP) are provided by manufacturers to decrease the cost of treatment. Patient assistance programs (PAP) focus on procuring medication at no cost to the patient.[1]

Despite there being approximately 372 programs covering more than 4,100 drugs, cancer patients are often unaware of them and do not have the ability to navigate the lengthy application process and complicated financial assessments required for authorization.[6]

There are cancer centers that employ pharmacy staff to coordinate MAP and

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PAP enrollment. However, this varies depending on the type of cancer center and the patients it serves.[1]

Embedding MAP specialists in oncology clinics has demonstrated multiple benefits: Medication procurement and initiation of treatment is efficient and timely when compared to cancer centers without dedicated MAP personnel.[5]

Cost of treatment can be zero, thus alleviating financial stress for patients. Studies have also highlighted cost savings to organizations in the $1 million and above range due to drug replacement.[5,7]

The cancer centers of Colorado are part of Intermountain Health (formerly Sisters of Charity of Leavenworth). Four outpatient clinics provide oncology and hematology services in communities throughout the Colorado Front Range.

At the downtown location, approximately 25% to 30% patients have no insurance and are accepted for treatment based on charity contract approval through the organization.

The downtown cancer center has been fortunate to have an embedded pharmacy program for several years. The clinical pharmacy team consists of an oncology pharmacist and pharmacy coordinator. Both work closely with physicians advanced practice providers (APPs), nurses, social workers and financial counselors to identify need for PAP or MAP enrollment.

Once an individual is identified as needing financial assistance for cost of medication, the pharmacy coordinator identifies available programs **(see Figure 1)** and assists patients in the application process **(see Figure 2)**. Turnaround time from applying for and receiving medication is approximately three days to one week.

The free oral medication provided in 2022 through PAP resulted in total cost savings of $4,209,037 for patients. Foundation and grant assistance totaled $98,400.

FIGURE 1

SAMPLE LIST OF COMMONLY USED PATIENT ASSISTANCE PROGRAMS*
FOUNDATION ASSISTANCE (GRANTS)
Patient Access Network Foundation
HealthWell Foundation Patient Assistance Program
Leukemia & Lymphoma Society
Intermountain Health Financial Assistance/Charity Care
FREE MEDICATION FROM MANUFACTURERS
Pfizer Oncology Together™
Amgen Safety Net Foundation
myAbbVie Assist
The Bristol Myers Squibb Patient Assistance Foundation
The Johnson & Johnson Patient Assistance Foundation, Inc.
Lilly Cares® Foundation Patient Assistance Program
The Novartis Patient Assistance Foundation, Inc.
Myovant Sciences Inc. Patient Assistance Program

**This figure is intended to be an example, and is not all inclusive.*

NO NATIONAL STANDARDS FOR MAP OR PAP

Despite the demonstrated benefits of MAP and PAP programs for patients and organizations, there is no national standard and utilization of pharmacy teams to assist with these programs. Guidelines vary throughout the United States.

For example, the Commission on Cancer (COC) produces standards that oncology practices need to meet to be recognized as centers of excellence. The major focus of the COC standards is to ensure multidisciplinary care.[8] The 2020 standards make no mention of pharmacists as part of the multidisciplinary team or recommend pharmacy-led PAP programs.

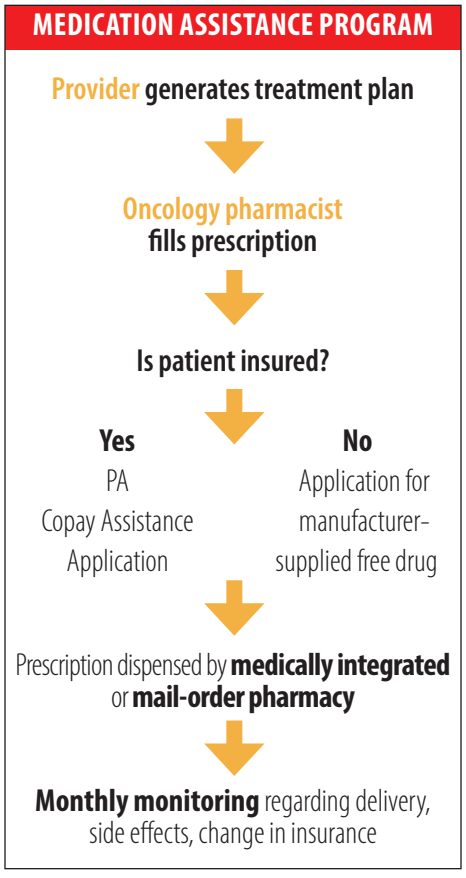
Throughout the standards, there is only one reference regarding financial toxicity. The recommendation is to include assessment of financial needs in cancer survivors. This is disappointing, especially when patients report financial insecurity as a major barrier to initial and ongoing care.

STAFFING BENEFITS

If the COC added pharmacy interventions to the multidisciplinary standards, it may increase the adoption of structured PAP programs with dedicated staff.

Many hospital and health systems are experiencing a shortage of staff,

FIGURE 2



resources and infrastructure to be able to continuously monitor hundreds of drug

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assistance programs, collect patient data and recoup savings.[6] Studies have shown a longer turnaround time for drug procurement at organizations without an embedded pharmacy team.[4]

This can lead to increased symptoms while waiting for medication and adverse outcomes if disease control is delayed. It has been found that there is a per-week increase in mortality for treatment delays especially in curative and early-stage cancers.[9]

Furthermore, the lack of dedicated personnel forces nurses, physicians and pharmacists to spend time handling prior authorizations, which can undermine their direct patient care responsibilities.

The financial burden on clinics associated with missed opportunities, such as lost productivity and administrative efficiency, has been estimated at $2,100 to $78,913 per physician per year.[10,11]

BARRIERS TO ASSISTANCE PROGRAMS

Although patient assistance programs are a lifeline for individuals with high out-of-pocket costs, they are not without issues.

For example, when a medication becomes generic, financial assistance is discontinued, the reasoning being that the medication will be less costly. However, that is not always the case, and patients have no avenue to obtain discounted or free medication.[1]

Another barrier to utilization of PAP programs is seen in patients lacking legal immigration status. Fear regarding deportation impacts the application process. There is reluctance to provide important information, which delays procurement of medication.[12]

There are arguments that patient financial assistance programs can cause a barrier to accessible cancer care. By removing the financial disincentive for use, manufacturers can keep costs high.[13]

Although this is a valid point and highlights the inadequacies in our current healthcare system, it should be addressed at a policy level. PAP programs are, put simply, a lifeline for patients and should not be discontinued.

Oncology practices should consider utilization of PAP programs with dedicated pharmacy staff to assist patients with navigating the difficult application process. Costs associated with pharmacy salaries and program operations can be offset by the millions of dollars in drug savings.

Oncology practices should consider utilization of PAP programs with dedicated pharmacy staff to assist patients with navigating the difficult application process. Costs associated with pharmacy salaries and program operations can be offset by the millions of dollars in drug savings.

Most importantly, patients will not need to be concerned about bankruptcy, debt and food insecurity while being treated for cancer.

▲ **Katie Snell**, AGNP-C, AOCNP is a nurse practitioner at Cancer Centers of Colorado in Denver, Colorado.

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DON'T TAKE NO FOR AN ANSWER

KEY TIPS FOR NAVIGATING HEALTH INSURANCE DENIALS

By Joanna Fawzy Doran, Esq.

At some point during cancer treatment, it is not uncommon for a patient to experience a denial of coverage from an insurance company, whether for a prescription drug, imaging scan, treatment, procedure or even a genetic test. This is sometimes called an "adverse benefit determination."

And, most people take "no" for an answer.

Many patients assume that their insurance company has made a correct decision, accept the denial of coverage and then try to find a way to pay for the medical care themselves. That can include applying for financial assistance programs, crowdfunding or even mortgaging their home.


Joanna Fawzy Doran

However, if an insurance company denies coverage, patients have the right to appeal the decision. Those who don't accept the denial, and pursue the appeals process, may actually win and get coverage for the care prescribed by their healthcare team, up to 60% of the time.

Key stakeholders in the continuum of a patient's care are uniquely positioned to help patients become aware of, and effectively navigate, the appeals process. That includes members of healthcare teams, pharmacists, community health workers and patient advocates.

Even if healthcare providers are not filing appeals on behalf of patients, they still play a key role in the appeals process and can help provide valuable information to help patients get access to the care that they need.

IDENTIFY THE TYPE OF COVERAGE

Appeals can look very different based on an individual's type of coverage:

- Employer-sponsored plans (insured or self-insured)
- Individual plans (e.g., Marketplace plans)
- Medicare (fee-for-service or managed care)
- Medicaid (fee-for-service or managed care)
- Military and veterans coverage

Medicare, Medicaid, military, and veteran's coverage each have specific appeals processes. The Patient Protection and Affordable Care Act (ACA) is a federal law that requires individual and employer-sponsored plans to provide an external appeals process, in addition to an internal appeals process. This is also sometimes referred to as External Medical Review or Independent Medical Review. Note: some states also have these consumer protections at the state level and may actually be more protective.

The regulation of the appeals process also depends on what type of plan patients have. It might be regulated by the U.S. Department of Health & Human Services (HHS) or a state agency or both. To learn more about the federal and state laws governing the appeals process, visit **TriageCancer.org/StateLaws**.

Certain types of coverage for healthcare are not considered insurance at all, such as a healthcare-sharing ministry, and may not be required to have an appeals process.

UNDERSTANDING INTERNAL VS. EXTERNAL APPEALS

If patients have a private insurance plan, like a Marketplace plan or a plan through their employer, they generally have two chances to appeal a denial of coverage: an internal appeal and an external appeal.

When an insurance company first denies coverage for their care, they can file an internal appeal, asking their insurance company to reconsider. Each insurance company has their own internal appeals process, but there are required time frames related to filing an internal appeal.

Standard appeal: For situations that are not medically urgent, a standard appeal can be filed within 180 days of receiving the denial.

If the denial is for a pre-authorization, the insurance company is required to provide an answer, in writing, within 30 calendar days of receiving an appeal.

If the denial is for care that has already been received, the insurance company is required to provide an answer, in writing, within 60 calendar days of receiving an appeal.

Expedited appeal: An expedited appeal

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INSURANCE DENIALS

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(or urgent appeal) can be filed when a delay in treatment would seriously jeopardize the life and/or overall health of a patient, affect a patient's ability to regain maximum function, or subject a patient to severe and intolerable pain. Decisions must be made within 72 hours of receiving the appeal.

If an insurance company denies the internal appeal, a patient can request an external appeal, where an independent entity decides whether or not the care that the patient is being prescribed by their healthcare provider is medically necessary. If they decide that it is, then the insurance company has to cover the care. The external appeals process is meant to ensure a fair and objective review of claim denials.

Standard appeal: Within four months of receiving an insurance company's denial of the internal appeal, a patient can file a written external appeal (note: some states provide additional time). External appeals are completed within 45 days of filing.

Expedited appeal: If urgent, reviews can be expedited, filed at the same time as an internal appeal, and decided within 72 hours.

A patient can file an external review if:

▲ The internal appeal was denied;

▲ The plan fails to return its decision for the internal appeal in the time allowed; or

▲ The patient has an extremely urgent issue and can request to have an external appeal at the same time as the internal appeal.

Appeals can be filed both before and after medical services are provided. The process for filing an appeal before care and after care are slightly different.

For example, if an insurance company has denied a pre-authorization for a prescription drug, the patient can appeal that denial using the internal and external appeals process, if needed.

State insurance agencies or HHS administer external appeals. The HHS process is free, but states cannot charge more than $25 for an external appeal.

USAGE OF THE APPEALS PROCESS

The nationwide data on external appeals shows that on average, external appeals are successful for patients about 50% of the time. Despite being successful for patients, the external appeals process is a very well-kept secret of the healthcare system.

The only types of plans that are required to report data on their numbers of claims, denials, and appeals are Marketplace plans. This requirement was contained in the ACA. Based on 2021 data for Marketplace plans, more than 43 million claims were denied. Only .01% of those claims were appealed to the internal appeals process.

That means that 99.9% of the time that patients were accepting "no" for an answer. And that means that those patients were either paying for that care out of pocket, or not getting access to the care that was prescribed by their healthcare team, because they couldn't afford to pay for it out-of-pocket.

Lack of patient and provider knowledge of the external appeals process is contributing to patients' challenges with access to care, and to the financial burden of a cancer diagnosis.

THREE STEPS TO THE APPEALS PROCESS

1 It is important for the patient to understand why the care was denied. That may be clear from the explanation of benefits. It might also require contacting the insurance company to ask for a detailed explanation of the denial and the company's internal appeals process.

There are several reasons why insurance companies may deny a claim, including:

Mistakes: There may be errors with the patient's information, billing details, or CPT/HCPCS codes. Review the bills, contact providers, and request they resubmit the claim with correct information, and explain the resubmission to the insurance company.

Pre-Authorization: Insurance companies are not required to pay for care if the patient did not get pre-authorization before receiving certain types of care, including prescription drugs.

"Experimental or Investigational": An insurance company may deny care, claiming that it is experimental or investigational. An appeal can be filed. Healthcare providers can help provide information about why they believe that the care is medically necessary.

Service Not Covered: If an insurance company says that the care is not covered, a patient can check their policy to see if the service is listed as "excluded." If not, a patient can contact the insurance company and ask for more information about the denial. They may claim the service was unnecessary. If so, a patient can contact their provider and ask for help showing that the care is medically necessary.

Timely Submission: Claims submitted too long after services were provided may be denied. However, if a provider is within network, fixing this error usually only requires a phone call to the provider. As they are in charge of submitting claims, providers are usually held responsible for this delay.

Coordination of Benefits (COB): If a patient has both a primary and a secondary insurance policy, it's essential to complete and submit COB forms every year. Failing to complete these forms can result in claim denials.

2 A patient should work with their providers to gather evidence for why the medical care should be covered. Evidence to support the appeal can include:

▲ Notes and/or letters of support from healthcare providers;

▲ Results of tests and procedures related to the care in question;

▲ Relevant medical literature, professional journals, and studies showing the effectiveness of the care, especially when appealing denials of care for being experimental or investigational; and

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INSURANCE DENIALS

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▲ A brief and factual personal statement from the patient, describing the need for the requested care.

3 Patients should make sure to pay attention to the deadlines and requirements for their insurance companies' appeals process.

EDUCATING PATIENTS ABOUT THE APPEALS PROCESS

This information can be shared with patients throughout the continuum of a patient's care.

If healthcare providers are not going to file an appeal on behalf of a patient when care is denied coverage, then they can educate patients on the steps to appeal. Healthcare providers can even proactively share the availability of the appeals process when they are discussing treatment options with a patient.

Financial and billing counselors can educate patients and help them understand steps to take if they have received a bill where the claim was denied coverage. And, pharmacists can educate patients about the appeals process if their medications are denied coverage.

For more information about the insurance appeals process, scan the QR code above.

Helping patients successfully navigate the appeals process 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.

Visit **TriageCancer.org/Cancer-Finances-Appeals** for details on the steps to the appeals process based on different types of health insurance plans.

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

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THE CRITICAL ROLE OF HEALTH ADVOCATES: EMPOWERING CHRONICALLY ILL PATIENTS

By Kafilat Salawu, DNP, FNP-C, AOCNP, BCPA

Health advocacy is a critical aspect of our complex healthcare system, emphasizing the importance of providing support and guidance to patients facing chronic illnesses, including cancer.

The Agency for Healthcare Research and Quality defines health advocate as a family member, friend, trusted coworker, or a hired professional who can support patients during their health journey while alleviating stress and enhancing positive recovery.[1]

Kafilat Salawu

Health advocacy goes beyond traditional patient care, offering a holistic approach to ensure patients' well-being. It involves empowering patients to make informed decisions, understanding their healthcare options, communicating effectively with healthcare teams, and navigating the complexities of the medical system.[2]

The role of health advocates in bridging the gap between patients and healthcare providers cannot be overstated. Research has shown that actively engaging patients in their care improves health outcomes, improves satisfaction with the care experience, reduces costs, and benefits the clinician experience.[3,5]

MY PERSONAL HEALTHCARE EXPERIENCE

I had a transformative experience as a caregiver to a sibling who battled a chronic illness. Witnessing the challenges and frustrations of navigating the healthcare system, I realized the urgent need for support and advocacy. My sibling's suboptimal care opened my eyes to the vulnerabilities patients face when trying to access proper medical attention.

My firsthand experience ignited a passion to create an organization that would advocate for patients, ensuring they receive the care they deserve.

Another defining moment in my journey occurred when I witnessed another family's struggle with cancer. I saw how the emotional burden combined with the complexities of treatment decisions left them feeling overwhelmed and lost.

This experience reinforced my belief that every patient should have someone by their side, guiding them through the maze of medical procedures and offering much-needed emotional support.

Personalized advocacy is conceived to be that guiding light for patients and their families, offering them a sense of hope and security during their darkest moments.

As an immigrant patient and caregiver, I faced unique challenges in navigating the healthcare system. Language barriers, cultural differences and unfamiliarity with the healthcare infrastructure added further complexity to the already difficult situation.

These experiences made me acutely aware of the need for culturally competent and sensitive health advocacy services. Professional advocates embrace diversity and strive to ensure that all patients, regardless of their background, receive personalized care and understanding.

My background as a hematology-oncology nurse practitioner significantly shaped my perspective on patient care. Working in a specialized field where the stakes are high, I witnessed the immense impact that patient advocacy can have on treatment outcomes. My experience provided valuable insights into the medical intricacies of chronic illnesses, including cancer, and highlighted the importance of personalized care plans tailored to

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HEALTH ADVOCATES

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each patient's unique needs.

Armed with this knowledge, I embarked on a mission to bridge the gap between clinical expertise and compassionate patient support through a personalized health advocacy approach.

Combining my personal experiences and professional expertise, I founded Fides Health Advocates, LLC, as a beacon of hope for patients facing chronic illnesses. The core values of the organization reflect their commitment to patient empowerment, unwavering support and personalized care:

▲ **EMPOWERING PATIENTS TO MAKE INFORMED DECISIONS:** Informed patients are better equipped to actively participate in their treatment decisions.[3] Health advocates work closely with patients, educating them about their medical conditions, treatment options, and potential outcomes. By fostering open communication between patients and healthcare providers, they empower patients to take charge of their health journey.

▲ **NAVIGATING THE COMPLEX HEALTHCARE SYSTEM:** The labyrinthine healthcare system can be daunting, especially for patients grappling with chronic illnesses. Research shows more than 52% of patients cannot navigate the healthcare system by themselves due to high complexity.[5] This statistic arguably supports the dire need for health advocates. Professional advocates serve as a steadfast guide, helping patients access appropriate medical resources and specialists. They streamline the process of scheduling appointments, coordinating tests, and ensuring seamless transitions between different healthcare settings.

▲ **PROVIDING EMOTIONAL SUPPORT AND UNDERSTANDING:** Chronic illnesses, such as cancer, can take an immense toll on patients and their families emotionally.[4] Professional advocates recognize the significance of psychological support during these challenging times. Health advocates lend a compassionate ear, offering a safe space for patients to express their fears and concerns. They aim to alleviate emotional distress by providing patients and their families with the reassurance that they are not alone in their journey.[2]

BENEFITS OF HEALTHCARE PROFESSIONAL & PROFESSIONAL ADVOCATE COLLABORATION

Professional advocates facilitate seamless communication by acting as a bridge between patients and healthcare providers, ensuring that vital information is shared accurately and promptly.[1,6,7]

Professional advocates enhance patient education and engagement by providing patients with comprehensive information about their conditions and treatment plans. They empower them to make informed decisions and actively participate in their care.[6,7]

Professional advocates identify and address barriers to care through their expertise of promptly recognizing and resolving potential obstacles that patients may encounter, leading to a smoother care experience and improved outcomes.[1,4,6,7]

Professional advocates promote care coordination, disease prevention, and health complications by collaborating with health organizations' care teams to streamline processes, reduce redundancies, and improve the overall efficiency of patient care.[4,6,7]

As noted earlier, the importance of advocating for patient rights and preferences cannot be overstated. Through close collaboration with patients and healthcare professionals, professional advocates ensure that patient preferences and values are respected, fostering a patient-centered approach to care.[5,7,8]

CONCLUSION

Professional health advocates stand as a testament to the transformative power of health advocacy. Grounded in the principles of compassion, empathy and personalized care, advocates' commitment to supporting patients with chronic illnesses, including cancer, has garnered critical acclaim.

Drawing from my personal healthcare experiences as a caregiver, an immigrant patient and a healthcare professional, professional advocates have become a guiding light for those navigating the complexities of chronic illnesses.

Through their unwavering dedication to patient empowerment and support, advocates have not only impacted individual lives but also redefined the role of health advocacy in modern healthcare.

▲ **Kafilat Salawu**, DNP, FNP-C, AOCNP, BCPA, is a Board-Certified Patient Advocate and hematology-oncology nurse practitioner with Fides Health Advocates, LLC, based in Atlanta, Georgia.

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Barry Brooks, MD, MBA, (Texas Oncology/McKesson), moderated a panel on state and federal legislation featuring (from left) Stephen Schleicher, MD, MBA, (Tennessee Oncology), Barbara McAneny, MD, (New Mexico Cancer Center), and Ben Jones, (McKesson).

NCODA ONCOLOGY INSTITUTE BRINGS TOGETHER HEALTHCARE LEADERS & INDUSTRY PARTNERS

More than 200 representatives from more than 40 industry partners and healthcare practices participated in the 2023 NCODA Oncology Institute held Aug. 15-16 in Minneapolis, Minnesota.

The event — **Understanding the Challenges Patients and Practices Face Today: Engaging Partners in Shaping Our Future Together** — now in its fifth year, featured a full day of programs highlighting current legislation, best practices and a variety of other issues.

The NCODA Oncology Institute provides an opportunity for industry partners to meet face-to-face with practice leaders and healthcare professionals to discuss relevant topics and provide better understanding of their needs and objectives.

Chairs for this year's institute were Kathy Oubre, MS, CEO | Pontchartrain Cancer Center, and Stacey McCullough, PharmD, Director of Clinical & Corporate Partner Strategy | NCODA, Paul Bailey, PhD, Senior Director | Pfizer, Shannon Hussey, Senior Director, Trade & Distribution | Sobi, and Matthew Schwarz, MBA, Marketing Director | AbbVie.

The NCODA Oncology Institute provides industry partners with an opportunity to share insight with healthcare leaders on a wide range of relevant topics.

Key presentations included:

▲ **State and Federal Legislation Update: Who Does State Legislation Benefit?** featuring moderator Barry Brooks, MD | Texas Oncology/McKesson, Ben Jones, Vice President, Government Relations & Public Policy | McKesson, Barbara McAneny, MD, CEO | New Mexico Cancer Center, and Stephen Schleicher, MD, MBA, Chief Medical Officer | Tennessee Oncology;

▲ **Best Practices and Current Challenges within the Oncology Landscape** featuring Paul Bailey, PhD (Pfizer), Brian Mulherin, MD, Oncologist | American Oncology Network/Hematology Oncology of Indiana, and Phil Stover, JD, MBA, CEO | Mission Cancer + Blood;

▲ **Understanding Precision Medicine and the Role of the Industry Partner with Medically Integrated Teams** featuring Jonas Congelli, RPh, Chief of Pharmacy, Laboratory, and Nutrition Services | Hematology Oncology Associates of Central New York, John Marshall, MD, Chief, Division of Hematology and Oncology | MedStar Georgetown University Hospital, and Jerry Mitchell, MD, MBA, Director Field Medical Oncology | Foundation Medicine; and

▲ **Breaking Down the Inflation Reduction Act and Its Impact on Patients, Practices and Industry Partners** featuring Erling Donnelly, PhD, Vice President, U.S. Breast Cancer Franchise Lead | Pfizer, and Liz Mahar, Director of Advocacy and Strategic Alliances | PhRMA.

LEGISLATIVE UPDATE

Speaking on the topic of state and federal legislation, McAneny noted that

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Precision medicine and the role industry plays in the medically integrated team is discussed by presenters (from left) Jonas Congelli, RPh, (Hematology Oncology Associates of Central New York), John Marshall, MD, (MedStar Georgetown University Hospital), and Jerry Mitchell, MD, MBA, (Foundation Medicine).

ONCOLOGY INSTITUTE

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the federal Employee Retirement Income Security Act (ERISA), which was designed to standardize insurance coverage across the U.S. for large regional carriers, has overridden any state legislation since 1974.

"It means when you pass a regulation in your state and you say, 'You have to cover cancer care,' the (carriers with) ERISA plans say 'Go pound sand, I don't have to do anything. You can have no control over my benefit design because we are an ERISA plan, not a local plan,'" McAneny said. "And that has stymied, for many, many years, the ability of states to make any difference in what plans pay for and public health issues. It's been a potent tool for the insurance industry that has allowed it to escape oversight by state regulators."

But things are beginning to change. In 2020, the U.S. Supreme Court ruled against an attempt to block state regulation by pharmacy benefit managers (PBMs), noting PBMs are not health plans but rather administrative contractors. As a result, ERISA cannot preempt a state's PBM regulations regarding cost of care.

The ruling has prompted a flurry of Congressional legislation — often bipartisan — including the Pharmacy Benefit Manager Reform Act S1339 and the Pharmacy Benefit Manager Transparency Act of 2023.

"They're looking for transparency, they want to know where the money is going," McAneny said. "But transparency is necessary but not sufficient to control this. If you have transparency, but don't have the teeth to control (abuses), it's sort of an exercise in futility."

The Oncology Institute provided networking opportunities for both healthcare professionals and industry partners.

But, she noted, at least Congress now knows what PBMs are and is beginning to understand the jargon.

"They now know that PBMs are doing all these shenanigans with cost-sharing, they know that they're doing copay maximizers and accumulators, and they know that they're doing spread pricing."

McAneny said she expects the multiple federal legislative initiatives eventually will congeal into one overall bill.

"It'll get watered down; there's a pretty potent lobby on the other side," she noted.

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INDUSTRY PARTNERS REPRESENTED AT THE ONCOLOGY INSTITUTE

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Sobi
Spectrum Pharmaceuticals
SpringWorks Therapeutics
Stemline Therapeutics
Sumitomo Pharma
Syndax
Taiho Oncology

From left: Phil Stover, JD, MBA, (Mission Cancer + Blood), and Paul Bailey, PhD, (Pfizer), presented on Best Practices and Current Challenges with the Oncology Landscape.

ONCOLOGY INSTITUTE

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"Which means that we, NCODA and other organizations need to be active on our side and involved in Congressional races and make sure your Congressperson, even if they're not on the committee of jurisdiction, know what's going on and what these issues are."

BEST PRACTICES

Bailey led a discussion on how industry partners could facilitate better access with practices and how these interactions could be optimized to the benefit of patients.

Mulherin noted that providers are busier than ever in the post-COVID era and possess less time for direct face-to-face interactions. Therefore, he said, partners need to be willing to communicate by other methods and on different schedules.

"You have to be flexible," Mulherin said. "Yes, in person is good because it's nice to put a face on it, it's easier to make connection, but that's not the only way to do it. It's more work on your part, but if you want to reach us, that's what you're going to have to do."

Content is also important, he noted. Physicians care much more about drugs that are new, different or have significant updates — especially drugs that are first in class, unusual or have different affects — than established drugs that will not significantly be updated for years.

Stover agreed. "When you're talking about physician engagement, you have to meet us where we are," he said. "And even then, I have some (physicians) that just won't do it. Still, the majority are interested in learning and hearing more but you really need to find what they need from you as opposed to what you need from them."

Stover noted one effective engagement strategy for representatives involved meeting with doctors at outreach clinics and providing lunch or snacks for the staff.

UNDERSTANDING PRECISION MEDICINE

Oncology has drastically and fundamentally changed over the last 10 years, Marshall noted. Once on the back burner, precision medicine is now at the forefront of cancer research. "We three believe that all cancer patients should be profiled," Marshall said of his co-presenters.

Yet the complexity and ever-evolving nature of the technology can be challenging for the clinician. "The technology is through the roof," he said. "The tests we ordered just a couple years ago are different today."

Mitchell explained that precision medicine focuses on somatic testing. "This is where you take the tumor and sequence the genes in only the tumor itself to determine what is driving it," he said, as opposed to germline testing, which sequences genes in every cell in the body.

The tests are highly nuanced and complex, and can be very difficult for the clinician to understand, Marshall said.

Further complicating the process, Congelli noted, is the testing reports often lack professional interpretation. "It's not always clear what you're supposed to do with the results," he said.

PARTICIPANT FEEDBACK

"This educational forum allows us to sit across the table with the clinical practices to really come up with some solutions, real-time solutions that will not only help enhance the partnerships that we have, but also enhance the clinical practices around the business needs."

Kelli Heathman
West Director of Accounts & Strategic Partners
BeiGene

"(It's an opportunity) to be able to hear, all in one setting, with all of our pharma partners, what's important to us, what's driving us right now, and what, what they can do differently or maybe even better, to help us get the care that our patients need."

Phil Stover, JD, MBA
Chief Executive Officer
Mission Cancer + Blood

"I recommend this to all the different levels of leadership at pharmaceutical companies and also the practices because in one room, you have all these different people coming together asking different questions, but at the same time sharing the same concerns."

Yen Ngyuen, PharmD
Executive Director of Pharmacy
Oncology Consultants

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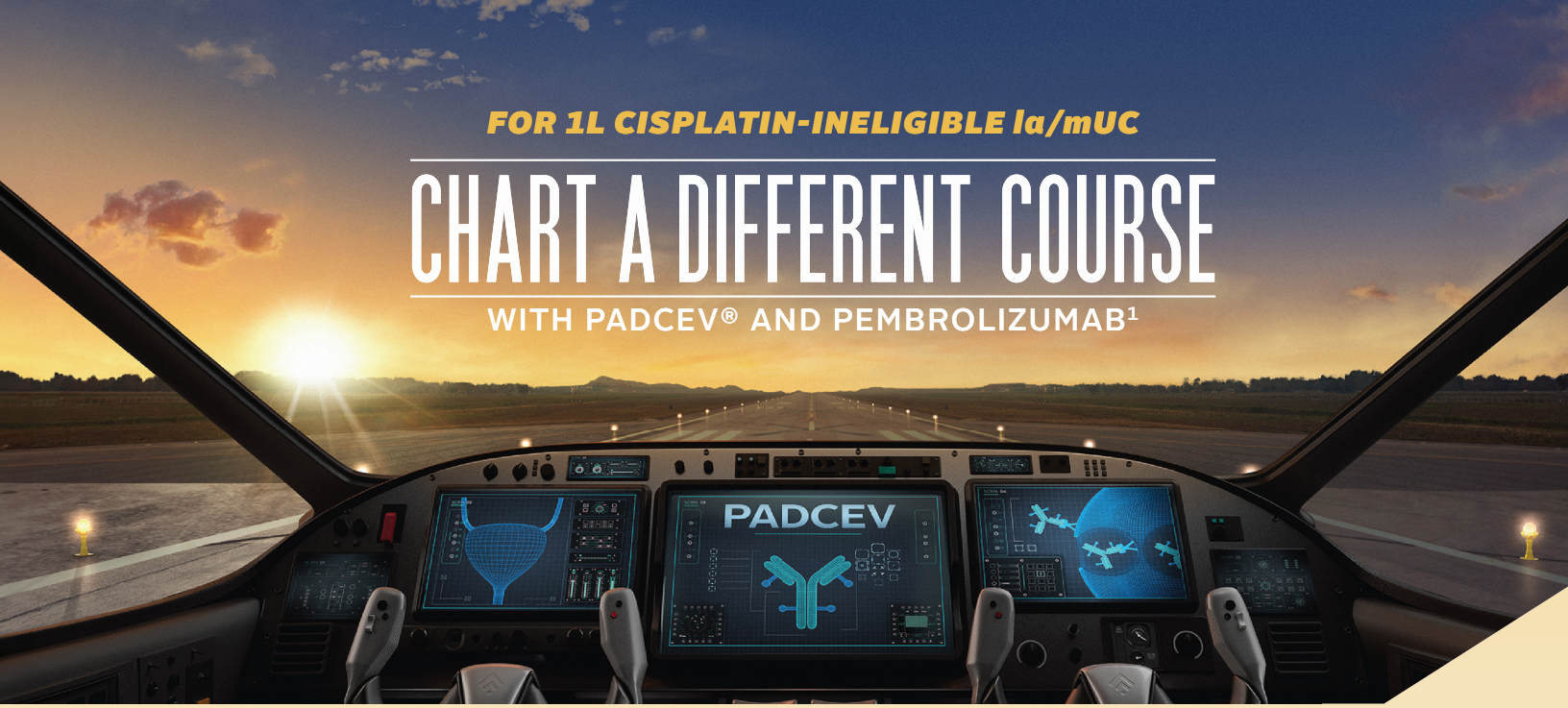

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INDICATION

PADCEV, as a single agent, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who:

- have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

PADCEV, in combination with pembrolizumab, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who are not eligible for cisplatin-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Skin reactions Severe cutaneous adverse reactions, including fatal cases of SJS or TEN occurred in patients treated with PADCEV. SJS and TEN occurred predominantly during the first cycle of treatment but may occur later. Skin reactions occurred in 56% (all grades) of the 753 patients treated with PADCEV as a single agent in clinical trials. Twenty-four percent (24%) of patients had maculo-papular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 12% of patients, including maculo-papular rash, erythematous rash, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. The median time to onset of severe skin reactions was 0.7 months (range: 0.1 to 6 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=59), 24% of patients restarting at the same dose and 16% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 2.6% of patients.

When PADCEV was given in combination with pembrolizumab, the incidence of skin reactions, including severe events, occurred at a higher rate. Skin reactions occurred in 72% (all grades) of the 121 patients treated with PADCEV in combination with pembrolizumab in clinical trials. The majority of the skin reactions that occurred with combination therapy included maculo-papular rash, macular rash and papular rash. Grade 3-4 skin reactions occurred in 20% of patients (Grade 3: 19%, Grade 4: 0.8%), including maculo-papular rash, bullous dermatitis, dermatitis, exfoliative dermatitis, pemphigoid, rash, erythematous rash, macular rash, and papular rash. A fatal reaction of bullous dermatitis occurred in one patient (0.8%). The median time to onset of severe skin reactions was 2.6 months (range: 0.3 to 16 months). Skin reactions led to discontinuation of PADCEV in 6% of patients.

Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated. For persistent or recurrent Grade 2 skin reactions, consider withholding PADCEV until Grade ≤1. Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for Grade 3 skin reactions. Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.

Hyperglycemia and diabetic ketoacidosis (DKA) Hyperglycemia and DKA, including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV. Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials. In clinical trials of PADCEV as a single agent, 14% of the 753 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. Fatal events of hyperglycemia and diabetic ketoacidosis occurred in one patient each (0.1%). The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20 months). Hyperglycemia led to discontinuation of PADCEV in 0.4% of patients. Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. If blood glucose is elevated (>250 mg/dL), withhold PADCEV.

Pneumonitis/Interstitial Lung Disease (ILD) Severe, life-threatening or fatal pneumonitis/ILD occurred in patients treated with PADCEV. In clinical trials of PADCEV as a single agent, 2.9% of the 753 patients treated with PADCEV had pneumonitis/ILD of any grade and 0.8% had Grade 3-4. The median time to onset of pneumonitis/ILD was 2.7 months (range: 0.6 to 6 months). The incidence of pneumonitis/ILD, including severe events occurred at a higher rate when PADCEV was given in combination with pembrolizumab. When PADCEV was given in combination with pembrolizumab, 9% of the 121 patients treated with combination therapy had pneumonitis/ILD of any grade and 3.3% had Grade 3. A fatal event of pneumonitis occurred in one patient (0.8%). The median time to onset of pneumonitis/ILD was 6 months (range: 0.6 to 26 months). Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations. Withhold PADCEV for patients who develop Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis/ILD.

Peripheral neuropathy (PN) Peripheral neuropathy occurred in 53% of the 753 patients treated with PADCEV as a single agent in clinical trials including 40% with sensory neuropathy, 7% with muscular weakness and 7% with motor neuropathy. Thirty percent of patients experienced Grade 2 reactions and 5% experienced Grade 3-4 reactions. Peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 peripheral neuropathy was 4.9 months (range: 0.1 to 20 months). Neuropathy led to treatment discontinuation in 7% of patients. Of the patients who experienced neuropathy who had data regarding resolution (N = 319), 14% had complete resolution, 46% had partial improvement, and 40% had no improvement at the time of their last evaluation. Of the 86% of patients with residual neuropathy at last evaluation, 51% had Grade 2 or greater neuropathy at the time of their last evaluation.

The incidence of peripheral neuropathy occurred at a higher rate when PADCEV was given in combination with pembrolizumab. When PADCEV was given in combination with pembrolizumab, 65% of the 121 patients treated with combination therapy had peripheral neuropathy of any grade, 45% had Grade 2 neuropathy, and 3.3% had Grade 3 neuropathy. The median time to onset of Grade ≥2 peripheral neuropathy was 6 months (range: 0.3 to 25 months).

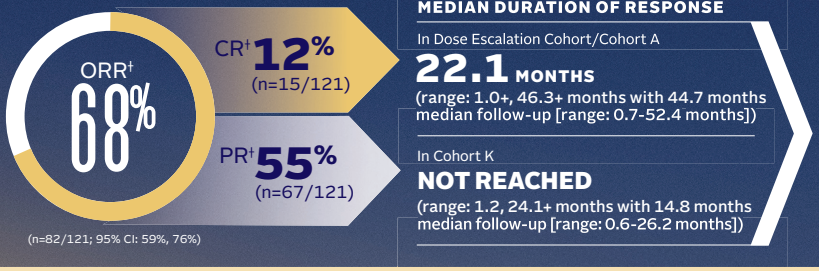
Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs. Permanently discontinue PADCEV in patients who develop Grade ≥3 peripheral neuropathy.

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV as a single agent in clinical trials in which ophthalmologic exams were scheduled. The majority of these events involved the cornea and included events associated with

IN EV-103 COMBINED COHORTS: DOSE ESCALATION, A, AND K*

MORE THAN TWO-THIRDS OF CISPLATIN-INELIGIBLE PATIENTS ACHIEVED A CONFIRMED RESPONSE WITH 1L PADCEV + PEMBROLIZUMAB[1]

MAJOR EFFICACY OUTCOME MEASURE: **CONFIRMED ORR PER BICR[1,2]**



PADCEV®
enfortumab vedotin-ejfv
Injection for IV infusion 20 mg & 30 mg vials

*The EV-103 trial was a phase 1b/2, open-label, multi-cohort (Dose Escalation Cohort [n=5], Cohort A [n=40], and Cohort K [n=76]) trial evaluating PADCEV in combination with pembrolizumab for treatment of la/mUC in 121 patients who were ineligible for cisplatin-containing chemotherapy and received no prior systemic therapy for locally advanced or metastatic disease.

Patients received PADCEV 1.25 mg/kg via IV infusion on days 1 and 8 of every 21-day cycle, in combination with pembrolizumab 200 mg IV on day 1 of every 21-day cycle. The major efficacy outcome measures, confirmed ORR and DOR, were assessed by BICR per RECIST v1.1.[1,2]

†ORR consisted of confirmed CR or PR. CR was defined as the disappearance of all target and nontarget lesions. PR was defined as a ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.[1-3]

dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy. Dry eye symptoms occurred in 34% of patients, and blurred vision occurred in 13% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19 months). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

Infusion site extravasation Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 753 patients treated with PADCEV as a single agent in clinical trials, 1.5% of patients experienced skin and soft tissue reactions, including 0.3% who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

Embryo-fetal toxicity PADCEV can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during PADCEV treatment and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

ADVERSE REACTIONS

Most common adverse reactions, including laboratory abnormalities (≥20%) (PADCEV monotherapy)

Rash, aspartate aminotransferase increased, glucose increased, creatinine increased, fatigue, peripheral neuropathy, lymphocytes decreased, alopecia, decreased appetite, hemoglobin decreased, diarrhea, sodium decreased, nausea, pruritus, phosphate decreased, dysgeusia, alanine aminotransferase increased, anemia, albumin decreased, neutrophils decreased, urate increased, lipase increased, platelets decreased, weight decreased and dry skin.

EV-301 Study: 296 patients previously treated with a PD-1/L1 inhibitor and platinum-based chemotherapy.

Serious adverse reactions occurred in 47% of patients treated with PADCEV; the most common (≥2%) were urinary tract infection, acute kidney injury (7% each) and pneumonia (5%). Fatal adverse reactions occurred in 3% of patients, including multiorgan dysfunction (1.0%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis and pelvic abscess (0.3% each). Adverse reactions leading to discontinuation occurred in 17% of patients; the most common (≥2%) were PN (5%) and rash (4%). Adverse reactions leading to dose interruption occurred in 61% of patients; the most common (≥4%) were PN (23%), rash (11%) and fatigue (9%). Adverse reactions leading to dose reduction occurred in 34% of patients; the most common (≥2%) were PN (10%), rash (8%), decreased appetite and fatigue (3% each). Clinically relevant adverse reactions (<15%) include vomiting (14%), AST increased (12%), hyperglycemia (10%), ALT increased (9%), pneumonitis (3%) and infusion site extravasation (0.7%).

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

Serious adverse reactions occurred in 39% of patients treated with PADCEV; the most common (≥3%) were pneumonia, sepsis and diarrhea (5% each). Fatal adverse reactions occurred in 8% of patients, including acute kidney injury (2.2%), metabolic acidosis, sepsis, multiorgan dysfunction, pneumonia and pneumonitis (1.1% each). Adverse reactions leading to discontinuation occurred in 20% of patients; the most common (≥2%) was PN (7%). Adverse reactions leading to dose interruption occurred in 60% of patients; the most common (≥3%) were PN (19%), rash (9%), fatigue (8%), diarrhea (5%), AST increased and hyperglycemia (3% each). Adverse reactions leading to dose reduction occurred in 49% of patients; the most common (≥3%) were PN (19%), rash (11%) and fatigue (7%). Clinically relevant adverse reactions (<15%) include vomiting (13%), AST increased (12%), lipase increased (11%), ALT increased (10%), pneumonitis (4%) and infusion site extravasation (1%).

EV-103 Study: 121 patients with previously untreated locally advanced or metastatic urothelial cancer who were not eligible for cisplatin-containing chemotherapy (PADCEV in combination with pembrolizumab)

The **most common adverse reactions** including laboratory abnormalities (≥20%), of PADCEV in combination with pembrolizumab were glucose increased, aspartate aminotransferase increased, rash, hemoglobin decreased, creatinine increased, peripheral neuropathy, lymphocytes decreased, fatigue, alanine aminotransferase increased, sodium decreased, lipase increased, albumin decreased, alopecia, phosphate decreased, decreased weight, diarrhea, pruritus, decreased appetite, nausea, dysgeusia, potassium decreased, neutrophils decreased, urinary tract infection, constipation, potassium increased, calcium increased, peripheral edema, dry eye, dizziness, arthralgia, and dry skin.

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab. The **most common serious adverse reactions** (≥2%) were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), sepsis (3.3%), pneumonia (3.3%), hematuria (3.3%), pneumonitis (3.3%), urinary retention (2.5%), diarrhea (2.5%), myasthenia gravis (2.5%), myositis (2.5%), anemia (2.5%), and hypotension (2.5%). **Fatal adverse reactions** occurred in 5% of patients treated with PADCEV in combination with pembrolizumab including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis/ILD (0.8%). Adverse reactions leading to discontinuation of PADCEV occurred in 36% of patients. The **most common adverse reactions (≥2%) leading to discontinuation** of PADCEV were peripheral neuropathy (20%) and rash (6%). Adverse reactions leading to dose interruption of PADCEV occurred in 69% of patients. The **most common adverse reactions (≥2%) leading to dose interruption** of PADCEV were peripheral neuropathy (18%), rash (12%), lipase increased (6%), pneumonitis (6%), diarrhea (4.1%), acute kidney injury (3.3%), alanine aminotransferase increased (3.3%), fatigue (3.3%), neutropenia (3.3%), urinary tract infection (3.3%), amylase increased (2.5%), anemia (2.5%), COVID-19 (2.5%), hyperglycemia (2.5%), and hypotension (2.5%). Adverse reactions leading to dose reduction of PADCEV occurred in 45% of patients. The **most common adverse reactions (≥2%) leading to dose reduction** of PADCEV were peripheral neuropathy (17%), rash (12%), fatigue (5%), neutropenia (5%), and diarrhea (4.1%).

DRUG INTERACTIONS

Effects of other drugs on PADCEV (*Dual P-gp and Strong CYP3A4 Inhibitors*) Concomitant use with dual P-gp and strong CYP3A4 inhibitors may increase unconjugated monomethyl auristatin E exposure, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with dual P-gp and strong CYP3A4 inhibitors.

SPECIFIC POPULATIONS

Lactation Advise lactating women not to breastfeed during treatment with PADCEV and for at least 3 weeks after the last dose.

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

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

DISCOVER ADDITIONAL PADCEV + PEMBROLIZUMAB 1L COMBINATION DATA

Scan the code to learn more at **PADCEV1LCombination.com**

1L=first-line; BICR=blinded independent central review; CI=confidence interval; CR=complete response; DOR=duration of response; IV=intravenous; la/mUC=locally advanced or metastatic urothelial cancer; ORR=objective response rate; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

References: 1. PADCEV [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Seagen Inc. and Astellas. PADCEV. Data on File. **3.** Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

astellas ONCOLOGY Seagen

PADCEV®
enfortumab vedotin-ejfv
Injection for IV infusion 20 mg & 30 mg vials

PADCEV® (enfortumab vedotin-ejfv) for injection, for intravenous use

The following is a brief summary of the full Prescribing Information. **Please see the package insert for full prescribing information including BOXED WARNING**.

WARNING: SERIOUS SKIN REACTIONS

- **PADCEV can cause severe and fatal cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which occurred predominantly during the first cycle of treatment, but may occur later.**
- **Closely monitor patients for skin reactions.**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.**

INDICATIONS AND USAGE

PADCEV, as a single agent, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who:

- have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

PADCEV, in combination with pembrolizumab, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who are not eligible for cisplatin-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dose of PADCEV as a single agent is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

When given in combination with pembrolizumab, the recommended dose of PADCEV is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. Refer to the pembrolizumab Prescribing Information for the recommended dosing information of pembrolizumab.

Dose Modifications

Table 1. Dose Modifications

Adverse Reaction	Severity[1]	Dose Modification[1]
Skin Reactions	For persistent or recurrent Grade 2 skin reactions	Consider withholding until Grade ≤1, then resume treatment at the same dose level or dose reduce by one dose level.
	Grade 3 skin reactions	Withhold until Grade ≤1, then resume treatment at the same dose level or dose reduce by one dose level.
	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 2-4 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
Hyperglycemia	Blood glucose >250 mg/dL	Withhold until elevated blood glucose has improved to ≤250 mg/dL, then resume treatment at the same dose level.
Pneumonitis/ Interstitial Lung Disease (ILD)	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade ≥3	Permanently discontinue.
Peripheral Neuropathy	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level.
	Grade ≥3	Permanently discontinue.
Other nonhematologic toxicity	Grade 3	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Permanently discontinue.
Hematologic toxicity	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Withhold until Grade ≤1, then reduce dose by one dose level or discontinue treatment.

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

Table 2. Recommended Dose Reduction Schedule

	Dose Level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

WARNINGS AND PRECAUTIONS

Skin Reactions

Severe cutaneous adverse reactions, including fatal cases of SJS or TEN occurred in patients treated with PADCEV. SJS and TEN occurred predominantly during the first cycle of treatment but may occur later.

Skin reactions occurred in 56% (all grades) of the 753 patients treated with PADCEV as a single agent in clinical trials. Twenty-four percent (24%) of patients had maculo-papular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 12% of patients, including maculo-papular rash, erythematous rash, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. The median time to onset of severe skin reactions was 0.7 months (range: 0.1 to 6 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=59), 24% of patients restarting at the same dose and 16% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 2.6% of patients.

When PADCEV was given in combination with pembrolizumab, the incidence of skin reactions, including severe events, occurred at a higher rate. Skin reactions occurred in 72% (all grades) of the 121 patients treated with PADCEV in combination with pembrolizumab in clinical trials. The majority of the skin reactions that occurred with combination therapy included maculo-papular rash, macular rash and papular rash. Grade 3-4 skin reactions occurred in 20% of patients (Grade 3: 19%, Grade 4: 0.8%), including maculo-papular rash, bullous dermatitis, dermatitis, exfoliative dermatitis, pemphigoid, rash, erythematous rash, macular rash, and papular rash. A fatal reaction of bullous dermatitis occurred in one patient (0.8%). The median time to onset of severe skin reactions was 2.6 months (range: 0.3 to 16 months). Skin reactions led to discontinuation of PADCEV in 6% of patients.

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

For persistent or recurrent Grade 2 skin reactions, consider withholding PADCEV until Grade ≤1. Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for Grade 3 skin reactions.

Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.

Hyperglycemia

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV.

Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials.

In clinical trials of PADCEV as a single agent, 14% of the 753 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. Fatal events of hyperglycemia and diabetic ketoacidosis occurred in one patient each (0.1%). The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20 months). Hyperglycemia led to discontinuation of PADCEV in 0.4% of patients.

Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia.

If blood glucose is elevated (>250 mg/dL), withhold PADCEV.

Pneumonitis/Interstitial Lung Disease (ILD)

Severe, life-threatening or fatal pneumonitis/ILD occurred in patients treated with PADCEV.

In clinical trials of PADCEV as a single agent, 2.9% of the 753 patients treated with PADCEV had pneumonitis/ILD of any grade and 0.8% had Grade 3-4. The median time to onset of pneumonitis/ILD was 2.7 months (range: 0.6 to 6 months).

The incidence of pneumonitis/ILD, including severe events occurred at a higher rate when PADCEV was given in combination with pembrolizumab. When PADCEV was given in combination with pembrolizumab, 9% of the 121 patients treated with combination therapy had pneumonitis/ILD of any grade and 3.3% had Grade 3. A fatal event of pneumonitis occurred in one patient (0.8%). The median time to onset of pneumonitis/ILD was 6 months (range: 0.6 to 26 months).

Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations.

Withhold PADCEV for patients who develop Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis/ILD.

Peripheral Neuropathy

Peripheral neuropathy occurred in 53% of the 753 patients treated with PADCEV as a single agent in clinical trials including 40% with sensory neuropathy, 7% with muscular weakness and 7% with motor neuropathy. Thirty percent of patients experienced Grade 2 reactions and 5% experienced Grade 3-4 reactions. Peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 peripheral neuropathy was 4.9 months (range: 0.1 to 20 months). Neuropathy led to treatment discontinuation in 7% of patients. Of the patients who experienced neuropathy who had data regarding resolution (N = 319) 14% had complete resolution, 46% had partial improvement, and 40% had no improvement at the time of their last evaluation. Of the 86% of patients with residual neuropathy at last evaluation, 51% had Grade 2 or greater neuropathy at the time of their last evaluation.

The incidence of peripheral neuropathy occurred at a higher rate when PADCEV was given in combination with pembrolizumab. When PADCEV was given in combination with pembrolizumab, 65% of the 121 patients treated with combination therapy had peripheral neuropathy of any grade, 45% had Grade 2 neuropathy, and 3.3% had Grade 3 neuropathy. The median time to onset of Grade ≥2 peripheral neuropathy was 6 months (range: 0.3 to 25 months).

Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs.

Permanently discontinue PADCEV in patients who develop Grade ≥3 peripheral neuropathy.

Ocular Disorders

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV as a single agent in clinical trials in which ophthalmologic exams were scheduled. The majority of these events involved the cornea and included events associated with dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy.

Dry eye symptoms occurred in 34% of patients, and blurred vision occurred in 13% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19 months). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

Infusion Site Extravasation

Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 753 patients treated with PADCEV as a single agent in clinical trials, 1.5% of patients experienced skin and soft tissue reactions, including 0.3% who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of enfortumab vedotin-ejfv to pregnant rats during the period of organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures similar to the clinical exposures at the recommended human dose of 1.25 mg/kg.

Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

ADVERSE REACTIONS

Clinical Trials Experience

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

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to PADCEV as a single agent at 1.25 mg/kg in 753 patients in EV-301, EV-201, EV-103, EV-101 (NCT02091999), and EV-102 (NCT03070990). In addition, certain subsections in the WARNINGS AND PRECAUTIONS describe adverse reactions observed with exposure to PADCEV in combination with pembrolizumab at 1.25 mg/kg in 121 patients in EV-103. Ocular disorders reflect 384 patients in EV-201, EV-101, and EV-102. Among 753 patients receiving PADCEV as a single agent, 25% were exposed for ≥6 months, and 13% were exposed for ≥12 months. In this pooled population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were rash, aspartate aminotransferase increased, glucose increased, creatinine increased, fatigue, peripheral neuropathy, lymphocytes decreased, alopecia, decreased appetite, hemoglobin decreased, diarrhea, sodium decreased, nausea, pruritus, phosphate decreased, dysgeusia, alanine aminotransferase increased, anemia, albumin decreased, neutrophils decreased, urate increased, lipase increased, platelets decreased, decreased weight and dry skin.

The data described in the following sections reflect exposure to PADCEV as a single agent from an open-label, randomized, study (EV-301); Cohort 1 and Cohort 2 of an open-label, single arm, two cohort study (EV-201); and Cohort K of an open-label, multi-cohort study (EV-103). Patients received PADCEV 1.25 mg/kg until disease progression or unacceptable toxicity.

The data described in the following section also reflects exposure to PADCEV in combination with pembrolizumab from the dose escalation cohort, Cohort A and Cohort K of EV-103. Patients received PADCEV 1.25 mg/kg in combination with pembrolizumab until disease progression or unacceptable toxicity.

Previously Treated Locally Advanced or Metastatic Urothelial Cancer

EV-301

The safety of PADCEV was evaluated as a single agent in EV-301 in patients with locally advanced or metastatic urothelial cancer (n=296) who received at least one dose of PADCEV 1.25 mg/kg and who were previously treated with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy. Routine ophthalmologic exams were not conducted in EV-301. The median duration of exposure to PADCEV was 5 months (range: 0.5 to 19 months).

Serious adverse reactions occurred in 47% of patients treated with PADCEV. The most common serious adverse reactions (≥2%) were urinary tract infection, acute kidney injury (7% each) and pneumonia (5%). Fatal adverse reactions occurred in 3% of patients, including multiorgan dysfunction (1.0%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis and pelvic abscess (0.3% each).

Adverse reactions leading to discontinuation occurred in 17% of patients; the most common adverse reactions (≥2%) leading to discontinuation were peripheral neuropathy (5%) and rash (4%).

Adverse reactions leading to dose interruption occurred in 61% of patients; the most common adverse reactions (≥4%) leading to dose interruption were peripheral neuropathy (23%), rash (11%) and fatigue (9%).

Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions (≥2%) leading to dose reduction were peripheral neuropathy (10%), rash (8%), decreased appetite (3%) and fatigue (3%).

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

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

Adverse Reaction	PADCEV n=296		Chemotherapy n=291	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash[1]	54	14	20	0.3
Alopecia	47	0	38	0
Pruritus	34	2	7	0
Dry skin	17	0	4	0
General disorders and administration site conditions				
Fatigue[2]	50	9	40	7
Pyrexia[3]	22	2	14	0
Nervous system disorders				
Peripheral neuropathy[4]	50	5	34	3
Dysgeusia[5]	26	0	8	0
Metabolism and nutrition disorders				
Decreased appetite	41	5	27	2
Gastrointestinal disorders				
Diarrhea[6]	35	4	23	2
Nausea	30	1	25	2
Constipation	28	1	25	2
Abdominal Pain[7]	20	1	14	3
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[8]	25	2	35	5
Eye Disorders				
Dry eye[9]	24	0.7	6	0.3
Blood and lymphatic system disorders				
Anemia	20	6	30	12
Infections and infestations				
Urinary Tract Infection[10]	17	6	13	3
Vascular disorders				
Hemorrhage[11]	17	3	13	2
Investigations				
Weight decreased	16	0.3	7	0

[1]Includes: blister, blood blister, conjunctivitis, dermatitis, dermatitis bullous, drug eruption, eczema, erythema, erythema multiforme, exfoliative rash, intertrigo, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, skin irritation, skin exfoliation, stomatitis

[2]Includes: fatigue, asthenia

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

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

[5]Includes: dysgeusia, ageusia, hypogeusia

[6]Includes: diarrhea, colitis, enterocolitis

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

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

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

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

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

Clinically relevant adverse reactions (<15%) include vomiting (14%), aspartate aminotransferase increased (12%), hyperglycemia (10%), alanine aminotransferase increased (9%), pneumonitis (3%) and infusion site extravasation (0.7%).

EV-201, Cohort 2

The safety of PADCEV was evaluated as a single agent in EV-201, Cohort 2 in patients with locally advanced or metastatic urothelial cancer (n=89) who received at least one dose of PADCEV 1.25 mg/kg and had prior treatment with a PD-1 or PD-L1 inhibitor and were not eligible for cisplatin-based chemotherapy. The median duration of exposure was 5.98 months (range: 0.3 to 24.6 months).

Serious adverse reactions occurred in 39% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were pneumonia, sepsis and diarrhea (5% each). Fatal adverse reactions occurred in 8% of patients, including acute kidney injury (2.2%), metabolic acidosis, sepsis, multiorgan dysfunction, pneumonia and pneumonitis (1.1% each).

Adverse reactions leading to discontinuation occurred in 20% of patients; the most common adverse reaction (≥2%) leading to discontinuation was peripheral neuropathy (7%).

Adverse reactions leading to dose interruption occurred in 60% of patients; the most common adverse reactions (≥3%) leading to dose interruption were peripheral neuropathy (19%), rash (9%), fatigue (8%), diarrhea (5%), aspartate aminotransferase increased (3%) and hyperglycemia (3%).

Adverse reactions leading to dose reduction occurred in 49% of patients; the most common adverse reactions (≥3%) leading to dose reduction were peripheral neuropathy (19%), rash (11%) and fatigue (7%).

Table 4 summarizes the All Grades and Grades 3-4 adverse reactions reported in patients in EV-201, Cohort 2.

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

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

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

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

[3]Includes: dysgeusia, ageusia, hypogeusia

[4]Includes: fatigue, asthenia

[5]Includes: diarrhea, colitis, enterocolitis

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

Clinically relevant adverse reactions (<15%) include vomiting (13%), aspartate aminotransferase increased (12%), lipase increased (11%), alanine aminotransferase increased (10%), pneumonitis (4%) and infusion site extravasation (1%).

Previously Untreated Cisplatin Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

EV-103

The safety of PADCEV was evaluated in combination with pembrolizumab in a multi cohort study (EV-103) in 121 patients with locally advanced or metastatic urothelial cancer who were not eligible for cisplatin-containing chemotherapy and received at least one dose of PADCEV 1.25 mg/kg and pembrolizumab. The median duration of exposure to PADCEV was 7 months (range: 0.6 to 33 months).

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab. The most common serious adverse reactions (≥2%) were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%),

sepsis (3.3%), pneumonia (3.3%), hematuria (3.3%), pneumonitis (3.3%), urinary retention (2.5%), diarrhea (2.5%), myasthenia gravis (2.5%), myositis (2.5%), anemia (2.5%) and hypotension (2.5%).

Fatal adverse reactions occurred in 5% of patients treated with PADCEV in combination with pembrolizumab including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis/ILD (0.8%).

Adverse reactions leading to discontinuation of PADCEV occurred in 36% of patients. The most common adverse reactions (≥2%) leading to discontinuation of PADCEV were peripheral neuropathy (20%) and rash (6%).

Adverse reactions leading to dose interruption of PADCEV occurred in 69% of patients. The most common adverse reactions (≥2%) leading to dose interruption of PADCEV were peripheral neuropathy (18%), rash (12%), lipase increased (6%), pneumonitis (6%), diarrhea (4.1%), acute kidney injury (3.3%), alanine aminotransferase increased (3.3%), fatigue (3.3%), neutropenia (3.3%), urinary tract infection (3.3%), amylase increased (2.5%), anemia (2.5%), COVID-19 (2.5%), hyperglycemia (2.5%), and hypotension (2.5%).

Adverse reactions leading to dose reduction of PADCEV occurred in 45% of patients. The most common adverse reactions (≥2%) leading to dose reduction of PADCEV were peripheral neuropathy (17%), rash (12%), fatigue (5%), neutropenia (5%), and diarrhea (4.1%).

The most common adverse reactions (≥20%), including laboratory abnormalities, of PADCEV in combination with pembrolizumab were glucose increased, aspartate aminotransferase increased, rash, hemoglobin decreased, creatinine increased, peripheral neuropathy, lymphocytes decreased, fatigue, alanine aminotransferase increased, sodium decreased, lipase increased, albumin decreased, alopecia, phosphate decreased, decreased weight, diarrhea, pruritus, decreased appetite, nausea, dysgeusia, potassium decreased, neutrophils decreased, urinary tract infection, constipation, potassium increased, calcium increased, peripheral edema, dry eye, dizziness, arthralgia, and dry skin.

Table 5 summarizes the most common (≥20%) adverse reactions in EV-103.

Table 5. Adverse Reactions ≥20% (All Grades) in Patients Treated with PADCEV in Combination with Pembrolizumab in EV-103

	PADCEV in combination with pembrolizumab n=121	
Adverse Reaction	**All Grades (%)**	**Grades 3-4 (%)**
Skin and subcutaneous tissue disorders		
Rash[1]	71	21
Alopecia	52	0
Pruritus	40	3.3
Dry skin	21	0.8
Nervous system disorders		
Peripheral neuropathy[2]	65	3.3
Dysgeusia	35	0
Dizziness	23	0
General disorders and administration site conditions		
Fatigue	60	11
Peripheral edema	26	0
Investigations		
Decreased weight	48	5
Gastrointestinal disorders		
Diarrhea	45	7
Nausea	36	0.8
Constipation	27	0
Metabolism and nutrition disorders		
Decreased appetite	38	0.8
Infections and Infestations		
Urinary tract infection	30	12
Eye disorders		
Dry eye	25	0
Musculoskeletal and connective tissue disorders		
Arthralgia	23	1.7

[1]Includes: blister, conjunctivitis, dermatitis, dermatitis bullous, dermatitis exfoliative generalized, erythema, erythema multiforme, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, pemphigoid, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, skin exfoliation, stomatitis

[2]Includes: dysesthesia, hypoesthesia, muscular weakness, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, gait disturbance

Clinically relevant adverse reactions (<20%) include vomiting (19.8%), pyrexia (18%), hypothyroidism (11%), pneumonitis (9%), myasthenia gravis (2.5%), myositis (3.3%), and infusion site extravasation (0.8%).

DRUG INTERACTIONS

Effects of Other Drugs on PADCEV

Dual P-gp and Strong CYP3A4 Inhibitors

Concomitant use with dual P-gp and strong CYP3A4 inhibitors may increase unconjugated monomethyl auristatin E (MMAE) exposure which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with dual P-gp and strong CYP3A4 inhibitors.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. There are no available human data on PADCEV use in pregnant women to inform a drug-associated risk. In an animal reproduction study, administration of enfortumab vedotin-ejfv to pregnant rats during organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures similar to the exposures at the recommended human dose of 1.25 mg/kg. Advise patients of the potential risk to the fetus.

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

Lactation

Risk Summary

There are no data on the presence of enfortumab vedotin-ejfv in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with PADCEV and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating PADCEV treatment.

Contraception

Females

PADCEV can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

Infertility

Females

Based on findings in animal studies with MMAE-containing antibody-drug conjugates (ADCs), PADCEV may impair female fertility. The effect on fertility is reversible.

Males

Based on findings from animal studies, PADCEV may impair male fertility.

Pediatric Use

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

Geriatric Use

Of the 753 patients treated with PADCEV as a single agent in clinical trials, 40% (n=300) were 65-74 years and 27% (n=202) were 75 years or older. Of the 121 patients treated with PADCEV in combination with pembrolizumab, 43% (n=52) were 65-74 years and 33% (n=40) were 75 years or older. No overall differences in effectiveness were observed between patients 65 years of age or older and younger patients.

Patients 65 years of age or older treated with PADCEV as a single agent experienced a higher incidence of serious and fatal adverse reactions than younger patients. In clinical trials, the incidence of serious adverse reactions was 42% in patients younger than 65 years, 45% in patients ages 65-74 years, and 49% in patients 75 years or older. The incidence of fatal adverse reactions was 4.4% in patients younger than 65 years, 6% in patients ages 65-74 years, and 11% in patients 75 years or older. The incidence of treatment discontinuations of PADCEV due to adverse reactions was 17% in patients younger than 65 years, 20% in patients ages 65-74 years, and 26% in patients 75 years or older.

There were an insufficient number of patients treated with PADCEV in combination with pembrolizumab in clinical trials to accurately characterize safety by age.

No significant difference was observed in the pharmacokinetics of PADCEV between patients 65 years and older and younger patients.

Hepatic Impairment

Avoid the use of PADCEV as a single agent in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and AST any). PADCEV has only been studied in a limited number of patients with moderate hepatic impairment (n=3) and has not been evaluated in patients with severe hepatic impairment. In another antibody-drug conjugate (ADC) that contains MMAE, the frequency of ≥ Grade 3 adverse reactions and deaths was greater in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment compared to patients with normal hepatic function. No adjustment in the starting dose is required when administering PADCEV to patients with mild hepatic impairment (total bilirubin 1 to 1.5 × ULN and AST any, or total bilirubin ≤ULN and AST >ULN).

Renal Impairment

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

Immunogenicity

The observed incidence of anti-drug antibody (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of PADCEV or of other enfortumab vedotin products.

In the 0.3-to-52.1-month treatment periods with ADA sampling in five clinical studies of PADCEV 1.25 mg/kg as a single agent in patients with locally advanced or metastatic urothelial cancer, the incidence of treatment emergent anti-enfortumab vedotin-ejfv antibody formation was 3.6% [23 of 640 total PADCEV-treated patients who were tested for ADA]. When PADCEV was administered in combination with pembrolizumab, the incidence of treatment emergent ADA against enfortumab vedotin-ejfv was 2.9% [3 of 105 total PADCEV-treated patients who were tested for ADA]. The incidence of treatment-emergent anti-enfortumab-ejfv antibody formation was consistent when assessed following PADCEV administration as a single agent and in combination with pembrolizumab.

Because of the low occurrence of ADA, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of PADCEV is unknown.

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CAREER LADDER DEVELOPMENT: EMPOWERING PHARMACY TECHS TO TAKE ON ADVANCED ROLES

By Tom Greenlee, PharmD, & Kayla Hodges, CPhT

Pharmacists have a history of seeking opportunities to expand their scope of practice and finding innovative ways to serve patients.

You need only look at the last three decades to find examples such as pharmacists immunizing, billing for Medication Therapy Management services, and capitalizing on state-level authority to prescribe medications such as oral contraceptives and nicotine replacement therapy.

Tom Greenlee

Kayla Hodges

For every expansion of pharmacist scope of practice, more duties are potentially added to the pharmacist workload. To keep up, healthcare organizations must decide whether to hold their pharmacists back from practicing at the top of their license, hire more pharmacists to account for new responsibilities, or find a way to empower pharmacy technicians to take on advanced roles to backfill pharmacist duties.

Pharmacy technicians across the country have answered this call, commonly performing advanced tasks which used to be exclusive to pharmacists. Common roles and associated tasks include:[1]

ACUTE CARE: lead technicians, technician coordinators, medication histories, infusion technician;

AMBULATORY CARE: completing prior authorizations and patient assistance requests, managing medication adherence, delivery of medications to the bedside, identifying patients that may benefit from pharmacist intervention;

TECHNOLOGY AND AUTOMATION: informatics, implementation/management of dispensing technology;

PURCHASING AND FINANCE: buyer, revenue recovery, accounts receivable;

COMPLIANCE AND AUDITING: controlled substance diversion monitoring, 340B, financial compliance such as retail payor audits; and

SUPERVISORY: management of schedules, training, operations and workflow management.

Technicians and pharmacists pushing in the same direction creates innovation and fosters an environment that supports an expanded scope of pharmacy practice.

DIRE SHORTAGE OF PHARMACY TECHNICIANS

Building out teams of pharmacy technicians in advanced roles within your practice setting seems like an obvious strategy to push pharmacy scope of practice. Unfortunately, community pharmacies and healthcare organizations across the country are facing a dire shortage of pharmacy technicians.

Building out pharmacy technician career ladders ... not only addresses the current challenges of hiring and retaining technicians, but also provides a pathway to elevated pharmacy practice and enhanced patient care.

A 2022 survey by the National Community Pharmacists Association found that 76% of community pharmacists reported staff shortages, with almost 90% reporting difficulty filling positions for pharmacy technicians.[2]

Just as the cause of the shortage is multifactorial, there are multiple strategies being deployed by healthcare organizations across the country to respond to the nationwide technician shortage.

Pharmacies are increasing technician wages, offering sign-on and retention bonuses, shortening hours of operation, embracing remote work opportunities, and building out technician career ladders.

It is this final strategy — building out pharmacy technician career ladders — that we wish to examine in more detail. This strategy not only addresses the current challenges of hiring and retaining technicians, but also provides a pathway to elevated pharmacy practice and enhanced patient care.

Note that an effective strategy to comprehensively address the pharmacy technician shortage will likely involve deploying multiple tactics simultaneously to meet your organization's clinical and operational pharmacy needs.

MANY SEEKING ADVANCEMENT

The American Society of Health-System Pharmacists' 2021 Survey reported that of nearly 75,000 technicians surveyed, 25% stated a desire for a career ladder with clear pathways to promotion.[3] Building out career ladders can be a powerful employee engagement tool, and increased employee engagement in healthcare settings leads to:[4]

- Improved quality of care;
- Enhanced financial performance;
- Increased patient safety; and
- Elevation of patient experience.

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CAREER LADDER

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The pharmacy department at University of Missouri Health Care (MUHC) has developed a pharmacy technician career ladder and now offers 17 unique pharmacy technician-level positions over six different levels of compensation.

Developing a more robust career ladder should be an intentional pursuit involving six key components:

1. Conducting department self-assessments.
2. Identifying opportunities.
3. Creating job descriptions.
4. Developing training and competencies.
5. Engaging key stakeholders (employees and organizational leadership buy-in).
6. Continuous formal and informal reviews.

These components are not sequential, and some may be done in parallel. For example, a complete department self-assessment may not be necessary if a leader identifies an opportunity to create a new advanced technician role to meet an organizational need.

However, consideration should be given to each of these components over time to ensure that your pharmacy technician career ladder is meeting the needs of your organization and driving pharmacy technician engagement.

A SUCCESSFUL STRATEGY

As mentioned earlier, the MUHC pharmacy department currently offers technicians 17 job codes over six different pay scales. As recent as 2017, MUHC only offered seven pharmacy technician job codes over five different pay scales.

Accelerated growth of this well-developed career ladder was not the result of a single push to expand opportunities for technicians within our department. Instead, it is the result of continually working the six components listed above and, most importantly, being opportunistic by matching unmet health system needs with formal opportunities to deploy pharmacy technicians in advanced roles.

From the healthcare organization perspective, investment in a well-developed technician career ladder should yield a return on investment, including increased employee engagement resulting in lower technician turnover rates.

MUHC technician turnover data from July 2022 through June 2023 (**Image 1**) supports the assumption that turnover rates decline as technicians progress through the career ladder and take on advanced roles.

MUHC is a large academic medical center and employs 160 pharmacy technicians that practice in various acute care and ambulatory settings. Can this strategy be applied to smaller practice settings, including community oncology practices that may employ as few as a single pharmacy technician?

The concept that career ladders allowing advancement drive engagement is applicable no matter the size of the

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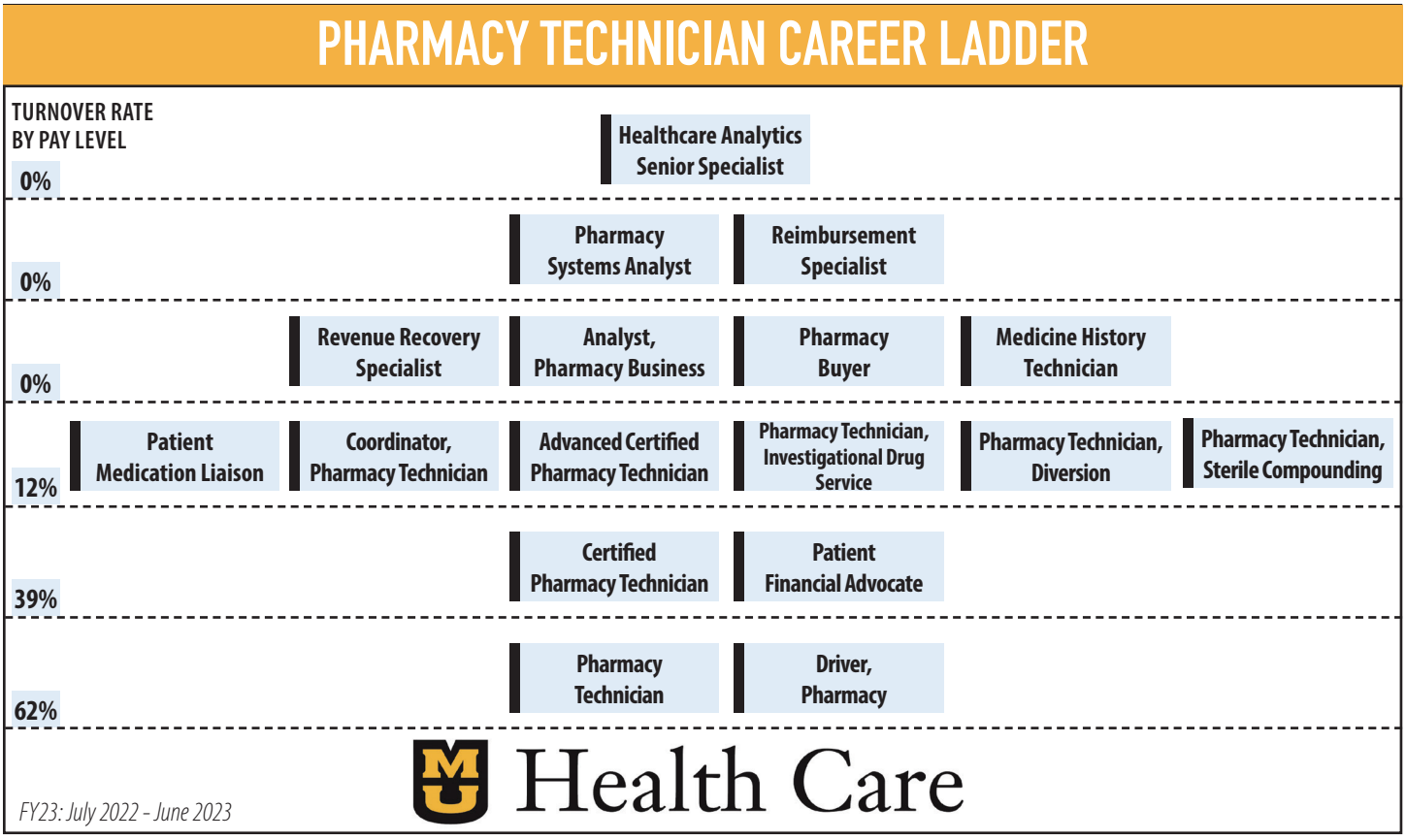
IMAGE 1: MUHC TECHNICIAN CAREER LADDER AND TURNOVER DATA



CAREER LADDER

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technician workforce when you view the career path taken by each technician as a unique, personal journey.

The execution of the strategy can look different based on the setting. For example, in a single-technician practice setting, the healthcare organization could develop three different yet formal job titles, each with increasing compensation and greater responsibility. As a technician achieves certain milestones (certifications, college degrees, etc.), they advance into a higher-level job title and take on additional responsibility.

Within every practice, there are likely tasks being completed by nurses or other professionals that could be reassigned to a properly trained, highly qualified technician. Similarly, you could have technicians completing informal responsibilities.

Do you have a technician that primarily fills sterile compounding shifts, for example? Think about informal responsibilities as missed opportunities to recognize and compensate technicians.

This may be an opportunity to create a formal role of Sterile Compounding Technician, to recognize and compensate the technician while building advanced skills. Create win-win scenarios where your practice benefits from pharmacy technician advancement.

AN MUHC EXAMPLE

To demonstrate the personal impact that a technician career ladder can have, let's highlight a single MUHC employee.

This employee has been a technician with MUHC since 2011 and is known for taking on advanced tasks and projects.

During her first four years at MUHC, she had the same title of Certified Pharmacy Technician although she filled many other informal roles such as sterile compounding technician, medicine history technician and lead technician.

If MUHC had formal roles in place during that time, she would have benefited from the opportunity for recognition and increased compensation, and MUHC would have benefited from a decreased probability that she would leave the organization.

Technicians want to know that their employer is committed to their growth and advancement. A well-developed technician career ladder is a healthcare organization's expression of that commitment.

Since the acceleration of career ladder development at MUHC, she has filled two separate formal roles that advanced her into higher-level job titles with increased compensation and greater responsibility. This is a testament to the impacts career ladders can have on technicians.

CONCLUSION

If you are a pharmacy technician and are interested in advocating for advancement opportunities within your organization, here are three helpful suggestions to get you started:

1. Achieve excellence within your current responsibilities to build credibility.

2. Form groups or committees and bring forward specific ideas/plans for pharmacy technicians to take on more responsibility. Do the legwork and make it easy for your organization to simply sign off on a plan versus asking leaders to create one on your behalf.

3. Speak the language of your organization. Are they looking for increased efficiency, expense reduction, enhanced patient experience or increased patient safety? Speak to these organizational priorities and tie pharmacy technician advancement to the achievement of these goals.

Career ladders serve many functions. They allow pharmacy technicians to practice at the top of their license, so that other healthcare professionals can practice at the top of theirs.

Career ladders also are an employee engagement tool and more highly engaged technicians are less likely to leave your organization.

Technicians want to know that their employer is committed to their growth and advancement. A well-developed technician career ladder is a healthcare organization's expression of that commitment.

If you have one technician on your team or 200, you have exactly what you need to begin building out a pharmacy technician career ladder that serves your technicians as well as your organization.

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PHARMACY TECHNICIAN CE AVAILABLE (0.25 HOURS)

ONCOLOGY PHARMACY TECHNICIAN CERTIFICATION PREP: DOMAINS I & II REVIEW

By Taryn Newsome, CPhT

The purpose of this Continuing Education (CE) article is to educate oncology pharmacy technicians on basic oncology pharmacy training, clinical oncology skills in preparation for the OPTA Oncology Pharmacy Technician Certification.


Taryn Newsome

This CE article will review Domains I and II of the OPTA Oncology Pharmacy Technician Certification Content Outline.

Domain I focuses on skills and application to apply necessary oncology pharmaceutical calculations, as well as practical understanding of pharmacy operation, quality assurance, safety compliance ordinances, and qualified accreditation regulations.

Domain II focuses on oncology clinical knowledge and patient side effect management.

Specific training and education are necessary for Pharmacy Technicians so they are able to best benefit their colleagues, patients, and practice.

Through participation in this CE activity, pharmacy technicians will have improved knowledge on oncology pharmaceutical calculations, pharmacy safety compliance ordinances, oncology clinical knowledge, management of patient side effects, and will be prepared to provide improved support to the pharmacy team.

LEARNING OBJECTIVES:

1. Discuss calculations, proper handling and storage, as well as risk evaluation and mitigation strategies of oral oncolytics relevant to oncology pharmacy technicians.

2. Interpret laboratory abnormalities associated with oral oncolytics including radiology and imaging as it relates to monitoring anticancer therapies.

3. Identify warnings, precautions, and adverse events associated with oral oncolytics.

ONCOLOGY PHARMACY TECHNICIAN CERTIFICATION CONTENT OUTLINE		
Domain I	**Core Oncology Pharmacy Training**	**20%**
Domain II	**Clinical Skills and Patient Management**	**30%**
Domain III	Oncology Pharmacy Billing	20%
Domain IV	Oral Oncolytics	30%

DISCLOSURE

Taryn Newsome, Julianne Darling and Tahsin Imam are employees of NCODA for which salary is received. There are no relevant conflicts of interest to disclose for this article.

INTRODUCTION

NCODA and the Oncology Pharmacy Technician Association (OPTA) have collaboratively developed a Certification Program to advance the professional development of oncology pharmacy technicians.

The purpose of the certification is to implement a sustainable oncology pharmacy technician certification program founded on innovative, high-quality and evidence-based programming that will raise the standards and optimize the care of individuals affected by cancer.

The certification will improve patient care by promoting the value of the Certified Oncology Pharmacy Technicians' specialized training, knowledge and skill in oncology pharmacy.

The certification exam is divided into four domains that are described in detail in the Oncology Pharmacy Technician Certification Content Outline. The content outline is the blueprint for the exam and was developed by a committee of pharmacists and pharmacy technicians.

Additionally, the content outline includes the percentage of questions that make up the certification exam. The content outline is the exam candidate's key resource tool on how to achieve certification.

The focus of this article will be on Domain I, Core Oncology Pharmacy Training and Domain II, Clinical Oncology Skills and Patient Management.

DOMAIN I DESCRIPTION

Skills and applications to apply necessary oncology pharmaceutical calculation. Practical understanding of pharmacy operation, pharmacy quality assurance, pharmacy safety compliance ordinances and qualified pharmacy accreditation regulations.

Domain I aims to assess the candidate's understanding of basic skills in fundamental oncology pharmacy technician knowledge.

Within the scope of a pharmacy technician, it is important to know oncology pharmaceutical calculations, proper storage and handling of

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CERTIFICATION PREP

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oral oncolytics and comprehension of pharmacy regulatory agencies and their standards.

PHARMACEUTICAL CALCULATIONS

It is imperative that pharmacy technicians understand everyday oncology pharmaceutical calculations encountered in the pharmacy. Math plays a major role for oncology pharmacy technicians in order to ensure patients are receiving the correct dosage of medicine.

Even though pharmacy technicians do not perform dose calculations and dose modifications, they should be familiar with specific pharmaceutical calculations associated with oral oncolytics.

A working knowledge of common pharmaceutical calculations include body surface area (BSA), pounds to kilogram conversation and the Cockcroft Gault's Equation.

BODY SURFACE AREA (BSA)

Anticancer therapies are often dosed individually using the patient's weight and height.

The Body Surface Area (BSA) is the total surface area of the human body. BSA is also expressed in meters squared (m2).[1]

BSA = (height cm x weight kg) / 3600, then take square root of this value

POUNDS TO KILOGRAMS

When calculating medication doses, weight is used in grams or kilograms (not pounds). A patient's weight in pounds is used in calculating weight dosed medication. To convert pounds to kilograms, take the mass and multiply it by 2.2.[2]

The pounds to kilograms calculation:

Kg to lbs = there are 2.2lbs in 1 kilogram

COCKCROFT GAULT EQUATION

The Cockcroft Gault Equation is often used to calculate a patient's creatine clearance (CrCl) based on their age, weight, serum creatinine, and gender. It may also be used to adjust doses for renally excreted medications.[3]

$$CrCl = \frac{140 - (\text{age of patient in years})}{(72)(\text{Serum Creatinine of patient})} \times \text{patient weight in kg } (\times 0.85 \text{ if female})$$

Patients receiving anticancer therapies require the assessment of their renal function for dosing of certain cytotoxic medications that are primarily eliminated through the kidneys or may cause kidney damage. Patients receiving these treatments with will have their serum creatinine checked before and during therapy.

QUESTION 1 (ANSWERS & RATIONALE ON PAGE 47)

If a patient weighs 197 pounds, what is the patient's weight in kilograms?

a. 433.4 kg

b. 35.36 kg

c. 89.54 kg

d. 546.1 kg

SAFE HANDLING AND STORAGE

Pharmacy technicians are at risk of exposure to hazardous medications every day. To help prevent exposure, national regulation standards have been placed to help protect the pharmacy team as well patients.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH)

The National Institute for Occupational Safety and Health (NIOSH) is a federal agency that oversees workplace hazards. NIOSH informs healthcare workers, including pharmacy technicians, about workplace hazards and ways to improve workplace safety.[4]

The NIOSH list of Antineoplastic and Other Hazardous Drugs in Healthcare Settings document provides a full list of hazardous medications, definition of hazardous medications, classifications and supplemental information to be used as standard precautions.[4]

NIOSH has also classified the list of hazardous medications into to three groups:

Group 1: Antineoplastic medications

Group 2: Non-antineoplastic medications

Group 3: Medications that may be hazardous to women's or men's fertility or that may be present in breast milk

WHAT DEFINES A HAZARDOUS DRUGS (HD)?

According to the NIOSH, a drug is hazardous if it displays any of the following characteristics:

▲ **Carcinogenicity:** Organism or agent capable of causing cancer

▲ **Developmental toxicity:** Interference with normal development and cause adverse effects in offspring

▲ **Reproductive toxicity:** Interference with reproductive ability or capacity

▲ **Organ toxicity at low doses:** Effect on cells of vital organs

▲ **Genotoxicity:** The ability to cause a change or mutation in genetic material

UNITED STATES PHARMACOPEIA (USP) <800>

The USP General Chapter 800 provides safety standards for handling of hazardous medications such as oral oncolytics to help prevent the risk of exposure.

USP 800 standards are the pharmacy's fundamental guide to ensure a minimum risk to patients as well as any pharmacy staff who comes in contact with hazardous drugs.

USP 800 outlines sections describing the responsibilities of pharmacy staff handling hazardous medications. The section descriptions include a list of hazardous medication defined by NIOSH, Personal Protective Equipment (PPE), personnel training and dispensing final dosage form.[5]

DISPENSING FINAL DOSAGE FORM & DESIGNATED AREAS

According to the USP 800 safety standards, medications that are not required to be mixed, formed or shaped, may be dispensed without further requirements. However, if the manufacturer has specific handling instructions, those requirements must be followed.[5]

Below is a list of handling instructions for dispensing final dosage form hazardous medications:

▲ Counting or repackaging of hazardous drugs must be done carefully

▲ Dedicated area and separate counting trays must be cleaned after each use

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▲ Tablet and capsule forms of antineoplastic medication must not be placed in automated counting or packaging machines

QUESTION 2 **(ANSWERS & RATIONALE ON PAGE 47)**

Which of the following are characteristics of Hazardous Drug as defined by NIOSH? Select all that apply.

a. Carcinogenicity

b. Development toxicity

c. Reproductive toxicity

d. Cytotoxicity

e. Genotoxicity

WHAT IS REMS?

A Risk Evaluation and Mitigation Strategy (REMS) is a medication safety program designed by the U.S. Food and Drug Administration (FDA) to help ensure medications are used safely, and the risks of serious side effects are minimized.[6]

A REMS program helps to ensure that the patient, care giver, and prescriber have all been educated on the medication risk factors.

While all oral oncolytics require safe handling and pose medication risks, it is important to note that not all medications require a REMS program. There three major factors the FDA has identified to distinguish a REMS medication:

▲ The medication is highly effective, but can cause a serious side effect

▲ It contains a new chemical structure that has not been used in the past

▲ The medication can treat a serious and rare disease, but the risk of taking the medication is very high

REMS DISPENSING & PRESCRIPTION REQUIREMENTS

There are a few oral oncolytic medications that require the REMS Program, but the certification will focus only on three medications: thalidomide, lenalidomide and pomalidomide. These REMS medications have very specific dispensing requirements.

Note: Not all medically integrated pharmacies are certified to dispense REMS products; however, pharmacy technicians seeking certification in oncology will need to be aware of the requirements.[6]

Physicians, Doctors of Osteopathic Medicine, Nurse Practitioners and Physicians' Assistants must be enrolled as a provider in the REMS program for each product they wish to prescribe.

Patients also must complete REMS enrollment and sign consent to be on medication.

An authorization number must be obtained by a provider from the REMS program to be written on a prescription.

REMS PRESCRIPTION REQUIREMENTS

Prescriptions must include both the authorization number as well as the corresponding patient risk factor:

▲ Adult male.

▲ Adult female of nonreproductive age.

▲ Adult female of reproductive age.

▲ Prescription cannot be written for more than a 28-day supply.

▲ No refills are allowed on prescription.

▲ A new prescription must be written for every fill.

▲ Patient surveys are required for each patient risk factor.

QUESTION 3 **(ANSWERS & RATIONALE ON PAGE 47)**

True or False: Patients being prescribed a REMS product may have more than a 28-day supply.

a. True

b. False

DOMAIN II DESCRIPTION

Comprehension of quality improvement through:

▲ Side effect management, adherence, compliance.

▲ Identifying when a pharmacist intervention is required.

▲ Description and interpretation of laboratory values associated with oral oncolytics.

▲ Comprehension of different diagnostic and interventional radiology studies with understanding and basic translation of findings.

Domain II aims to assess the candidate's clinical knowledge in oncology. Main areas of knowledge include identifying laboratory values and understanding what they represent. These skills would be used in the pharmacy to assist with patient side effect management, adherence, and compliance.

Additionally, candidates will be tested on their knowledge of different diagnostic and interventional studies used for cancer staging and restaging. Pharmacy technicians who can recognize and interpret these areas of study will master this section of the exam.

LABORATORY VALUES

It is important for an oncology pharmacy technician to understand laboratory values for patients receiving anticancer treatments. Lab tests provide insight into a patient's health and help determine whether a medication is having any negative side effects. Note that each practice may have different lab reference value ranges.

COMPLETE BLOOD COUNT

A Complete Blood Count (CBC) is a common blood test to have checked when receiving anticancer therapies. Another common blood test you will see is a CBC with differential, which provides additional lab values that would be monitored. The CBC measures three types of cells: red blood cells (RBC), white blood cells (WBC) and platelets (PLT).[7]

RED BLOOD CELLS

Red blood cells carry oxygen throughout the body. The Hematocrit (HCT) and Hemoglobin (HgB) are two red blood cell measurements to evaluate a patient's red blood cells. The HgB is a very important value that will indicate if a patient is anemic. The term "anemic" means that the patient has a low Hgb value and may be having symptoms such as fatigue or shortness of breath.[7]

WHITE BLOOD CELLS

White blood cells help the body fight

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infection. There are many types of white blood cells within the body, but there is one value that pharmacy technicians should become familiar with: the Absolute Neutrophil Count (ANC). The ANC estimates the ability for the body to fight infections.[7]

The term neutropenia is used for a patient who has a low ANC value. The term leukocytosis is used for a patient who has an elevated ANC value.

Pharmacy technicians may also see an elevated ANC count if a patient has received a growth factor, such as a filgrastim, which is used to help the body produce more white blood cells to help fight against infections.

PLATELETS

Platelets (PLT) help to prevent and stop bleeding by forming clots. The PLT count is often monitored to see if the patient is at risk of bleeding during therapy. The term "thrombocytopenia" refers to a patient with a low platelet count, while "thrombocytosis" refers to an elevated platelet count.

COMPREHENSIVE METABOLIC PANEL

A Comprehensive Metabolic Panel (CMP) is another common blood test for patients on anticancer therapies. A CMP checks a variety of body functions and processes such as the kidneys and liver.

In addition, a CMP can be used to monitor the side effects of oral oncolytic medications.[7] **Table 1** includes the values that make up the CMP:

TABLE 1[7]

Glucose	Total Protein
Calcium	Alkaline Phosphate (ALP)
Sodium	Alaine Transaminase (ALT)
Potassium	Aspartate Aminotransferase (AST)
Carbon Dioxide	Bilirubin
Chloride	Blood Urea Nitrogen (BUN)
Albumin	Creatinine

The next section will focus on the two most important CMP values oncology pharmacy technicians will need to be familiar with: BUN and serum creatinine.

BUN AND CREATININE

BUN and creatine measure the patients renal (kidney) function. A measurement of creatinine in your blood or urine provides clues to help your doctor determine how well the kidneys are working.[8]

A BUN test can reveal whether your urea nitrogen levels are higher than normal, suggesting that your kidneys may not be working properly.[8]

Often you will see patients having their BUN and creatinine tested before a CT scan. The contrast used in a CT scan can cause damage to the patient's kidneys; especially for those with poor kidney function. Additionally, the BUN and creatinine are used to help monitor medication adverse events, including, but not limited to, renal toxicity.

TUMOR MARKERS

A tumor marker is anything present in or produced by cancer cells or other cells of the body in response to cancer or certain benign (noncancerous) conditions that provides information about a cancer; such as how aggressive it is, whether it is responding to treatment, or what kind of treatment it may respond to.[9]

High tumor marker levels can be a sign of cancer. Along with other tests, tumor marker tests can help doctors diagnose specific types of cancer and plan treatment. **Table 2** shows specific cancer diagnosis and corresponding tumor marker test.[9]

TABLE 2[9]

Breast Cancer	Lung Cancer	Colorectal Cancer
• CA 15-3 • CA 27-29 • CA 125 • CEA	• EGFR • KRAS • ALK • CEA	• CEA • CA 19-9

CA = Cancer Antigen

Tumor markers can be tested in a patient's blood, urine, stool, or other bodily fluids of patients with cancer. Tumor markers are sometimes used to:

- ▲ Estimate prognosis
- ▲ Determine the stage of cancer
- ▲ Detect cancer that remains after treatment or that has returned after treatment
- ▲ Assess how well a treatment is working
- ▲ Monitor whether the treatment has stopped working

QUESTION 4 **(ANSWERS & RATIONALE ON PAGE 47)**

Which of the following laboratory tests help to monitor if a patient has a low white blood cell count?

a. CMP

b. CBC

c. Tumor Markers

d. PSA

IMAGING STUDIES

Imaging studies are vital to helping healthcare providers locate tumors, identify cancer stages, and other changes in the disease.

Additionally, imaging studies are used in biopsies and other surgical procedures.[10] By using imaging, physicians can make more accurate diagnoses and prescribe targeted treatments and therapies.

POSITRON EMISSION TOMOGRAPHY SCAN

A Positron Emission Tomography (PET) scan is a procedure in which a small amount of radioactive glucose (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is taken up.[11]

In some cancers, PET scans can help identify cancer in the body as well as help assist in staging the cancer. Because cancer cells often take up more glucose than normal cells, the pictures can be used to find cancer cells in the body.[11]

Often you will notice that physicians order a Computed Axial Tomography (CAT) scan along with the PET scan, which provides more information about the cancer.

BONE SCAN

A bone scan is a test that uses nuclear imaging to help diagnose and track several types of bone disease and cancers. A bone scan can also be an important tool

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for detecting cancer that has spread (metastasized) to the bone from the tumor's original location, such as the breast or prostate.[12]

MAGNETIC RESONANCE IMAGING

Magnetic Resonance Imaging (MRI) is a medical imaging technique that uses a magnetic field and computer-generated radio waves to create detailed images of the organs and tissues in your body. MRI can also help find a tumor in the body as well as find out if it is cancerous.[13]

QUESTION 5 **(ANSWERS & RATIONALE ON PAGE 47)**

Which of the following radiology studies helps to diagnose bone disease?

a. PET scan

b. Bone scan

c. MRI

d. CAT scan

ORAL ONCOLYTIC PRESCRIBING INFORMATION

The Prescribing Information (PI) reflects the FDA's findings regarding the safety and effectiveness of a human prescription drug under the labeled condition of use.[14] It is extremely important that oncology pharmacy technicians understand how to read the PI in order to submit an accurate prior authorization for approval and process oral oncolytic prescriptions.

The PI includes information on the following:

- Indications and Usage
- Dosage and Administration
- Dosage Forms and Strengths
- Contraindications
- Drug Interactions
- Warnings and Precautions
- Adverse Reactions

INDICATIONS AND USAGE

The Indication and Usage section is one of the most important sections oncology pharmacy technicians should be familiar with. The purpose of this section is to provide the specific diagnosis for which the FDA has approved the medication.

For example, enzalutamide is indicated for patients who have castration-resistant prostate cancer or metastatic castration-sensitive prostate cancer.

DOSAGE AND ADMINISTRATION

This section describes the recommended dosage of the medication per indication as well as whether this medication should be taken with or without food. Additionally, this section provides information on whether the medication can be chewed, crushed, or broken.

DOSAGE FORMS AND STRENGTHS

This section describes the medication's color, form (i.e., capsule or tablet), and different strengths the medication may come in. Many oral oncolytics come in different forms and strengths to accommodate dose reductions.

CONTRAINDICATIONS

This section describes the condition for which a medication should not be used at all or with caution. An example of a contraindication is if a patient has had an allergic reaction to the medication or something very similar.

DRUG INTERACTIONS

This section describes possible interactions with other medications and foods which may cause an adverse reaction or lead to the medication being less effective. For example, the medication capecitabine has a drug interaction with allopurinol and taking both medications together should be avoided as it may decrease efficacy.

WARNING AND PRECAUTIONS

This section discusses serious side effect that may occur in people who take this medication. This section does not mean that every side effect will happen to the patient, but it is important to pay attention to these warnings so that patients are able to recognize any symptoms that could suggest a serious problem.

This section also provides specific days throughout the patient's cycle of therapy where a precaution side effect should be monitored.

For palbociclib, as an example, it is suggested in the PI to monitor neutropenia. Patients should have a complete blood count checked prior to start of palbociclib and at the beginning of each cycle, as well as on Day 15, of the first 2 cycles and as clinically indicated.

ADVERSE REACTIONS

The Adverse Reaction section lists all of the side effects that were reported in people who took this medication while it was being tested.

Side effects, which is also a term for adverse reactions, are effects that are different from what the medication was developed to do. These effects are grouped according to the body system affected (i.e., liver, skin and stomach), the group of people tested (i.e., adults, children) and also how many people reported having each side effect.[15]

Examples of adverse reactions include diarrhea, vomiting, rash or nausea.

GRADING SYSTEMS OF ADVERSE EVENTS

The National Institutes of Health (NHI) has created the Common Terminology Criteria for Adverse Event (CTCAE) resource.[15] This resource includes a table of contents for an adverse event according to specific disorders such as blood disorders, nervous system disorders and immune disorders.

CTCAE displays Grades 1 through Grade 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.

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▲ **Grade 5:** Death related to AE.

QUESTION 6 (ANSWERS & RATIONALE AT RIGHT)

In what section of the Prescribing Information can you find out if a medication can be chewed, crushed or split?

a. Dosage and Administration

b. Indication and Usage

c. Contraindication

d. Dosage Forms and Strengths

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CE INFORMATION

CONTACT TIME / CEU	0.25 HOURS / 0.03 CEU
CE Registration Link	
Note	Credit requirements must be completed within three years of the program activity date (October 25, 2026). Upon completion, credit will be transferred electronically to ACPE. All credit will be viewable in your CPE Monitor profile within 24 hours.
CE Code	QYXCKQ

ANSWERS TO CERTIFICATION PREP QUESTIONS

QUESTION 1: If a patient weighs 197 pounds, what is the patient's weight in kilograms?
Answer: C. 89.54 kg
Rationale: When calculating medication doses, weight is used in grams or kilograms (not pounds). Therefore, pounds would need to be converted to grams or kilograms in order to dose the patient's medication correctly. Take the patient's weight and divide it by 2.2 in order to obtain the patient's weight in kilograms.

QUESTION 2: Which of the following are characteristics of Hazardous Drug as defined by NIOSH? Select all that apply.
Answers: A. Carcinogenicity, B. Development toxicity , C. Reproductive toxicity, E. Genotoxicity
Rationale: NIOSH has defined five characteristics that make up hazardous drugs which include Carcinogenicity, Development toxicity, Reproductive toxicity, Genotoxicity and Organ toxicity. Cytotoxicity is not a characteristic of a hazardous medication according to NIOSH.

QUESTION 3: True or False: Patients being prescribed a REMS product may have more than a 28-day supply.
Answer: B. False
Rationale: REMS prescription have specific dispensing requirements. Prescriptions cannot be written for more than a 28-day supply and require a new prescription prior to dispensing additional medication.

QUESTION 4: Which of the following laboratory tests help to monitor if a patient has a low white blood cell count?
Answer: B. CBC
Rational: The CBC measures the amount of white blood cells (among other cells) a patient has. The ANC is a type of white blood cell that indicates the patient's ability to fight infections. If the ANC value is low, the patient may be at risk and would need further evaluation.

QUESTION 5: Which of the following radiology studies helps to diagnose bone disease?
Answer: B. Bone scan
Rationale: A bone scan is an imaging study to help diagnose bone disease and other cancers. It is a nuclear imaging study that uses a special camera and computer to see such images such as bones and skeletal fractures that does not pick up on regular X-ray machines.

QUESTION 6: In what section of the Prescribing Information can you find out if a medication can be chewed, crushed or split?
Answer: A. Dosage and Administration
Rationale: The Dosage and Administration section of the PI provides information on the recommended dosage for that medication as well as instructions on how the medication can be taken.

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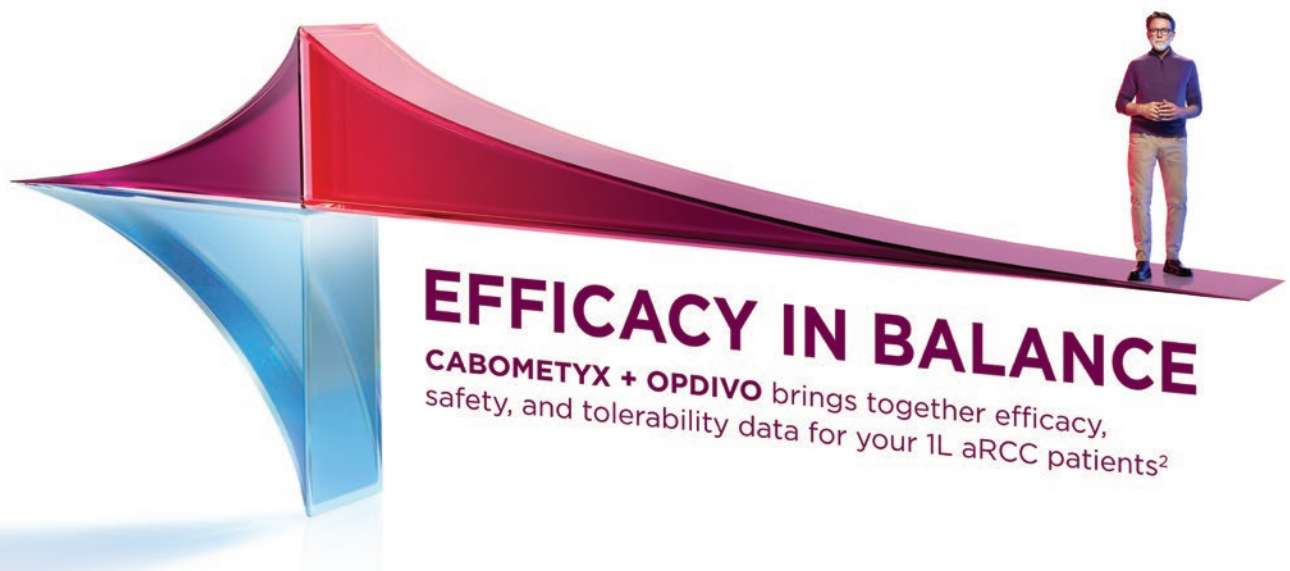
1L aRCC

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

#1 PRESCRIBED TKI+IO COMBINATION IN 1L aRCC

Based on IQVIA claims data as of March 2023. Subject to change without notice.[1]



EFFICACY IN BALANCE

CABOMETYX + OPDIVO brings together efficacy, safety, and tolerability data for your 1L aRCC patients[2]

A BALANCE OF DATA*

1L aRCC treatment that offers a balance of data:
superior OS, safety and tolerability, and patient-reported quality of life[2-4] *

*Superior OS vs sunitinib in patients with previously untreated aRCC. Primary analysis OS results: 40% reduction in risk of death with CABOMETYX + OPDIVO vs sunitinib (HR=0.60; 98.89% CI: 0.40-0.89; *P*=0.001); median OS was not reached in either arm. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and the clinical significance is unknown.[1,2]

Explore the balance of data

1L=first-line; aRCC=advanced renal cell carcinoma; CI=confidence interval; FKSI-19=Functional Assessment of Cancer Therapy-Kidney Symptom Index 19; HR=hazard ratio; IO=immunotherapy; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor.

INDICATION

CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

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.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information for CABOMETYX on following pages.

Superior PFS and ORR results in the ITT population[2]

Median follow-up time of 18.1 months; range: 10.6-30.6 months[3]

MEDIAN PFS WAS DOUBLED[2]*

16.6 months CABOMETYX + OPDIVO (95% CI: 12.5-24.9; n=323)

vs

HR=0.51 (95% CI: 0.41-0.64) *P*<0.0001

8.3 months sunitinib (95% CI: 7.0-9.7; n=328)

ORR WAS DOUBLED[2]*

55.7% CABOMETYX + OPDIVO (95% CI: 50.1-61.2; n=323)

vs

P<0.0001

27.1% sunitinib (95% CI: 22.4-32.3; n=328)

CR

8% (n=26/323) CABOMETYX + OPDIVO vs **4.6%** (n=15/328) sunitinib

PR

48% (n=154/323) CABOMETYX + OPDIVO vs **23%** (n=74/328) sunitinib

Consistent results for PFS were observed across the prespecified subgroup of IMDC risk categories[2]

*PFS and ORR were assessed by BICR.[2]

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) RECOMMENDED OPTION

Cabozantinib (CABOMETYX) + nivolumab (OPDIVO) is the only TKI + IO regimen with an NCCN recommendation in both clear cell and non–clear cell aRCC[5]

NCCN CATEGORY 1, PREFERRED OPTION IN CLEAR CELL RCC

- **Category 1**, preferred option across all risk groups in 1L clear cell RCC[5]
- NCCN Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate[5]

NCCN OTHER RECOMMENDED OPTION IN NON–CLEAR CELL RCC

- **Category 2A**, other recommended option in non–clear cell RCC[5]
- NCCN Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate[5]

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CR=complete response; IMDC=International Metastatic RCC Database Consortium; ITT=intent to treat; RCC=renal cell carcinoma; PR=partial response.

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

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.

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 withholding CABOMETYX and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

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.

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.

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

Secondary endpoint

CheckMate-9ER study design[1,2,5]

A randomized (1:1), open-label, Phase 3 trial vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO 240 mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) PO once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. PFS and ORR were assessed by BICR. Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and the clinical significance is unknown. Other exploratory endpoints included biomarkers, PK, immunogenicity, and PFS-2. An updated efficacy analysis was conducted when 271 events were observed based on the pre-specified number of events for the pre-planned final analysis of OS.

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

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

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

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

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

ADVERSE REACTIONS

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

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

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on following pages.

BICR=blinded independent central review; CR=complete response; ITT=intent to treat; IV=intravenous; PFS-2=progression-free survival after subsequent therapy; PK=pharmacokinetics; PO=by mouth; PR=partial response.

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis Inc; 2022. **2.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384(9):829-841. **3.** Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial. Presented at The European Society for Medical Oncology (ESMO) Virtual Congress 2020; September 19-21, 2020. Presentation 6960. **4.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [supplementary appendix]. *N Engl J Med*. 2021;384(9):829-841. **5.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [protocol]. *N Engl J Med*. 2021;384(9):829-841. **6.** Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(7):888-898. **7.** Data on file. Exelixis, Inc.

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

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CABOMETYX® (cabozantinib) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

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

1 INDICATIONS AND USAGE

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

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

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

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

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Renal Cell Carcinoma

METEOR

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

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

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

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

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

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

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

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

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

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

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

CABOSUN

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

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

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

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

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

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

CHECKMATE-9ER

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

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

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

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

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

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

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

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

Toxicity was graded per NCI CTCAE v4.

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

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

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

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

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

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

[h] Includes primary hypothyroidism.

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

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis

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

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

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

Hepatocellular Carcinoma

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

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

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

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

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

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

[2] NCI CTCAE Version 4.0

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

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

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

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

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

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

Differentiated Thyroid Cancer

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

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

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

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

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

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

[2] NCI CTCAE Version 5.0

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

[4] Includes the following terms: fatigue, asthenia

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

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

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

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

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

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

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CABOMETYX

Strong CYP3A4 Inhibitors

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

Strong CYP3A Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

Infertility

Females and Males

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

8.4 Pediatric Use

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

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

The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner's gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physeal hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

8.5 Geriatric Use

In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older. In COSMIC-311, 50% of 125 patients treated with CABOMETYX were age 65 years and older, and 12% were 75 years and older.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 320 patients randomized to CABOMETYX administered with nivolumab in CHECKMATE-9ER, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

8.7 Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

10 OVERDOSAGE

One case of overdosage was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

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

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.

Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX.

Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Adrenal insufficiency: Advise patients receiving with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency.

Proteinuria: Advise patients to contact their healthcare provider for signs or symptoms of proteinuria.

Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.

Impaired wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.

Thyroid dysfunction: Advise patients that CABOMETYX can cause thyroid dysfunction and that their thyroid function should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction.

Hypocalcemia: Advise patients that CABOMETYX can cause low calcium levels and that their serum calcium levels should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of hypocalcemia.

Embryo-fetal toxicity:

- Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort.

Important administration information

Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information

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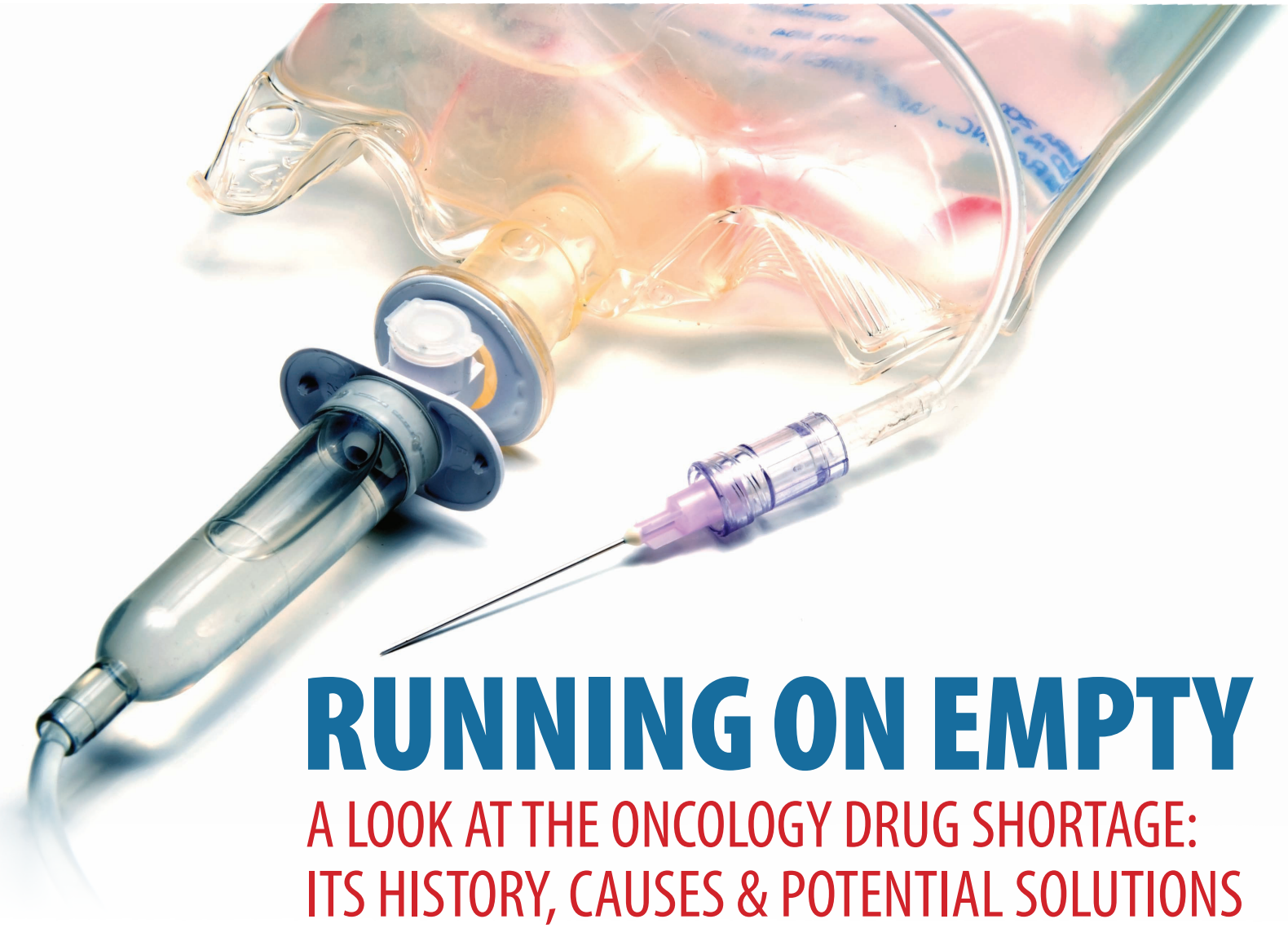

RUNNING ON EMPTY

A LOOK AT THE ONCOLOGY DRUG SHORTAGE: ITS HISTORY, CAUSES & POTENTIAL SOLUTIONS

By Karen Hagerty, MD

While the medical community has been grappling with drug shortages for more than a decade, there are few areas where these shortages are felt more acutely than in oncology.

The inability to obtain lifesaving drugs — usually older generic injectables — is the cause of much consternation and distress to patients and physicians alike.

In addition to the human cost, it has been estimated that shortages cause $230 million in additional costs each year, related to rising prices of the drugs in shortage plus the higher costs of substitute drugs.[1] The results of a survey published in 2019 found that the financial impact of managing shortages adds up to just under $360 million annually in labor costs.[2]

Prior to the current crisis with cisplatin and carboplatin, a 2022 Hematology Oncology Pharmacy Association (HOPA) survey showed that 63% of the 68 respondent institutions reported one or more drug shortages per month.[3] Treatment delays, reduced doses or alternative regimens were reported by 75% of respondents.

A 2023 survey by the National Comprehensive Cancer Network limited to cisplatin and carboplatin found that 93% of respondents reported a shortage of carboplatin, with 16% saying that they were unable to treat all patients according to the intended dose and schedule. For cisplatin, these numbers were 70% and 100%, respectively.[4]

Why these shortages? The U.S. pharmaceutical market is complex and no one entity has complete visibility into all aspects of the supply chain. Regulatory requirements, business practices and market factors all play a role. These include:

- Reliance on foreign sources for finished drugs and their precursors;
- Barriers to market entry;
- "Just-in-time" inventory practices;

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▲ Consolidation and decreased diversification;

▲ Contracting practices;

▲ Often extremely low margins for generic drugs; and

▲ Geographic concentration of manufacturing facilities, among others.

Drug shortages predominantly affect older generic drug products. In oncology, the majority of shortages are in sterile injectables. Generic drugs account for approximately 90% of drugs sold domestically, and account for 18% of all drug costs.[5]

The U.S. Food and Drug Administration (FDA) analyzed 163 drugs that went into shortage between 2013 and 2017 and found that 67% were drugs with generic versions on the market. These drugs had a median time since first approval of almost 35 years and of note, in the year prior going into shortage, the median unit price was just $11.05 for sterile injectables.[6]

SHORTAGES BY THE NUMBERS

In 2001, the number of new national drug shortages numbered 120. New shortages peaked in 2011 at 267. So far in 2023 (from the period of January 1, 2023 through June 30), 88 new shortages been identified.[7,8]

In 2001, 73% of new drugs in shortage were injectables. At the peak of the 2011 new drug shortage, 57% were injectables. So far this year, 43% of new drugs in shortage are injectables.

While at first glance these statistics may make it appear that shortages are decreasing since their peak, it is important to note that the figures above refer to *new* drug shortages and do not include older, ongoing shortages.

Looking at *active* (new plus old) shortages by quarter tells a different story. The 10-year trend of active shortages by quarter shows that, in fact, current (2023) shortages are the worst in almost a decade.

Factors such as regulatory requirements, business practices and market considerations all play a role in drug shortages. These include an overreliance on foreign sources, barriers to market entry and extremely low margins on generic drugs, among other factors.

Beginning with the second quarter of 2014 through the second quarter of 2023, active shortages numbered anywhere from 174 to 320. Second-quarter 2023 data shows that there are currently 309 active drug shortages; this was surpassed only in 2014, with a total of 320 active shortages.

OVERSEAS SOURCING AND MANUFACTURING

In March 2021, 52% of all FDA-registered finished dosage form (FDF) manufacturing facilities were overseas, while 73% of all FDA-registered active pharmaceutical ingredient (API) manufacturing facilities were overseas.[9] Looking at only generic drug manufacturing facilities, the percentages were even greater: 63% of FDF facilities and 87% of API facilities were overseas.

However, facility information does not necessarily translate to volume information. In other words, while 87% of API facilities are overseas, the FDA does not have data on the actual volume of API produced overseas — it could be higher (or lower).

It is also important to note that the FDA only has data for API and FDF facilities and does not include data from facilities that produce the precursor fine chemicals, as these amounts are not reported through registration requirements.[10]

According to a Homeland Security and Governmental Affairs Committee Majority Staff Report in March 2023, the number of Chinese-based API manufacturers registered with the FDA increased from 188 in 2010 to 445 in 2015.[11]

According to the same report, the Administration for Strategic Preparedness and Response (ASPR) told the Majority Committee staff that its "biggest concerns" are that 90% to 95% of generic sterile injectable drugs for critical acute care in the U.S. rely on key starting materials and drug substances from China and India.

LEGISLATION

The American Society of Clinical Oncology (ASCO) and other groups have previously issued recommendations and suggestions for ways to mitigate shortages and strengthen the pharmaceutical supply chain through legislation or regulations.[12,13,14]

Congress and multiple government agencies have produced numerous reports aimed at identifying the root causes of drug shortages and addressing potential mitigation. The most recent legislation aimed directly at addressing drug shortages was the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), signed into law on March 27, 2020.[15]

The act gave the FDA new authority in three areas.[16] The CARES Act:

▲ Expands the requirement for manufacturers of certain drugs to notify FDA about permanent discontinuances in manufacturing or interruptions in

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DRUG SHORTAGE

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manufacturing that are likely to lead to a meaningful disruption in supply in the United States, and the reasons for such discontinuances or interruptions;

▲ Requires each manufacturer of a drug or of any API to develop, maintain and implement, as appropriate, a redundancy risk management plan that identifies and evaluates risks to the supply of the drug, as applicable, for each establishment in which the drug or API of the drug is manufactured; and

▲ Requires each person (including repackers and relabelers) who register with the FDA to annually report the amount of each listed drug that was manufactured, prepared, propagated, compounded or processed by such person for commercial distribution.

Prior to the CARES Act, the FDA Safety and Innovation Act of 2012 (FDASIA) broadened the scope of an existing early notification provision by requiring all manufacturers of certain medically important prescription drugs to notify the FDA of a permanent discontinuance or a temporary interruption of manufacturing.[17]

However, even where reporting requirements intended to increase available information do exist, they are not always helpful.

While manufacturers are supposed to report reasons for shortages to the FDA, according to an investigation by the University of Utah Drug Information Service (UUDIS) in 2022, for more than half the reports (56%) "unknown" or "would not provide" was given as the reason.[18]

ASCO RESOURCES

ASCO currently maintains a dedicated drug shortages page at **www.asco.org/drug-shortages**. Content includes:

▲ Updates on drug availability as ASCO receives new information;

▲ Congressional and regulatory activities;

It will likely take a combination of public and private sector initiatives, legislation and regulations to achieve market stability of these drugs and, most importantly, patient access to desperately needed therapies.

▲ Ethics principles and implementation strategies; and

▲ Clinical guidance.

The latter includes disease-specific guidance — in the setting of the cisplatin/carboplatin shortage — for a variety of cancer types, including breast, gastrointestinal, genitourinary, head and neck, and thoracic.

ASCO also has endorsed the Society of Gynecologic Oncology's gynecologic cancer-specific guidance.

CONCLUSION

Given the complexities involved in drug shortages, it is apparent that no one entity will be able to "fix" this problem. It will likely take a combination of public and private sector initiatives, legislation and regulations to achieve market stability of these drugs and, most importantly, patient access to desperately needed therapies.

▲ **Karen Hagerty**, MD, is the Chief Regulatory Affairs Officer at the American Society of Clinical Oncology in Alexandria, Virginia.

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STARK LAW FAQ CREATES NEW CHALLENGES FOR MEDICALLY INTEGRATED PHARMACIES

The federal Ethics in Patient Referrals Act — more commonly referred to as the Stark Law — prohibits physicians and other healthcare professionals from referring Medicare and Medicaid patients to facilities in which they or their immediate family members have ownership or invested interest.

The law was created to address concerns of "self-referral" policies where physicians would recommend certain referrals more than medically necessary, resulting in an unwarranted drain of taxpayer funding.

EXCEPTIONS TO THE STARK LAW

Several exceptions to the general prohibition are included under the Stark Law, including:

- Referral for in-office ancillary services including laboratory testing and radiological tests in which they are performed within the same location as the provider;
- Referral to another physician of the same practice as the referring provider;
- Referral of a patient to a family member for Designated Health Services (DHS) in rural areas as designated by The Centers for Medicare & Medicaid Services (CMS);
- Referral to pre-paid organizational health services, such as health maintenance organizations (HMOs);
- Referral to academic medical centers;
- Referral for preventative services, including screening exams/tests and vaccines; and
- Equity in publicly-traded security as issued by a corporation.

Of these, the ancillary services exemption has been of particular importance to oncology practices as it provided a means for medically integrated practices to mail life-saving oncolytics to patients.

A BRIEF HISTORY OF THE STARK LAW

The legislation was introduced in Congress in 1988 by Rep. Pete Stark (D-CA). Stark I, as the original bill came to be known, was eventually included in the Omnibus Budget Reconciliation Act of 1989 (OBRA 1989). The original law barred self-referrals for clinical laboratory services under the Medicare program beginning January 1, 1992.

In 1993, Stark II was introduced under OBRA 1993. Stark II updated the DHS list, expanding restrictions to 11 different health services under both Medicare and Medicaid, including imaging, medical devices, prosthetics and outpatient prescription drugs.

Approval and rule finalization of Stark II took place over three phases, in 2001, 2004 and 2007.

As with various laws and regulations over the years, CMS has published Frequently Asked Questions (FAQ) documents to address provisions of Stark Law that needed clarification. One such FAQ was published in September 2021. It stated that outpatient prescription drugs mailed to patients would not meet the "location requirement" included under the ancillary services exemption.

In a nutshell, it requires providers to distribute prescription drugs to Medicare/Medicaid patients solely through their facility or one of their group's facilities. Mailing of prescription drugs to such patients is not permitted, a ruling, CMS maintained, that had remained unchanged from Stark II Phase 1 in 2001.

This ruling, however, was overruled by the 1/31/2020 COVID-19 Public Health Emergency Act (PHE), in essence providing a waiver to the Stark II Phase 1 mailing prohibition during the pandemic.

After the PHE ended on May 11, 2023, CMS published a Post-Public Health Emergency FAQ on May 19. In its final section, the FAQ addressed the mailing of Part D outpatient prescription medications to Medicare beneficiaries. It stipulated that since the PHE waiver was now terminated, physician practices would no longer be able to rely on the ancillary service exception to fill Part D prescriptions being mailed to the beneficiary's home, as was previously noted in the September 2021 FAQ.

The FAQ further stated that Medicare beneficiaries could get medications through the Part D plan's network of mail-order and other network pharmacies.

IMPLICATION OF THE LATEST FAQS

The two FAQs have a significant impact on all Medicare patients, particularly the 9.5 million Medicare patients with cancer, most of whom are age 66 or older.

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To access the **Stark Law FAQ**, scan the QR code above.

To access the **Post-Public Health Emergency FAQ**, scan the QR code above.

STARK LAW

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Patients who once relied on mailings because they were unable to pick up in-office prescriptions due to health conditions and/or distance must now depend on caretakers or switch to pharmacy services that are not directly affiliated with their physicians.

Medicare providers also are affected. Violations of the Stark Law require the lowest possible standard of proof and can be enforced by the U.S. Department of Justice, the U.S. Department of Health & Human Services and CMS. Enforcement is further enhanced through the Affordable Care Act and amendments to the False Claims Act.

Penalties can include civil fines, claims denial and takebacks, as well as exclusion from provider status in federal healthcare programs.

HOW PRACTICES ARE ADJUSTING TO STARK

At a recent NCODA Town Hall meeting, three pharmacy executives discussed how their medically integrated pharmacy (MIP) practices were adjusting to the recent Stark Law FAQs:

▲ **Neal Dave**, PharmD, Executive Director of Pharmacy and Admix Services | Texas Oncology (280 practice sites, 45 MIPs);

▲ **Kyle Kitchen**, PharmD, MBA, Senior Director of Pharmacy and Clinical Services | Utah Cancer Specialists (14 practice sites, one MIP): and

▲ **Eric Soong**, PharmD, Director of Pharmacy, | South Carolina Oncology Associates (one practice site, one MIP).

How have your new patients have been affected by the Stark Law update?

Dave: Only about 5% of our Medicare prescriptions are shipped. But it has changed our operations, how we educate patients, what we talk to them about and how they pick up their prescriptions. We have 45 pharmacies across Texas … so most of our patients are able to come in and pick up their medications.

Kitchen: We estimate our mail prescriptions at about 50 per month. Of those, roughly half are Medicare patients. Our process now is to work one-on-one with each patient and try to find the most suitable way of picking up their medication within one of our sites. It's not foolproof. There's a lot of challenges for patients who live further out. We're still working though some of that.

Soong: We service a lot of rural areas in South Carolina and so the ability to ship was a great benefit to those patients. The biggest sticking point for us — probably for all of us in practice — is when they ask, "Can you ship it?" We have to tell them "No," and then tell them why we can't. It's hard to explain to a patient.

That brings up a good point. How do you educate patients about such complex federal regulations?

Dave: We put together a letter trying to explain Stark as best we could and mailed it out preemptively before we started transitioning patients away from shipping. We also added

Neal Dave

Kyle Kitchen

Eric Soong

a QR code at the bottom where patients could contact their Congressperson to log a complaint or at least voice their opinion.

Kitchen: We created a spreadsheet of the overall impact to our operations, including how many Medicare patients were receiving prescriptions via the mail. We distilled that down to about 30 patients. As each patient was due for a refill, we contact them and talk about the change on an individual basis. We inform them that we need them to try to pick up their prescription within the clinic. Some are able to comply, so that was easy. Others are more challenging, often because of the proximity to one of our clinics. We're continuing to try and address their needs while complying with the Stark rules. We're also looking into the value-based exception to determine if there is a legitimate way to address this issue.

Soong: We also created a spreadsheet. We had a small percentage as well. Most of our patients come to the clinic to pick up their prescriptions. We ship to only about 10% of our Medicare patients. We called them one by one to explain the situation and ask if they were willing to come and pick up their prescriptions from our clinic. Overall, only about 18% opted for shipping from a mail-order pharmacy.

Is there any anticipation of higher waste if the patient doesn't show up to pick up their prescription, or if there's a delay?

Dave: I absolutely have a concern about waste. But the drug is still in our possession. If there is a dose change, we can return and redispense. If it's not picked up in seven days, it returns to stock. We can reach out to the patient to ensure they're coming.

Kitchen: Since we have one central pharmacy, it hasn't really created additional work to have the Medicare patients pick up, but if it's a new process for your practice, it can sometimes be a logistical headache. There are a number of issues that can come up when you're filling a prescription a few days before an appointment where their dose could potentially change.

How do you handle patients that choose to have their prescriptions mailed through a network or mail-order pharmacy?

Soong: It can be complicated depending on the insurance. Sometimes the plans have a specific mail-order pharmacy they want patients to use so our team has to figure out where the

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STARK LAW

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prescription needs to go. It can impact a lot of other things, like copays. We try to avoid certain pharmacies that we've had negative experiences with if possible. Sometimes it's not.

Does using a mail-order pharmacy change how your pharmacy manages the patient?

Soong: It's really on the mail-order pharmacy to follow-up with the patient, but we don't disown the patient. If there are any problems or issues, they come to us, and we try to fix them. But it's very difficult to manage it once it goes outside the walls of the clinic. So, we've developed relationships with contacts at different specialty providers. You have to in order to navigate and reach out if there are any issues.

Kitchen: As Eric was saying, most of the work when a prescription is transitioned to a specialty pharmacy falls back onto the physician and the supporting nurses at the clinic. It's a huge challenge. But we need to be thoughtful about the impact we're having on the care of these patients.

We see script abandonment rates of 25% or higher in the specialty arena for various reasons. Time to fill takes too long. The patient can't reach the pharmacy. The pharmacy can't reach the patient. And the high copays. How do you deal with these types of issues?

Dave: We use an ePRO (Electronic Patient Reported Outcomes) system and enroll all of our patients into it so that they have some connection with the clinic, even if they're getting their prescriptions outside. But it's very difficult. You can't control the external pharmacy to fill the drug on time. The high copays are another challenge. It's hard to combat abandonment (outside of the MIP).

Have any of you had feedback from Medicare patients that have had to switch to a mail-order pharmacy because of the new Stark Law FAQ?

Soong: We had a patient who couldn't come in, so her prescription was changed to a mail-order. She is a primary caregiver for her 89-year-old mother. We had to ship it off to a mail-order pharmacy and for whatever reason that pharmacy could not coordinate to come to the house. So, they tell her, "You have to go to this pharmacy to pick up your medication." So, now she has to coordinate having someone watch her mother while she drives to another town to pick up her prescription from the pharmacy. So she calls that pharmacy to ask about the prescription. And they have no idea what she is talking about. So, they put her on hold and later come to find out it's just sitting at the front counter with the cashier (I just had to laugh when I think about our CMS requirements to maintain a secure location). She was not very happy about the situation and was very vocal with us. We tried to help as best we could. Her message to CMS is this: "I would hope that your first priority is to help patients get their meds without hardship," she said. "But in my case, this is not true."

What can we as healthcare professionals do to help change this situation?

Dave: Every patient story needs to be shared with our representatives and CMS. NCODA Town Halls are great platforms to share these types of stories. I understand there's been discussion with US Oncology and CMS and they didn't really understand how many cancer treatments are now oral, and how cancer treatment has changed so much. So I think the impact of stories like Eric's are huge. Also, I think there's a silver lining here. This is our chance to show why MIP is so important, and what we do, why we do it, what quality metrics we look at and how we actually look at quality vs. star ratings or whatever PBMs use to measure data points. This is our chance to put information out there and really talk to our representatives.

"I would hope that (CMS's) first priority is to help patients get their meds without hardship. But in my case, this is not true."

Medicare Patient, who was forced to switch to a mail-order pharmacy because of the Stark Law enforcement

Kitchen: I think it's easy to say about these kinds of issues, "Call your representatives and make your voice heard." Sometimes that answer gets overplayed. But in this situation, I think it's really a good fit. Our representatives care about the Medicare constituents and oftentimes have family members dealing with these issues. We have a broad reach as community oncology. Couple that with patient outreach, if they're willing to voice their concerns, and I really think we can make a difference. There's a lot of complexity behind Stark, but when you distill it down, it's simple: Medicare patients are being disadvantaged and not given the opportunity to fill their prescriptions when they want to. That's a pretty compelling message, and I don't think it's too hard to understand.

WHERE NCODA STANDS ON THE ISSUE

While the Stark Law attempts to insure the best possible care for patients, NCODA believes that the current approach creates barriers that are needless and can negatively impact the health of cancer patients across the United States. The benefits of integrated care are well established and include reducing prescription abandonment, medication errors, and waste associated with medication changes while increasing medication compliance.

NCODA will remain focused on the work of our members in order to amplify their voices in the pursuit of essential access to best-in-class oncology care for the patients they serve.

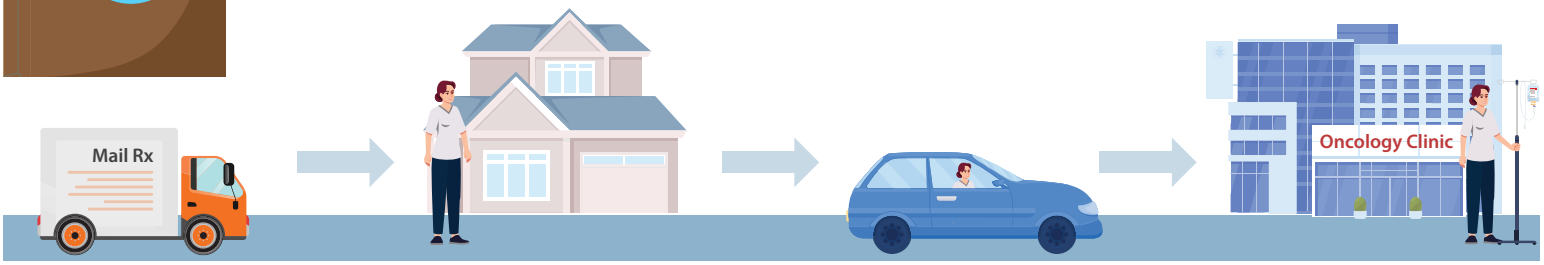
PHARMACY "BAGGING" OVERVIEW

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

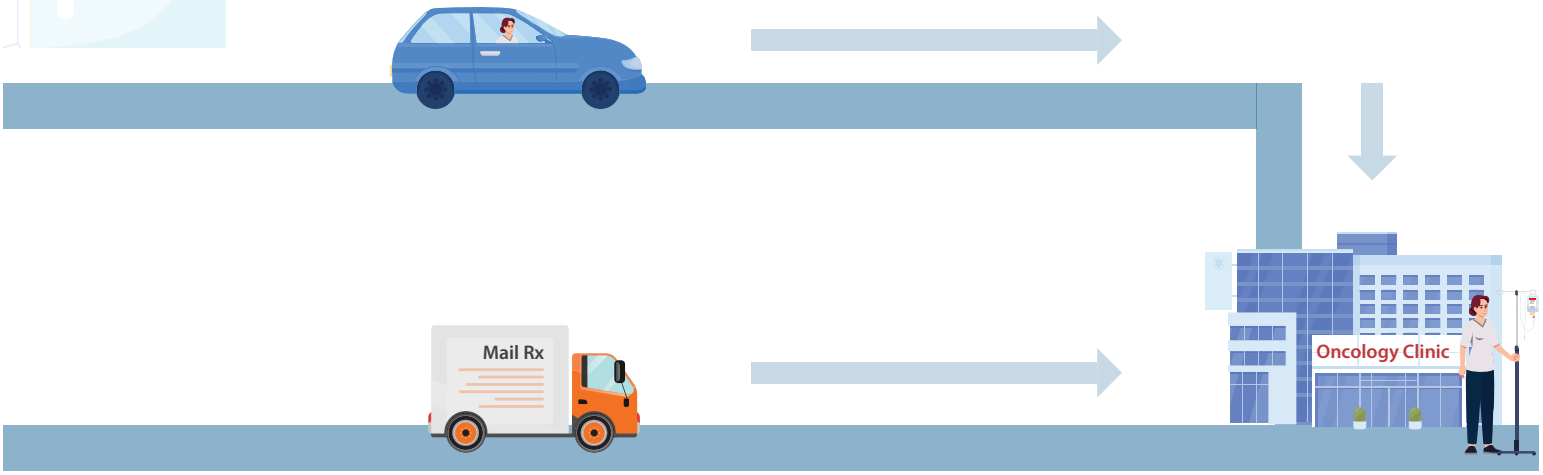
- Cost-savings for insurance companies
- Theoretically, lower risk of treatment delay as patient receives medication before appointment

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

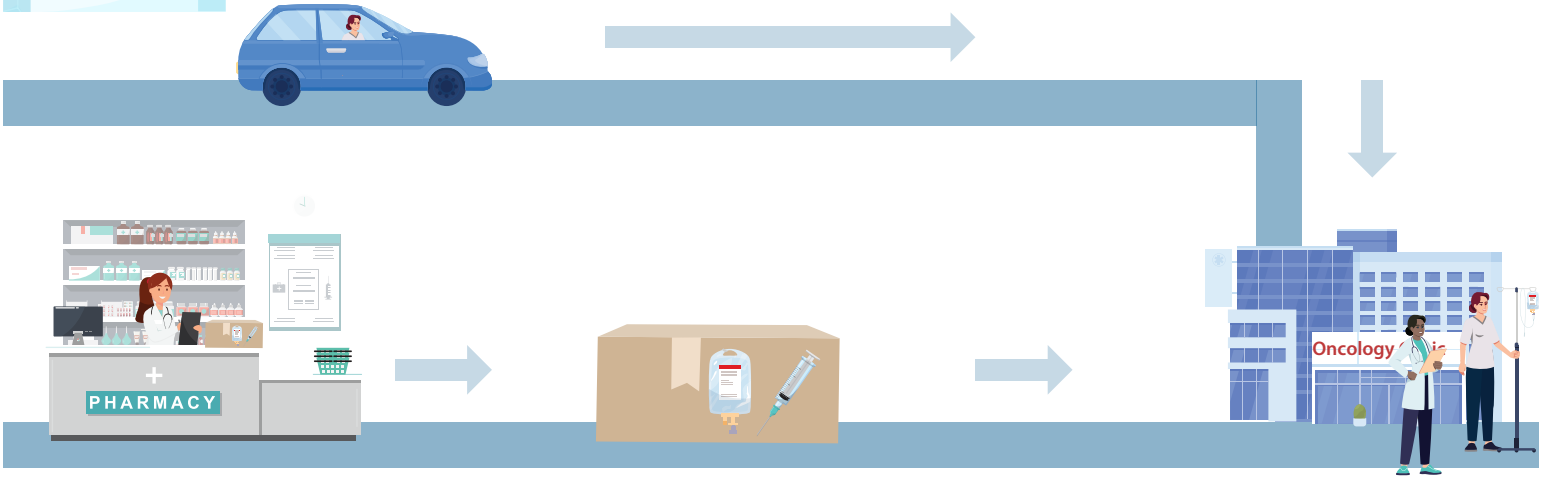
- Cost-savings for insurance companies
- No responsibility for patient regarding medication storage and handling

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 coordiation 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?
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IT'S TIME FOR CONGRESS TO BAN ALTERNATIVE FUNDING PROGRAMS

By Amy Niles, MBA

Employer-sponsored health plans use alternative funding programs (AFPs) as a way to lower their costs by forcing patients who need specialty medications to search for funding elsewhere.

This often leads to patients delaying or going without their critical treatment that should have been covered by their health plan from the start.

AFPs also put additional strain on an already limited safety net of patient assistance programs by directing patients to use such programs when their health plans should cover their specialty medications, leaving qualifying patients who deserve such support out in the cold.

Amy Niles

At the end of the day, AFPs are hurting the very patients they should be helping. As a leading charitable patient assistance foundation, those of us at the PAN Foundation (PAN) believe these programs should be banned.

HOW DO AFPS WORK?

With AFPs, health plan sponsors — such as employers who fund their own health coverage —exclude some or all specialty medications from coverage, labeling them as nonessential health benefits (EHBs). This happens despite prescription drugs being one of 10 EHB categories included in the Affordable Care Act (ACA).

Without coverage, a patient's out-of-pocket spending on these medications no longer counts toward their annual deductible or out-of-pocket maximum.

Health plan sponsors then direct patients to alternative funding vendors — non-health insurance companies that are separate from the health plan itself. Through separate financial relationships with the health plans, these third-party vendors attempt to connect patients with financial assistance from a pharmaceutical manufacturer or charitable assistance foundation, such as PAN.

Patients may be asked to sign a power of attorney and disclose confidential information, and, at times, they even may direct patients to illegally import medications from outside the United States.

HOW DO AFPS HARM PATIENTS?

▲ **AFPs discriminate based on health factors protected under the Health Insurance Portability and Accountability Act of 1996 (HIPAA):** Group health plans use AFPs to discriminate against individuals with serious health conditions who have been prescribed specialty medications. AFPs do not apply to participants/plan beneficiaries who are not prescribed specialty medications. By imposing benefit restrictions or limitations only on participants and beneficiaries prescribed specialty medications, and charging these individuals the same premium as other plan beneficiaries, the plan is charging more for coverage based on a health factor.

Notably, HIPAA prohibits group health plans from determining plan benefits on specific health factors and preexisting conditions. HIPPA also prohibits an individual from being charged more for coverage than any similarly situated individual is being charged based on any health factor.

▲ **AFPs fall short of plans' fiduciary responsibilities to employees:** Employees who pay to participate in their employer group health plan have a reasonable expectation that their employer will use their payments and manage the plan and its assets with the goal of providing them with benefits.

Unfortunately, when it comes to AFPs, the opposite is true. Instead, employers implement AFPs to avoid providing benefits to certain participants so that the plan can save money. AFPs impose harmful barriers and limitations on these employees' access to specialty medications.

Examples of AFP behaviors that fall short of plans' fiduciary responsibilities include:

- Requiring participants and beneficiaries to sign a power of attorney as a prerequisite to accessing specialty medications;
- Requiring participants and beneficiaries to provide financial and other personal information as a prerequisite to accessing specialty medications;
- Providing participants and beneficiaries with illegally imported, non-FDA-approved medications that pose a health and safety risk to participants and beneficiaries; and
- Delaying participants' and beneficiaries' timely access to specialty medications by requiring the completion and submission of applications and supporting materials to PAPs, potentially causing negative health consequences to participants and beneficiaries.

It's also important to note that plan sponsors have a fiduciary duty to fulfill their responsibilities in the interest of providing benefits to participants and their beneficiaries. Health plan sponsors who use AFPs to cut costs are not meeting this fiduciary duty.

▲ **AFPs discriminate based on income:** Despite low-income and high-income employees

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ALTERNATIVE FUNDING

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paying the same premiums — thus entitling them to the same benefits under their health plan — AFPs leverage Patient Assistance Program (PAP) income eligibility requirements to force low-income employees to use PAP funds to access their specialty medication instead of plan funds. This is done for the express purpose of saving the plan money.

This income-based distinction creates an inequitable system that discriminates against lower-income employees by charging them the same premium as higher-income colleagues for less benefits and coverage.

▲ **AFPs discriminate under the ACA:** Self-funded and large group plans are not required to provide coverage for the ACA's 10 categories of essential health benefits (EHBs). However, self-funded or large group plans that choose to cover one or more categories of EHBs must comply with the ACA's requirements for EHBs.

The communities we advocate on behalf of have serious chronic health conditions that require prescription drugs (referred to as specialty drugs or specialty medications) to treat their condition. The restrictions and limitations on access to medications specifically target participants and beneficiaries with serious, chronic health conditions that are prescribed specialty medications.

▲ **AFPS use questionable business practices:** Some of the practices used by AFPs with plan beneficiaries are of concern. For example:

• Participants and beneficiaries receive written notification that their specialty medication is either no longer covered under the plan or has been denied prior authorization.

• Participants and beneficiaries are pressured into complying with AFP requirements by being told that failure to do so will result in their being responsible for the full cost of the specialty medication and, even if paid, none of those expenses will count toward their out-of-pocket cost-sharing responsibilities.

• In many instances, AFPs require participants and beneficiaries to provide sensitive information and documents, including a power of attorney, tax returns, and answers to financial and personal inquiries.

• Third-party AFP vendors tell participants and beneficiaries how to answer PAP application questions on coverage issues.

▲ **AFPs import medications from outside the United States:** AFPs may direct patients to import or provide participants and beneficiaries with illegally imported, non-FDA-approved medications. While AFPs may or may not provide notification to participants and beneficiaries that their drug may be sourced from overseas, participants and beneficiaries have no control over where AFPs get the medications.

Illegally imported, non-FDA-approved medications pose potentially serious health risks to participants and beneficiaries. The introduction of unapproved new drugs and misbranded drugs into interstate commerce violates the Federal Food, Drug and Cosmetic Act.

HOW CAN WE BAN AFPS?

Several federal agencies are aware of the egregious practices of AFPs — including the U.S. Department of Labor, U.S. Federal Trade Commission and the FDA. And while we remain hopeful that AFPs can be banned through the regulatory process, ultimately, federal legislation may be needed.

Unfortunately, there is no legislation pending that would prohibit the use of AFPs by commercial health plans.

WHAT CAN YOU DO TO TAKE ACTION?

There are several steps patients and healthcare professionals alike can take to address AFPs:

▲ **Know your coverage:** If you are on an employer-sponsored health plan and your plan has told you that your specialty medication is nonessential, or that specialty drugs are excluded from its formulary, and that another company can help find financial assistance, you may be involved in an alternative funding scheme. It is important to understand your plan's position on coverage of specialty medications.

▲ **Education is key:** While AFPs have grown in popularity, general awareness about these programs and how they operate is low. Educating patients, patient advocacy groups, healthcare professional groups/associations, and elected officials about the dangers of AFPs is critical.

▲ **Patient stories bring the issues to life:** Sharing patient stories about their own experiences with AFPs can go a long way to educating the public and policymakers about the dangers of these programs. At PAN, we make it easy to share your story. Visit **panfoundation.org** for more information.

To share your story with PAN, scan the QR code above.

WHAT'S PAN DOING TO ADDRESS AFPS?

Access to specialty medications prescribed by healthcare professional should be deemed an EHB and their costs should be covered by health plans.

Health plan sponsors who use AFPs to save themselves money not only limit access to these life-saving medications by deeming them nonessential, but they also put further strain on an already limited safety net system of charitable patient assistance.

Recognizing the harm caused by AFPs, we at PAN are adamantly opposed to these programs and are working diligently alongside our patient advocates and partners to ensure all patients can access and afford their prescribed medications, specialty or otherwise.

We urge Congress to ban AFPs and put patients first.

▲ **Amy Niles**, MBA, is Chief Advocacy and Engagement Officer at PAN Foundation in Washington, D.C.

UNDERSTANDING THE INFLATION REDUCTION ACT & ITS IMPLICATIONS FOR ONCOLOGY CARE: AN INTERVIEW WITH GOVIND PERSAD

Members of NCODA's PQI Podcast team recently interviewed **Govind Persad**, PhD, JD, an Associate Professor at University of Denver - Sturm College of Law. A specialist in health law, Persad conducts research on health, law and bioethics.

Persad also writes an ethics columns in the American Society of Clinical Oncology (ASCO) newsletter, *The ASCO Post*.

Persad holds a PhD in philosophy from Stanford University and a law degree from Stanford Law School, as well as a BS in biological sciences from Stanford.

Persad was interviewed by **Ginger Blackmon**, PharmD, Assistant Director of Clinical Initiatives at NCODA, and **Sarder Sadid**, PharmD, Associate Manager of Clinical Initiatives & Legislative Affairs at NCODA.

You recently wrote an article entitled "Understanding the Health Provisions and Inflation Reduction Act and Their Implications for Oncology Care" for *The ASCO Post*. Could you walk us through some of the issues included in the article starting with negotiating Medicare Part D and drug pricing? Also, what does the act mean for pricing?

Medicare Part D is the part of Medicare that handles outpatient medications, as opposed to most infusions, which come under Medicare Part B, and are not covered by this provision until 2028. For Medicare Part D, there is a provision where Medicare will be able to negotiate the price of a list of drugs that are both the highest-priced drugs and don't fall within certain exceptions. And that list will broaden over time.

So what does that mean overall for oncology practices?

Negotiations on the first 10 drugs won't start until 2026, so Medicare and the Secretary of Health and Human Services (HHS), who will be conducting the negotiation, and manufacturers might make plans in advance for negotiation. That number increases to 15 in 2026 and eventually 20 drugs are subject to negotiation.

In the initial years, 2026 and 2027, you'll only have the Part D drugs, but eventually Medicare Part B drugs will be subject to negotiation as well. That will be in 2028 and beyond. These drugs are going to be picked from a short list of 50 qualifying drugs with the highest total spending approved for these seven years, though there are exceptions.

So, in terms of implications for practices, I think the big question is going to be which drugs that oncology practices are using right now might potentially be subject to negotiation. That could lead to lower prices for that drug because the negotiations create a cap on the maximum fair price as well as excise taxes and other penalties if manufacturers don't negotiate. So you might expect lower prices for the drugs that fall inside that set of drugs being negotiated.

There have been some health policy researchers that are already looking at certain specific drugs that they think are likely to come up for negotiation. Obviously, we're focusing here on oncology, so the question is going to be which, if any, of the drugs will turn out to be oncology drugs.

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Editor's note: On Aug. 29, the Biden administration released the list of the first 10 drugs targeted for price cuts. Targeted drugs include the blood cancer drug Imbruvica, as well as blood thinners Eliquis and Xarelto; diabetes drugs Jardiance, Januvia, Farxiga and Fiasp/ Novolog insulin; and Enbrel and Stelara, which are used to treat autoimmune diseases.

INFLATION REDUCTION ACT

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So, then what does this mean for manufacturers?

One question is going to be whether manufacturers alter their decisions in response to this legislation. Does this lead manufacturers to try to seek indications for drugs or pursue development or other things in ways that would avoid being subject to negotiation? I think that's something that folks have worried about. Are you going to see a sort of regulatory evasion by manufacturers by choosing to pursue, for instance, some of the exceptions that exist?

I think the other question is how are manufacturers going to engage in these negotiations? What are the factors that manufacturers are going to point to? Right now, HHS and manufacturers are supposed to look at things like manufacturing and production costs, and R&D costs. What interventions are available for the same condition? Are you going to see manufacturers aiming at areas where they would be able to show a justification for a higher price when negotiating?

Manufacturers are thinking about being able to bring in revenues. One way you might bring in revenues is by charging a higher price per dose or course of treatment.

Another way would be if you were reaching more people, even if at a lower price. So, for drugs that have exclusivity, you have an effective monopoly. Manufacturers might actually be willing to negotiate if they think, at the end, the burden of the negotiation on them may not be that large if they are able to reach a sort of broader market at these costs.

I think it's really going to be an open question how manufacturers respond, and whether different manufacturers respond to different ways. Are they going to avoid developing drugs that will be subject to negotiation? Or will they be happy to negotiate because that means their drug is a top-selling drug?

Do you feel that Inflation Reduction Act (IRA) will actually help provide more affordable healthcare? And, if so, how will that happen?

I am hopeful that it will provide more affordable healthcare costs down the road when you get these negotiation provisions into action. But I think it's hard to know how much that will lower drug prices. There are areas where I think you'll see a more immediate effect. In 2025, the out-of-pocket maximum in Part D out-of-pocket — meaning what the patient is going to pay after insurance and everything else and the price of the drug itself — that's going to go down to $2,000 a year, and that's going to even include situations where you have a subsidy from health insurance. So, it really brings down the out-of-pocket maximum for Part D, which is pretty big from the pharmaceutical side.

More broadly on the patient's side, you have a sort of continuation of the expanded health insurance subsidies for people in households that made a little bit too much money to qualify for subsidized insurance and the Affordable Care Act marketplaces.

If you were above 400% of the federal poverty line before these changes, you didn't get subsidies at all and so you could see a real spike in your health insurance costs. During COVID, the American Rescue Plan extended subsidies to people with income above the 400% threshold. IRA extends those same subsidies further. So that's going to lower out-of-pocket insurance premium costs that those patients are paying.

The other provision that I think is interesting is a provision starting this year. Pharmaceutical manufacturers will actually have to pay rebates to Medicare if they increase the prices of Part B or Part D drugs faster than inflation. So that's something that might actually lower costs for Medicare, which then indirectly could translate into lower premiums for Medicare beneficiaries.

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How do you think the IRA will affect vaccinations?

We were talking about Medicare Part D earlier. What this provision (focuses on is) certain specific vaccines, ones that are recommended by the Advisory Committee on Immunization Practices, but not covered by cost-sharing within Medicare Part D. Historically, the ACA required that some of those vaccines be covered by cost-sharing for people participating in Marketplace plans. This provision extends that to Part D as well. Also there are provision to expand vaccine access for Medicaid enrollees.

Another sort of targeted reduction in healthcare costs would be costs around vaccinations. I think going from having to pay coinsurance to not having to pay anything can have a nice psychological effect. Even if it seems small from the large scale perspective of Medicare or a practice, a $40 charge can be a deterrent to patients from getting a vaccination that could end up being very important.

Are there any other important points of the IRA that you'd like our listeners to know about?

There's a big portion of the act that doesn't have to do with the healthcare system specifically, but instead focuses on things like electric vehicles, subsidies for various green energy-related efforts. So I think these may also have some environmental health implications given the extent to which, for instance, particulate pollution is a driver of bad health outcomes.

Are there any other pieces of legislation that our members should keep an eye on?

During negotiations over the debt ceiling, the majority in the House suggested they wanted to see the whole IRA or parts of it repealed. Medicaid also was on the table. So will we eventually see policies adopted that might lead to people being thrown off Medicaid? Discussion tends to focus on Medicaid work requirements, which leads to people getting thrown off not because they aren't working, but rather because it leads to a lot of onerous administrative burdens to show that they still qualify for Medicaid.

There are some really interesting drug pricing initiatives happening at the state level. States are setting up "prescription drug affordability boards" that set up lists of high price drugs in the state, potentially creating negotiation structures for state Medicaid or other state health insurance programs.

There's been a recent Supreme Court decision that may give states a potentially broader leeway to regulate in the pricing area without violating an arcane legal doctrine called the Dormant Commerce Clause. That could potentially have some effects on national markets, especially with the gridlock we see at the federal level.

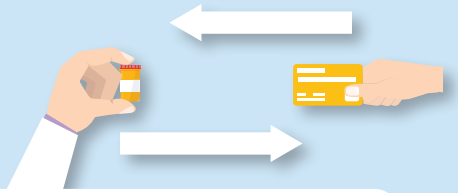
Pharmaceutical policies are a really interesting area to be looking at to see the innovations being proposed. Maryland, for instance, had created some drug pricing legislation that ran into some legal challenges. They reconfigured that legislation, and it'll be interesting to see if other states similarly adopt legislation around pricing.

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

COPAY ACCUMULATORS

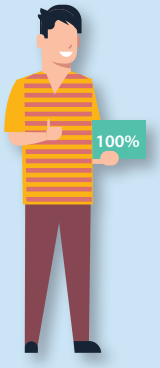
what to know & what's the difference?

Without accumulator programs



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

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



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

RX 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

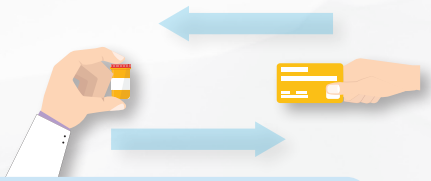
$0.00
Remaining Deductible After Coupon*

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

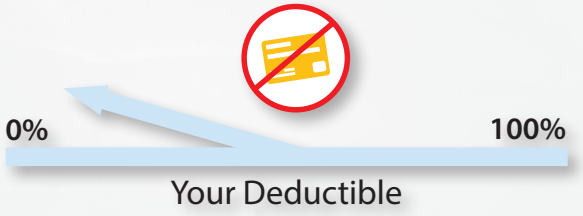
VS.

An example of what happens at the pharmacy counter

With accumulator programs



Patients can still use their coupon cards but ...



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

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

RX 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!

NCODA

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

FIXING THE 340B SAFETY NET IS CRITICAL FOR UNDERSERVED AMERICANS BATTLING CANCER

By Thomas Johnson, JD

Cancer is not an equal-opportunity offender. Those who live in underserved communities have a greater likelihood of being afflicted with the disease and worse odds of surviving it.


Thomas Johnson

According to the National Cancer Institute, "the intersectionality of structural and institutional level factors along with persistent poverty results in increased cancer incidence, delayed cancer diagnosis and treatment, increased morbidity, treatment, related toxicity, and subsequently lower rates of survival."[1]

To counteract some of these factors, the U.S. has several healthcare policies in place that operate at the federal and state levels. However, one of those critical assistance programs – the 340B Drug Pricing Program – is facing serious challenges that hamper its ability to deliver on its intended purpose.

340B: A VITAL RESOURCE FOR CANCER PATIENTS

As originally envisioned, the 340B program is a resource for health facilities serving patients in need. Created by Congress as part of the Public Health Service Act, the 340B program requires pharmaceutical manufacturers participating in the Medicaid program to provide discounted drugs to safety net providers, including community health centers and other institutions serving low-income populations.

Since 2010, participation by free-standing cancer centers in the 340B program has greatly expanded. This, in theory, should mean that vulnerable communities battling cancer have more resources available.

But in recent years, the 340B program has suffered from a lack of transparency, oversight, and accountability that has enabled some participants to use the savings they receive from discounted drugs for purposes that range far afield from the program's intended mission of helping those in need.

For example, as recently documented by the New York Times, Bon Secours Mercy Hospital System in Virginia took advantage of a provision that enables participating hospitals to register smaller facilities and specialty practices – referred to as "child sites" – into the program that are eligible for discounts.[2]

Bon Secours bought Richmond Community Hospital, a 340B provider located in a low-income neighborhood. The hospital system then registered many child sites of that hospital and reinvested the 340B savings to expand services at the sites in wealthier areas, while reducing services at the original Richmond Community site.

In another example, despite being geographically close to Cleveland, the Cleveland Clinic qualified for a program through a "quirk in federal law" as a

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designated rural healthcare provider.[3] The hospital then expanded its footprint from its primary campus in a part of the city with many low-income residents to wealthier suburban areas but continued to receive 340B discounts.

The hospital system used the "child site" loophole to register dozens of sites elsewhere in the city that serve residents with higher incomes and a higher likelihood of having private health insurance. The worst part was that the hospital then turned around and didn't provide the discounted drugs to low-income, nor did it increase its financial assistance to these patients.

And perhaps most egregiously, the University of Miami UHealth System – which participates in 340B – reportedly used revenue from their health system to help pay the salary of the university's football coach.[4]

In contrast to these examples, true safety net providers rely on 340B to fulfill their mission of expand accessing to care in underserved communities. Federal law requires Community Health Centers and other federal grantees to invest every penny of their 340B savings into meeting the unique needs of their communities. When health centers lose access to 340B savings, 31 million low-income patients lose access to cancer screenings, dental and behavioral healthcare, copay assistance, and other healthcare services.

Further, recent research suggests that the 340B program may have the unintended consequence of driving up prescription drug spending.

According to a study published in *JAMA Health Forum*, participating hospitals reported substantially higher cancer drug spending after joining the program, especially for patients with commercial insurance.[5] The wholesale acquisition cost of the pharmaceuticals purchased under the program increased from $32.6 billion in 2015 to $93.6 billion in 2021; estimated hospital savings were $20.4 billion in 2015 and $49.7 billion in 2021.[6]

In recent years, the 340B program has suffered from a lack of transparency, oversight and accountability that has enabled some participants to use the savings they receive from discounted drugs for purposes that range far afield from the program's intended mission of helping those in need.

This suggests that some hospitals may be using the program to bolster their ability to secure higher reimbursement from commercial insurers, even as they're receiving discounted prescription drugs from manufacturers.

An article published in *Health Affairs* summarized these major shortcomings: 340B "does not limit the application of discounts received by hospitals to medications used in the care of indigent patients, nor do they require hospitals to pass their cost savings along to payers or patients."[7]

The 340B program also faces challenges regarding the role of pharmaceutical benefit managers or PBMs. These drug middlemen operate without any rules or requirements and engage in discriminatory business practices that siphon 340B savings away from safety net providers and to their own bottom lines.

In their annual reports, both CVS[8] and Walgreens[9] have touted their access to 340B as a reason for exceeding their profit projections. Congress did not intend for 340B to benefit for-profit, Fortune 500 companies – but increasingly, that is exactly what is happening.[10]

Corrective action is sorely needed, and it's incumbent upon us all to ensure that changes to the 340B program provide low-income patients and underserved communities have more healthcare options rather than fewer.

PRACTICAL, ACHIEVABLE SOLUTIONS

Earlier this year, a broad and diverse group of stakeholders representing Community Health Centers, patient advocates, healthcare providers, consumer organizations, and leaders from the biopharmaceutical industry came together to form the Alliance to Save America's 340B Program (ASAP 340B). This partnership aims to pursue practical and achievable solutions that will put the 340B program on a sustainable footing for the future and ensure it can continue to benefit true safety net providers.

The members of this partnership have not always seen eye-to-eye on how to improve the 340B program. But they have come together now because they recognize the urgent need for action to ensure its long-term viability.

ASAP 340B's 10 policy principles reflect the consensus of its members and are guiding efforts to realign the 340B program in the interest of safety net providers and the communities they serve.[11] Taken together, these proposed changes to the program will ensure at least 50 million Americans are eligible to receive affordable medicines and services at 340B providers.

Below are some of the key changes the coalition is proposing:

Clarifying Participant and Program Eligibility:

▲ Ensure the program is structured to enable true safety net providers to help low-income and other vulnerable patients access more affordable medicines and healthcare services.

▲ Require hospitals participating in the program to implement a sliding fee scale for medicines for uninsured patients and privately insured patients with incomes

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340B

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under 200% of the federal poverty level.

▲ Update and clarify the definition of "patient" and ensure that eligibility for a discount reflects a direct connection between the patient's medical condition and the services being provided or managed by the covered entity.

Clearer Criteria for Contract Pharmacies & PBMs:

▲ Clarify when contract pharmacy arrangements should be permitted, such as when covered entities are located in a medically underserved area or an area serving a medically underserved population or for grantees providing care to a specific population, such as patients with HIV or chronic illness, for qualified prescriptions provided within the scope of the grantee's 340B-qualifying Department of Health and Human Services (HHS) grant.

▲ Require that contract pharmacies be located near the covered entity, provide the same patient affordability assistance for 340B prescriptions that is provided at the covered entity, and take certain steps to prevent diversion and duplicate discounts.

▲ Implement protections to prevent for-profit companies, like pharmacy benefit managers, from siphoning off 340B savings intended to help patients and limit fees that these entities charge for 340B-related services.

Hospital Participation & "Child Sites:"

▲ Condition hospital participation in the program on them not engaging in aggressive debt collection practices that penalize the most at-risk communities.

▲ Maintain existing eligibility requirements for rural hospitals, specifically critical access hospitals and sole community hospitals.

▲ Create strong eligibility standards for hospital offsite clinics — or "child sites" — to prevent abuse of the program. This includes verifying that these sites are an integral part of the hospital, have the same sliding fee scale requirement, and provide a meaningful range of clinically relevant services beyond dispensing, infusing, or otherwise providing prescriptions.

New Claims & Data Reporting Mechanisms:

▲ Create a neutral, independent clearinghouse for Medicare, Medicaid, and commercial claims data related to 340B and require covered entities to report information about their involvement with the program back to HHS.

▲ Make public the state or local government contracts that are the basis for certain private nonprofit hospitals' program eligibility.

CONCLUSION

In recent years, policymakers have spent a lot of time talking about how to make prescription drugs more affordable. They shouldn't overlook the fact that we already have a program in place that accomplishes this goal for the patients who have the greatest need for assistance.

What's needed now is action to ensure the 340B program works as intended. Lawmakers have introduced several bills that aim to fix the program, but to date, none constitute the comprehensive solution that is needed.

Throughout the rest of the year, ASAP 340B and our partners will continue our efforts to educate lawmakers about our policy principles and the urgent need for solutions that are in the best interest of safety net providers and their patients.

▲ **Thomas Johnson**, JD, is the Executive Director of ASAP 340B in Washington, D.C.

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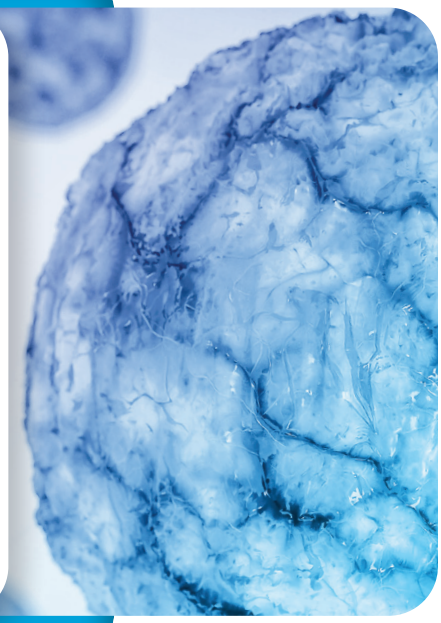
Brukinsa® 80 mg
zanubrutinib capsules

BRUKINSA IS THE ONLY BTK INHIBITOR CURRENTLY APPROVED TO TREAT FOUR DIFFERENT B-CELL MALIGNANCIES

BRUKINSA WAS DESIGNED TO MEET THE CHALLENGES OF BTK INHIBITION



High potency and affinity for BTK[1,2]

Inhibition in PBMCs is 100% with both twice-daily and once-daily dosing. Inhibition in lymph nodes is 100% with twice-daily and 94% with once-daily dosing.

The clinical significance of 100% inhibition has not been established.

Sustained 24-hour inhibition[2]

Concentration levels continuously maintained above the IC_{50} for 24 hours.

Low off-target binding[2,3]

High affinity for BTK with low off-target binding, including TEC, HER4, and JAK3.

To learn more about the BTK inhibitor BRUKINSA and all its indications, visit BRUKINSA.com

INDICATIONS

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with:

- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
- Waldenström's macroglobulinemia (WM)
- Mantle cell lymphoma (MCL) who have received at least one prior therapy.
- Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one anti-CD20-based regimen.

The MCL and MZL indications are approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage, including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

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

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

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

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

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%) and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

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

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately, and consider the risks and benefits of continued BRUKINSA treatment.

Embryo-Fetal Toxicity

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

ADVERSE REACTIONS

In this pooled safety population, the most common adverse reactions, including laboratory abnormalities, in ≥30% of patients who received BRUKINSA (N=1550) included decreased neutrophil count (42%), upper respiratory tract infection (39%), decreased platelet count (34%), hemorrhage (30%), and musculoskeletal pain (30%).

DRUG INTERACTIONS

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

CYP3A Inducers: Avoid coadministration with strong or moderate CYP3A inducers. Dose adjustment may be recommended with moderate CYP3A inducers.

SPECIFIC POPULATIONS

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

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

Abbreviations: BTK, Bruton tyrosine kinase; HER4, human epidermal growth factor receptor 4; IC_{50}, half maximal inhibitory concentration; JAK3, Janus kinase 3; PBMC, peripheral blood mononuclear cell; TEC, tyrosine kinase expressed in hepatocellular carcinoma.

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BeiGene MARKET ACCESS

Brukinsa® zanubrutinib 80mg capsules

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

1 INDICATIONS AND USAGE

1.1 Mantle Cell Lymphoma

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

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

1.2 Waldenström's Macroglobulinemia

BRUKINSA is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) *[see Clinical Studies (14.2)]*.

1.3 Marginal Zone Lymphoma

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

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

1.4 Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

BRUKINSA is indicated for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) *[see Clinical Studies (14.4)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Fatal and serious hemorrhage has occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher hemorrhage including intracranial and gastrointestinal hemorrhage, hematuria, and hemothorax was reported in 3.6% of patients treated with BRUKINSA monotherapy in clinical trials, with fatalities occurring in 0.3% of patients. Bleeding of any grade, excluding purpura and petechiae, occurred in 30% of patients.

Bleeding has occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Coadministration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

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

5.2 Infections

Fatal and serious infections (including bacterial, viral, or fungal infections) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 24% of patients, most commonly pneumonia (11%), with fatal infections occurring in 2.9% of patients. Infections due to hepatitis B virus (HBV) reactivation have occurred.

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

5.3 Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (22%), thrombocytopenia (8%), and anemia (7%) based on laboratory measurements, developed in patients treated with BRUKINSA monotherapy *[see Adverse Reactions (6.1)]*. Grade 4 neutropenia occurred in 11% of patients, and Grade 4 thrombocytopenia occurred in 2.8% of patients.

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

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 13% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was non-melanoma skin cancer, reported in 7% of patients. Other second primary malignancies included malignant solid tumors (5%), melanoma (1.2%), and hematologic malignancies (0.5%). Advise patients to use sun protection and monitor patients for the development of second primary malignancies.

5.5 Cardiac Arrhythmias

Serious cardiac arrhythmias have occurred in patients treated with BRUKINSA. Atrial fibrillation and atrial flutter were reported in 3.7% of 1550 patients treated with BRUKINSA monotherapy, including Grade 3 or higher cases in 1.7% of patients. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher ventricular arrhythmias were reported in 0.2% of patients.

Monitor for signs and symptoms of cardiac arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea, chest discomfort), manage appropriately *[see Dosage and Administration (2.4)]*, and consider the risks and benefits of continued BRUKINSA treatment.

5.6 Embryo-Fetal Toxicity

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

The data in the WARNINGS AND PRECAUTIONS reflect exposure to BRUKINSA as a single-agent in nine clinical trials, administered at 160 mg twice daily in 1445 patients and at 320 mg once daily in 105 patients. Among these 1550 patients, the median duration of exposure was 26 months, 80% of patients were exposed for at least 12 months, and 58% of patients were exposed for at least 24 months.

In this pooled safety population, the most common adverse reactions (≥30%), including laboratory abnormalities, included neutrophil count decreased (42%), upper respiratory tract infection (39%), platelet count decreased (34%), hemorrhage (30%), and musculoskeletal pain (30%).

Mantle Cell Lymphoma (MCL)

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

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

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

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

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

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

Body System	Adverse Reaction	Percent of Patients (N=118)	
		All Grades %	Grade 3 or Higher %
Infections and infestations	Upper respiratory tract infection[a]	39	0
	Pneumonia[b]	15	10[c]
	Urinary tract infection	11	0.8
Skin and subcutaneous tissue disorders	Rash[d]	36	0
	Bruising[e]	14	0
Gastrointestinal disorders	Diarrhea	23	0.8
	Constipation	13	0
Vascular disorders	Hypertension	12	3.4
	Hemorrhage[f]	11	3.4[c]
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[g]	14	3.4
Respiratory, thoracic and mediastinal disorders	Cough	12	0

[a] Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract infection viral.
[b] Pneumonia includes pneumonia, pneumonia fungal, pneumonia cryptococcal, pneumonia streptococcal, atypical pneumonia, lung infection, lower respiratory tract infection, lower respiratory tract infection bacterial, lower respiratory tract infection viral.
[c] Includes fatal adverse reaction.
[d] Rash includes all related terms containing rash.
[e] Bruising includes all related terms containing bruise, bruising, contusion, ecchymosis.
[f] Hemorrhage includes all related terms containing hemorrhage, hematoma.
[g] Musculoskeletal pain includes musculoskeletal pain, musculoskeletal discomfort, myalgia, back pain, arthralgia, arthritis.

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

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

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

[a] Based on laboratory measurements.
[b] Asymptomatic lymphocytosis is a known effect of BTK inhibition.

Waldenström's Macroglobulinemia (WM)

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

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

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

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

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

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

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

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

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

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

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

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

Table 6 summarizes the laboratory abnormalities in ASPEN.

Table 6: Select Laboratory Abnormalities[a] (≥20%) that Worsened from Baseline in Patients with WM Who Received BRUKINSA in Cohort 1

Laboratory Abnormality	BRUKINSA[b]		Ibrutinib[b]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	50	24	34	9
Platelets decreased	35	8	39	5
Hemoglobin decreased	20	7	20	7
Chemistry abnormalities				
Glucose increased	45	2.3	33	2.3
Creatinine increased	31	1	21	1
Calcium decreased	27	2	26	0
Potassium increased	24	2	12	0
Phosphate decreased	20	3.1	18	0
Urate increased	16	3.2	34	6
Bilirubin increased	12	1	33	1

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

Marginal Zone Lymphoma

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

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

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

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

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

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

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

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

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

Table 8 summarizes select laboratory abnormalities.

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

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

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

Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

The safety data described below reflect exposure to BRUKINSA (160 mg twice daily) in 675 patients with CLL from two randomized controlled clinical trials *[see Clinical Studies (14.4)]*. The trial required patients to be unsuitable for fludarabine, cyclophosphamide, and rituximab (FCR) therapy defined as age ≥65 years, or age 18 to <65 years with either a total Cumulative Illness Rating Scale (CIRS) >6, creatinine clearance 30 to 69 mL/min, or history of serious or frequent infections. The trial excluded patients with AST or ALT ≥2 times the upper limit of normal (ULN) or bilirubin ≥3 times (ULN) and patients requiring a strong CYP3A inhibitor or inducer.

SEQUOIA

The safety of BRUKINSA monotherapy in patients with previously untreated CLL/SLL was evaluated in a randomized, multicenter, open-label, actively controlled trial *[see Clinical Studies (14.4)]*. Patients without deletion of chromosome 17p13.1 (17p deletion) (Cohort 1) received either BRUKINSA 160 mg twice daily until disease progression or unacceptable toxicity (n=240) or bendamustine plus rituximab (BR) for 6 cycles (n=227). Bendamustine was dosed at 90 mg/m^2/day intravenously on the first 2 days of each cycle, and rituximab was dosed at 375 mg/m^2 on day 1 of Cycle 1 and 500 mg/m^2 on day 1 of Cycles 2 to 6.

Additionally, the same BRUKINSA regimen was evaluated in 111 patients with previously untreated CLL/SLL with 17p deletion in a non-randomized single arm (Cohort 2).

Randomized cohort: Previously untreated CLL/SLL without 17p deletion

In patients with previously untreated CLL/SLL without 17p deletion, the median age was 70, 62% were male, 89% were White, 2% were Asian, and 2% were Black. Most patients (93%) had an ECOG performance status of 0 to 1.

The median duration of exposure to BRUKINSA was 26 months, with 71% exposed for more than 2 years.

Serious adverse reactions occurred in 36% of patients who received BRUKINSA. Serious adverse reactions that occurred in ≥5% of patients were COVID-19, pneumonia, and second primary malignancy (5% each). Fatal adverse reactions occurred in 11 (4.6%) patients with the leading cause of death being COVID-19 (2.1%).

Adverse reactions led to permanent discontinuation of BRUKINSA in 8% of patients, dose reduction in 8%, and dose interruption in 46%. The most common adverse reactions leading to permanent discontinuation were second primary malignancy and COVID-19. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and hemorrhage.

Table 9 summarizes select adverse reactions in this randomized cohort.

Table 9: Adverse Reactions in ≥10% Patients with Previously Untreated CLL/SLL Without 17p Deletion in SEQUOIA

System Organ Class Preferred Term	CLL/SLL without 17p deletion			
	BRUKINSA (N=240)		BR (N=227)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[a]	33	1.7	17	0.4
Infections and infestations				
Upper respiratory tract infection[b]	28	1.3	15	0.9
Pneumonia[c]	13*	5	8†	4
Vascular disorders				
Hemorrhage[d]	27*	4	4	0.4
Hypertension[e]	14	7	5	2.6
Skin and subcutaneous tissue disorders				
Rash[f]	24	1.3	30	5
Bruising[g]	24	0	2.6	0
Respiratory, thoracic and mediastinal disorders				
Cough[e]	15	0	10	0
Gastrointestinal disorders				
Diarrhea	14	0.8	12†	0.9
Constipation	10	0.4	18	0.0
Nausea	10	0	33	1.3
General disorders				
Fatigue[h]	14	1.3	21	1.8
Neoplasms				
Second primary malignancy[i]	13*	6	1.3	0.4
Nervous system disorders				
Headache[e]	12	0	8	0
Dizziness[j]	11	0.8	5	0

* Includes 3 fatal outcomes.
† Includes 2 fatal outcomes.
[a] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, spinal pain, musculoskeletal discomfort, bone pain.
[b] Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, upper respiratory tract congestion, laryngitis, tonsillitis and upper respiratory tract inflammation, and related terms.
[c] Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung infiltration, and related terms including specific types of infection.
[d] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[e] Includes multiple similar adverse reaction terms.
[f] Rash: Rash, dermatitis, drug eruption, and related terms.
[g] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[h] Fatigue: fatigue, asthenia, and lethargy
[i] Second primary malignancy: includes non-melanoma skin cancer, malignant solid tumors (including lung, renal, genitourinary, breast, ovarian, and rectal), and chronic myeloid leukemia.
[j] Dizziness: dizziness and vertigo.

Other clinically significant adverse reactions occurring in <10% of BRUKINSA recipients in this cohort included COVID-19 (9%), edema (8%), abdominal pain (8%), urinary tract infection (7%), and atrial fibrillation or flutter (3.3%).

Table 10 summarizes select laboratory abnormalities in this cohort.

Table 10: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Previously Untreated CLL/SLL without 17p Deletion in SEQUOIA

Laboratory Abnormality[a]	BRUKINSA		BR	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	37	15	80	53
Hemoglobin decreased	29	2.5	66	8
Platelets decreased	27	1.7	61	11
Leukocytes increased	21[b]	21	0.4	0.4
Chemistry abnormalities				
Glucose increased[c]	55	7	67	10
Creatinine increased	22	0.8	18	0.4
Magnesium increased	22	0	14	0.4
Alanine aminotransferase increased	21	2.1	23	2.2

[a] The denominator used to calculate the rate was 239 in the BRUKINSA arm and 227 in the BR arm, based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.
[b] Lymphocytes increased in 15%.
[c] Non-fasting conditions.

Single-arm cohort: Previously untreated CLL/SLL and 17p deletion

In 111 patients with previously untreated, 17p del CLL/SLL, the median age was 70, 71% were male, 95% were White, and 1% were Asian. Most patients (87%) had an ECOG performance status of 0 to 1. The median duration of exposure to BRUKINSA was 30 months.

Fatal adverse reactions occurred in 3 (2.7%) patients, including pneumonia, renal insufficiency, and aortic dissection (1 patient each).

Serious adverse reactions occurred in 41% of patients treated with BRUKINSA. Serious adverse reactions reported in ≥5% of patients were pneumonia (8%) and second primary malignancy (7%).

Adverse reactions led to treatment discontinuation in 5% of patients, dose reduction in 5%, and dose interruption in 51%. The leading causes of dose modification (≥5% of all patients) were pneumonia, neutropenia, second primary malignancy, and diarrhea.

Table 11 summarizes select adverse reactions in this cohort.

Table 11: Adverse Reactions in ≥10% of Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

System Organ Class Preferred Term	CLL/SLL with 17p Deletion	
	BRUKINSA (N=111)	
	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations		
Upper respiratory tract infection[a]	38	0.0
Pneumonia[b]	20*	8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[c]	38	2.7
Skin and subcutaneous tissue disorders		
Rash[d]	28	0.0
Bruising[e]	26	0.9
Vascular disorders		
Hemorrhage[f]	28	4.5
Hypertension[g]	11	5.4
Neoplasms		
Second primary malignancy[h]	22†	6
Gastrointestinal disorders		
Diarrhea	18	0.9
Nausea	16	0.0
Constipation	15	0.0
Abdominal pain[g]	12	1.8
Respiratory, thoracic and mediastinal disorders		
Cough[g]	18	0.0
Dyspnea[g]	13	0.0
General disorders and administration site conditions		
Fatigue[i]	14	0.9
Nervous system disorders		
Headache	11	1.8

* Includes 1 fatal outcome.
† Includes non-melanoma skin cancer in 13%.
[a] Upper respiratory tract infection: upper respiratory tract infection, nasopharyngitis, sinusitis, rhinitis, pharyngitis, upper respiratory tract congestion, upper respiratory tract inflammation, viral upper respiratory tract infection, and related terms.
[b] Pneumonia: pneumonia, COVID-19 pneumonia, lower respiratory tract infection, and related terms including specific types of infection.
[c] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, bone pain.
[d] Rash: Rash, dermatitis, toxic skin eruption, and related terms.
[e] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[f] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[g] Includes multiple similar adverse reaction terms.
[h] Second primary malignancy: includes non-melanoma skin cancer, malignant solid tumors (including bladder, lung, renal, breast, prostate, ovarian, pelvis, and ureter), and malignant melanoma.
[i] Fatigue: fatigue, asthenia, and lethargy.

Clinically significant adverse reactions occurring in <10% of BRUKINSA recipients in this cohort included urinary tract infection (8%), edema (7%), atrial fibrillation or flutter (4.5%), and COVID-19 (3.6%).

Table 12 summarizes select laboratory abnormalities in this cohort.

Table 12: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with Previously Untreated CLL/SLL and 17p Deletion in SEQUOIA

Laboratory Abnormality[a]	BRUKINSA	
	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities		
Neutrophils decreased	42	19[b]
Hemoglobin decreased	26	3.6
Platelets decreased	23	0.9
Chemistry abnormalities		
Glucose increased[c]	52	6
Magnesium increased	31	0
Creatinine increased	27	0.9

[a] The denominator used to calculate the rate varied from 110 to 111 based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.
[b] Grade 4, 9%.
[c] Non-fasting conditions.

ALPINE

The safety of BRUKINSA monotherapy was evaluated in patients with previously treated CLL/SLL in a randomized, multicenter, open-label, actively controlled trial *[see Clinical Studies (14.4)]*. In ALPINE, 324 patients received BRUKINSA monotherapy, 160 mg orally twice daily and 324 patients received ibrutinib monotherapy, 420 mg orally daily until disease progression or unacceptable toxicity.

In ALPINE, the median duration of exposure was 24 months for BRUKINSA. Adverse reactions leading to death in the BRUKINSA arm occurred in 24 (7%) patients. Adverse reactions leading to death that occurred in >1% of patients were pneumonia (2.8%) and COVID-19 infection (1.9%).

One hundred and four patients in the BRUKINSA arm (32%) reported ≥1 serious adverse reaction. Serious adverse reactions occurring in ≥5% of patients were pneumonia (10%), COVID-19 (7%), and second primary malignancies (5%).

Adverse reactions led to treatment discontinuation in 13% of patients, dose reduction in 11%, and dose interruption in 42%. The leading cause of treatment discontinuation was pneumonia. The leading causes of dose modification (≥5% of all patients) were respiratory infections (COVID-19, pneumonia) and neutropenia.

Table 13 summarizes select adverse reactions in ALPINE.

Table 13: Adverse Reactions in ≥10% of Patients with Relapsed or Refractory CLL/SLL Who Received BRUKINSA in ALPINE

System Organ Class Preferred Term	BRUKINSA (N=324)		Ibrutinib (N=324)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations				
Upper respiratory tract infection[a]	27	1.2	22	1.2
Pneumonia[b]	18*	9	19†	11
COVID-19[c]	14*	7	10†	4.6
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[d]	26	0.6	28	0.6
Vascular disorders				
Hemorrhage[e]	24*	2.5	26†	3.7
Hypertension[f]	19	13	20	13
Skin and subcutaneous tissue disorders				
Rash[g]	20	1.2	21	0.9
Bruising[h]	16	0.0	14	0.0
Gastrointestinal disorders				
Diarrhea	14	1.5	22	0.9
General disorders				
Fatigue[i]	13	0.9	14	0.9
Respiratory, thoracic and mediastinal disorders				
Cough[f]	11	0.3	11	0.0
Nervous system disorders				
Dizziness[f]	10	0.0	7	0.0

* Includes fatal outcomes: pneumonia (9 patients), COVID-19 (8 patients), and hemorrhage (1 patient).
† Includes fatal outcomes: pneumonia (10 patients), COVID-19 (9 patients), and hemorrhage (2 patients).
[a] Upper respiratory tract infection: upper respiratory tract infection, sinusitis, pharyngitis, rhinitis, nasopharyngitis, laryngitis, tonsillitis, and related terms.
[b] Pneumonia: Pneumonia, COVID-19 pneumonia, lower respiratory tract infection, lung infiltration, and related terms including specific types of infection.
[c] COVID-19: COVID-19, COVID-19 pneumonia, post-acute COVID-19 syndrome, SARS-CoV-2 test positive.
[d] Musculoskeletal pain: musculoskeletal pain, arthralgia, back pain, pain in extremity, myalgia, neck pain, spinal pain, bone pain, and musculoskeletal discomfort.
[e] Hemorrhage: all terms containing hematoma, hemorrhage, hemorrhagic, and related terms indicative of bleeding.
[f] Includes multiple similar adverse reaction terms.
[g] Rash: Rash, Dermatitis, and related terms.
[h] Bruising: all terms containing bruise, bruising, contusion, or ecchymosis.
[i] Fatigue: asthenia, fatigue, lethargy.

Clinically relevant adverse reactions in <10% of patients who received BRUKINSA included urinary tract infection (9%), supraventricular arrhythmias (9%) including atrial fibrillation or flutter (4.6%), abdominal pain (8%), headache (8%), pruritus (6.2%), constipation (5.9%), and edema (4.6%).

Table 14 summarizes select laboratory abnormalities in ALPINE.

Table 14: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients Who Received BRUKINSA in ALPINE

Laboratory Abnormality[a]	BRUKINSA		Ibrutinib	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic abnormalities				
Neutrophils decreased	43	15	33	16
Hemoglobin decreased	28	4	32	3.7
Lymphocytes increased	24	19	26	19
Platelets decreased	22	4	24	3.4
Chemistry abnormalities				
Glucose increased	52	5	29	2.8
Creatinine increased	26	0.0	23	0.0
Phosphate decreased	21	2.5	13	2.2
Calcium decreased	21	0.6	29	0.0

[a] The denominator used to calculate the rate was 321 in the BRUKINSA arm, and varied from 320 to 321 in the ibrutinib arm, based on the number of patients with a baseline value and at least one post-treatment value. Grading is based on NCI CTCAE criteria.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRUKINSA

Table 15: Drug Interactions that Affect Zanubrutinib

Moderate and Strong CYP3A Inhibitors	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inhibitor increases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may increase the risk of BRUKINSA toxicities.
Prevention or management	• Reduce BRUKINSA dosage when coadministered with moderate or strong CYP3A inhibitors *[see Dosage and Administration (2.3)]*.
Moderate and Strong CYP3A Inducers	
Clinical Impact	• Coadministration with a moderate or strong CYP3A inducer decreases zanubrutinib C_{max} and AUC *[see Clinical Pharmacology (12.3)]* which may reduce BRUKINSA efficacy.
Prevention or management	• Avoid coadministration of BRUKINSA with strong CYP3A inducers *[see Dosage and Administration (2.3)]*. • Avoid coadministration of BRUKINSA with moderate CYP3A4 inducers *[see Dosage and Administration (2.3)]*. If these inducers cannot be avoided, increase BRUKINSA dosage to 320 mg twice daily *[see Dosage and Administration (2.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

BRUKINSA can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

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

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with BRUKINSA and for 1 week following the last dose of BRUKINSA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to a fetus.

Males

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1550 patients with MCL, MZL, WM, and CLL/SLL in clinical studies with BRUKINSA, 61% were ≥65 years of age, and 22% were ≥75 years of age. Patients ≥65 years of age had numerically higher rates of Grade 3 or higher adverse reactions and serious adverse reactions (63% and 47%, respectively) than patients <65 years of age (57% and 36%, respectively). No overall differences in effectiveness were observed between younger and older patients.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

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A NOVEL THERAPEUTIC CLASS IS TAKING A BiTE OUT OF ANTICANCER THERAPY

By Matthew Milone, PharmD, MBA, BCOP

T cell-engaging therapies have transformed the landscape of systemic treatment options for patients diagnosed with both hematologic and solid malignancies within the last decade.

Immune checkpoint inhibitors (ICIs) and chimeric antigen receptor (CAR)-T cell therapies have circumvented how therapeutic options can utilize our own immune systems to engage and kill off cancer cells.

Matthew Milone

The newest therapies to hit the market are a part of the T cell-engaging bispecific antibodies (BiTE) class.

BiTE is a novel therapeutic class of anticancer therapies that target two different antigens against cancer cells, via redirecting immune cells to tumor cells, acting as a delivery mechanism where these therapies have the ability to deliver drugs to tumors, and also blocking two biological pathways significant in the tumor proliferation process.[1]

The ability of BiTE to redirect T cells to target cancer cells is the most prominent function of this therapeutic class. BiTE has a relatively small molecular size, typically consisting of two single-chain variable fragments (scFvs) from an antitumor-associated antigen (TAA) and an anti-CD3 monoclonal antibody.[2]

The TAAs are expressed on tumor cells and interact with the T cell receptor (TCR) on T cells. This induces T cell activation to eliminate malignant cells. BiTE therapy has the ability to crosslink cytotoxic T cells and malignant cells, activating the T cells to proliferate and induce the formation of the immunologic synapse.[2]

The activated T cells secrete perforins and granzymes at the site of the immunologic synapse, resulting in the lysis of cancer cells.[3] In relation to other T cell-engaging therapies, BiTE has an approximately 10,000 fold higher efficacy to induce tumor cell lysis utilizing a lower ratio of T cells to target cancer cells.[4]

AVAILABLE PRODUCTS

There are currently six approved BiTE products utilized to treat both hematologic and solid tumor malignancies.

▲ **BLINATUMOMAB:** Beginning in 2014, BLINCYTO® (blinatumomab) was the first Food and Drug Administration (FDA) approved BiTE therapy. It binds to CD19 expressed on the surface of B cells and CD3 expressed on the surface of T cells, forming cytolytic synapse between the cytotoxic T cell and the cancerous B cell by connecting CD3 in the TCR complex to CD19 on benign and malignant B cells.[5]

Blinatumomab received U.S. Food and Drug Administration (FDA) approval for patients with Philadelphia (Ph)-negative relapsed/refractory (R/R) B cell acute lymphoblastic leukemia (ALL) based on the results of an open-label, single-arm, phase 2 trial.[6] There were 189 patients enrolled in the study and after 2 cycles, 81 patients (43%, 95% CI 36-50) achieved complete response (CR). Overall survival (OS) was 6.1 months

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(95% CI 4.2-7.5) with a median follow-up of 9.8 months.

Most common grade ≥ 3 adverse events were febrile neutropenia (25%), neutropenia (16%) and anemia (14%). The trial observed 2% of patients enduring CRS; grade ≥ 3 and ≥ 4 neurotoxicity occurred in 11% and 2% of patients, respectively.

Blinatumomab expanded its utilization in patients with Ph(-) ALL with MRD based on the phase-2 BLAST trial. Patients must have had hematologic CR after three or more intensive chemotherapy treatments and MRD.

In the trial, 116 patients received treatment; after 1 cycle 88 (78%) [95% CI, 69%–85%]) obtained complete MRD response; complete MRD response after all cycles (4) was 80%.[7] Based on the results of these two studies, blinatumomab is to be utilized in patients with R/R and MRD Ph(-) ALL.

▲ **TEBENTAFUSP-TEBN:** KIMMTRAK® (tebentafusp-tebn) followed with its FDA approval in 2022 for the treatment of patients diagnosed with unresectable or metastatic, HLA-A*02:-01 positive uveal melanoma.[8]

Its approval came based on the results of a randomized, open-label, multicenter, phase III clinical trial, IMGgp100-202. The primary endpoint was OS with additional outcomes including progression-free survival (PFS) and objective response rate (ORR). Median OS was 21.7 months (95% confidence interval [CI] = 18.6-28.6) for patients in the treatment group and 16 months (95% CI = 9.7-18.4) for patients in the investigator's choice arm (hazard ratio [HR], 0.51, 95% CI = 0.37-0.71, p < 0.0001). PFS was 3.3 months in patients treated with tebentafusp versus (vs.) 2.9 months in the investigator's choice arm (HR, 0.73, 95% CI = 0.58-0.94, p = 0.0139).

The most common treatment-related adverse events (≥ 30%) in patients treated with tebentafusp-tebn were cytokine CRS (89%), rash (83%), pyrexia (76%), pruritis (69%), chills (47%), nausea (43%), fatigue (41%) and hypotension (38%).

The most common safety concern seen with BiTE therapy is cytokine release syndrome, which is an uncontrolled systemic inflammatory response with elevated levels of pro-inflammatory cytokines, primarily IL-6, which is triggered by T cell activation in T cell-engaging immunotherapies such as BiTE.

Within the trial, 60% of patients experienced grade 2 or higher CRS after more than one infusion and 84% of CRS events started the day of infusion with the median time to resolution of CRS episodes being approximately two days.[9]

▲ **MOSUNETUZUMAB-AXGB:** LUNSUMIO™ (mosunetuzumab-axgb) is the first bispecific T-cell engager to be approved for the treatment of patients diagnosed with Follicular Lymphoma, a specific subtype of non-Hodgkin Lymphoma in 2022.[10] Mosunetuzumab engages both B and T lymphocytes by binding to CD3 on T cells and CD20 on the surface of lymphoma cells.

Its approval came based on the GO29781 study, a single-arm, multicenter, phase 2 study that included patients with relapsed or refractory follicular lymphoma after two or more previous lines of therapy. Mosunetuzumab yielded 54% CR with a median time to complete response of three months and median duration of response (DoR) of 22.8 months. Progression-free survival was 17.9 months and an 18-month event-free rate of 37%.

In terms of safety, the most common adverse events were CRS (44%), fatigue (37%), and headache (31%).[11]

▲ **TECLISTAMAB-CQYV:** TECVAYLI® (teclistamab-cqyv) also was approved in 2022 under accelerated approval for the treatment of adult patients with R/R multiple myeloma. Teclistamab-cqyv binds to both the CD3 receptor on T-cells and the B-Cell Maturation Antigen (BCMA), leading to T-cell activation, release of cytokines into the tumor environment, and subsequent lysis of myeloma cells.[12]

Teclistamab-cqyv was evaluated and approved based on the MajesticTEC-1 trial, a phase I/II, multicenter, open-label, single-arm study that included patients with relapsed or refractory multiple myeloma, and previously had received at least three lines of therapy. With a median follow-up of 14.1 months, ORR occurred in 63% of patients (95% CI, 55.2-70.4). A very good partial response or better occurred in 58.8% of patients and a complete response or better occurred in 39.4%. [13]

The most common adverse events that were noted in the trial included pyrexia (76%), hypogammaglobulinemia (74.5%), injection site reaction (37%), fatigue (33%), musculoskeletal pain (44%), upper respiratory tract infection (26%), pneumonia (25%), nausea (24%), headache (25%) and diarrhea (21%). CRS occurred in 72% patients, most events occurred during the step-up doses in cycle 1, however 3.6% of the patients experienced CRS in cycle 2 or later.[13]

▲ **EPCORITAMAB & GLOFITAMAB:** More recently in 2023, EEPKINLY™ (epcoritamab) and COLUMVI™ (glofitamab), were the first BiTE products approved for patients diagnosed with diffuse large B cell lymphoma (DLBCL). Both products target CD3 receptors expressed on the surface of T cells and CD 20 receptors on lymphoma cells and healthy B cells.[14,15]

Glofitamab differentiates by having a 2:1 tumor-T cell binding configuration that allows for bivalency for CD20 receptors and monovalency for CD3

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PRODUCT	INDICATION	DOSE
BLINCYTO® (blinatumomab)	ALL MRD (≥ 0.1%)	**≥45 kg C1-C4:** • 28 mcg CIVI days 1 to 28 of six-week cycle **≤ 45 kg C1-C4:** • 15mcg/m^2/day (max. 28mcg/day) CIVI days 1 to 28 of six-week cycle
	ALL R/R	**≥45 kg (C1 to C5 - six-week cycles)** • C1: 9mcg CIVI days 1 to 7, 28mcg CIVI days 8 to 28 • C2 to C5: 28mcg CIVI days 1 to 28 • C6 to C9: 28mcg CIVI days 1 to 28 (12-week cycle) **≤ 45 kg (C1 to C5 - six-week cycles)** • C1: 5mcg/m^2/day (max. 9mcg/day) CIVI days 1 to 7, then 15mcg/m^2/day (max. 28mcg/day) CIVI days 8 to 28 • C2 to C5: 15mcg/m^2/day (max. 28mcg) CIVI days 1 to 28 • C6 to C9: 15mcg/m^2 (max. 28mcg) CIVI days 1 to 28 of 12-week cycle
KIMMTRA® (tebentafusp)	Uveal melanoma, HLA-A*02:01 (+)	Day 1: 20mcg IV; Day 8 30mcg IV; Day 15; 68mcg IV; Day 22 and beyond: 68mcg IV once weekly
LUNSUMIO™ (mosunetuzumab)	Follicular Lymphoma, R/R	Cycle 1: • Day 1: 1mg IV: Day 8: 2mg IV; Day 15 60mg IV Cycle 2: • Day 1: 60mg IV Cycle 3 and beyond: • Day 1 30mg IV
TECVAYL® (teclistamab)	Multiple myeloma, R/R	Day 1: 0.06mg/kg once SQ; Day 4: 0. mg/kg once SQ; Day 7 and beyond: 1.5mg/kg SQ
EPKINLY™ (epcoritamab)	DLBCL, R/R	Cycle 1: • Day 1: 0.16mg SQ; day 8: 0.8mg SQ; Day 15: 48mg SQ; Day 22: 48mg SQ Cycles 2 and 3: • Days 1,8,15,22: 48mg SQ Cycles 4 to 9: • Days 1 and 15: 48mg SQ Cycles 10 and beyond: • Day 1: 48mg SQ
COLUMVI™ (glofitamab)	DLBCL, R/R	Cycle 1: • Day 1: give obinutuzumab; Day 8: 2.5mg IV; Day 15: 10mg IV Cycle 2 and beyond: • Day: 30mg IV

**Definitions: ALL – acute lymphoblastic leukemia; MRD – minimal residual disease; R/R – relapsed/refractory; C – cycle; CIVI – continuous intravenous infusion; DLBCL – diffuse large B cell lymphoma*

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receptors, providing improved target-effector cell binding for competing Cd20 antibodies given previously.[15]

Both epcoritamab and glofitamab were studied in phase I/II, single-arm, open-label, multicenter studies, showing ORR of 63.1% (95% CI: 55-70.6) and 59% (95% CI: 42-60); CR of 39.5% (95% CI 31.2-46.9) and 40% (95% CI: 32-48) respectively. Overall survival was also reported as 18.5 months and 11.5 months, respectively.

For safety, CRS occurred in 50% of patients with epcoritamab (47.5% grade 1 or 2) and 70% for glofitamab (59% grade 1 or 2).[16,17] Differing factors between the products include epcoritamab is given subcutaneously and glofitamab is administered IV, epcoritamab is given until disease progression where glofitamab is given for 12 weeks and to be utilized in conjunction with obinutuzumab.

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PRODUCT	PRE-MEDICATION	RATE OF CRS	SETTING
BLINCYTO® (blinatumomab)	**ALL MRD:** IV equivalent 100mg prednisone or dexamethasone 16mg IV prior to first dose of each cycle and if treatment is interrupted ≥ 4 hours	3% overall • Grade 1: 1%	Inpatient first three days of C1 then first two days of C2
	ALL R/R: Dexamethasone 20mg prior to each dose of each cycle, prior to step-up dose, and if treatment is interrupted ≥ 4 hours	• Grade 3: 3.9% *overall not reported	Inpatient first nine days of C1 then first two days of C2
KIMMTRAK® (tebentafusp)	None recommended per package insert, refer to institution policy if necessary	89% overall • Grade 1 or 2: 88%	Inpatient for the first three infusions (can proceed outpatient if no grade 2 hypotension present)
LUNSUMIO™ (mosunetuzumab)	Dexamethasone 20mg IV or equivalent, diphenhydramine 50mg to 100mg PO or IV, acetaminophen 500mg to 1,000mg PO • Not required for C3 if no reaction occurred	44% overall • Grade 1 or 2: 42%	Outpatient management throughout treatment
TECVAYLI® (teclistamab)	Dexamethasone 16mg IV or PO, diphenhydramine 50mg or equivalent, acetaminophen 650mg to 1,000mg • If no CRS present after first three doses, can be omitted	72% overall • Grade 1 or 2: 71%	Inpatient for 48 hours after first two step-up doses and first full dose
EPKINLY™ (epcoritamab)	Dexamethasone 15mg PO or IV • Prior to weekly doses and for three days following each dose in C1 Diphenhydramine 50mg PO or IV • Prior to weekly doses Acetaminophen 650mg to 1,000mg PO • Prior to weekly doses	50% overall • Grade 1 or 2: 47.5%	Inpatient for 24 hours following cycle 1, day 15 dose
COLUMVI™ (glofitamab)	Cycle1 (days 8 and 15), cycle 2, cycle 3 – dexamethasone 20mg IV, acetaminophen 500mg to 1000mg PO, diphenhydramine 50mg PO or IV	70% overall • Grade 1 or 2: 59%	Inpatient during infusion and for 24 hours following dose 1; if CRS present during dose 1, inpatient admission required for dose 2

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CYTOKINE RELEASE SYNDROME

The most common safety concern seen with BiTE therapy is cytokine release syndrome (CRS). CRS is an uncontrolled systemic inflammatory response with elevated levels of pro-inflammatory cytokines, primarily IL-6, which is triggered by T cell activation in T cell-engaging immunotherapies such as BiTE.[18]

CRS commonly presents as mild flu-like symptoms but can escalate quickly to severe and fatal multi-organ failure. A majority of CRS occurs in the first several days after infusion and has higher incidences with higher tumor burden and drug doses.[18]

In patients treated with blinatumomab, CRS is primarily seen within the first cycle having a median time to onset of approximately two days and median time to resolution of about five days. Systemic steroids (i.e., dexamethasone) help manage CRS and in severe cases, tocilizumab can be utilized to combat symptoms.[19]

To mitigate the risk of CRS, it is recommended to start treatment for patients within the inpatient setting in case escalation of care is necessary.[5]

Tebentafusp-tebn poses the greatest risk of CRS with the first dose and has a median time to resolution of symptoms of approximately two days. Patients must be monitored for at least 16 hours following the first three infusions in the appropriate healthcare setting.[8]

Mosunetuzumab-associated CRS were primarily low-grade in nature within clinical trials, occurring with days 1 and 15 of cycle 1. Management of CRS is either with corticosteroids or tocilizumab; 32% of patients in the approval trial were treated with tocilizumab where 10% of patients received both corticosteroids and tocilizumab.

Teclistamab-cqyv CRS occurred in 72% of patients within clinical trials with tocilizumab being the main form of symptom management, given to 36.4%. Most patients experienced CRS within step-up doses in cycle 1.

Teclistamab is the only BiTE therapy utilizing Risk Evaluation and Mitigation

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Strategies (REMS) to further limit the risk of CRS and neurologic toxicity. The purpose of the REMS program is to educate prescribers on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity. Patients are to begin treatment inpatient with outpatient treatment appropriate after step-up dosing has been concluded.[20]

Within the clinical trials for epcoritamab and glofitamab, CRS was the most prevalent toxicity observed. Each product had lower grade (i.e., grade 1 or 2) CRS, 47.5% and 59%, than high grade.[16,17] Both products require hospitalization for 24 hours observation due to the risk of CRS. Epcoritamab doses are given in the outpatient setting whereas glofitamab patients must be inpatient to receive their first dose.

Most CRS events with epcoritamab occurred with first full dose on day 15 of cycle 1 (median time to onset of 0.8 days), the median time to resolution from onset was two days.[16]

With glofitamab, grade 2 or higher CRS occurred just after the first infusion, there were no events of grade 2 or higher after the second or subsequent infusions.[17]

CONCLUSION

The advances in immunotherapy with the development of BiTE have created a new path for anticancer therapy across a wide range of patient populations.

Providing new hope to patients that previously had run out of options, BiTE brings a lot of excitement for what is to come in the next few years.

There will be further expansion of BiTE therapy into malignancies such as non-small cell and small cell lung cancer, prostate cancer, and more, with the hopes of even greater success that has been seen previously.

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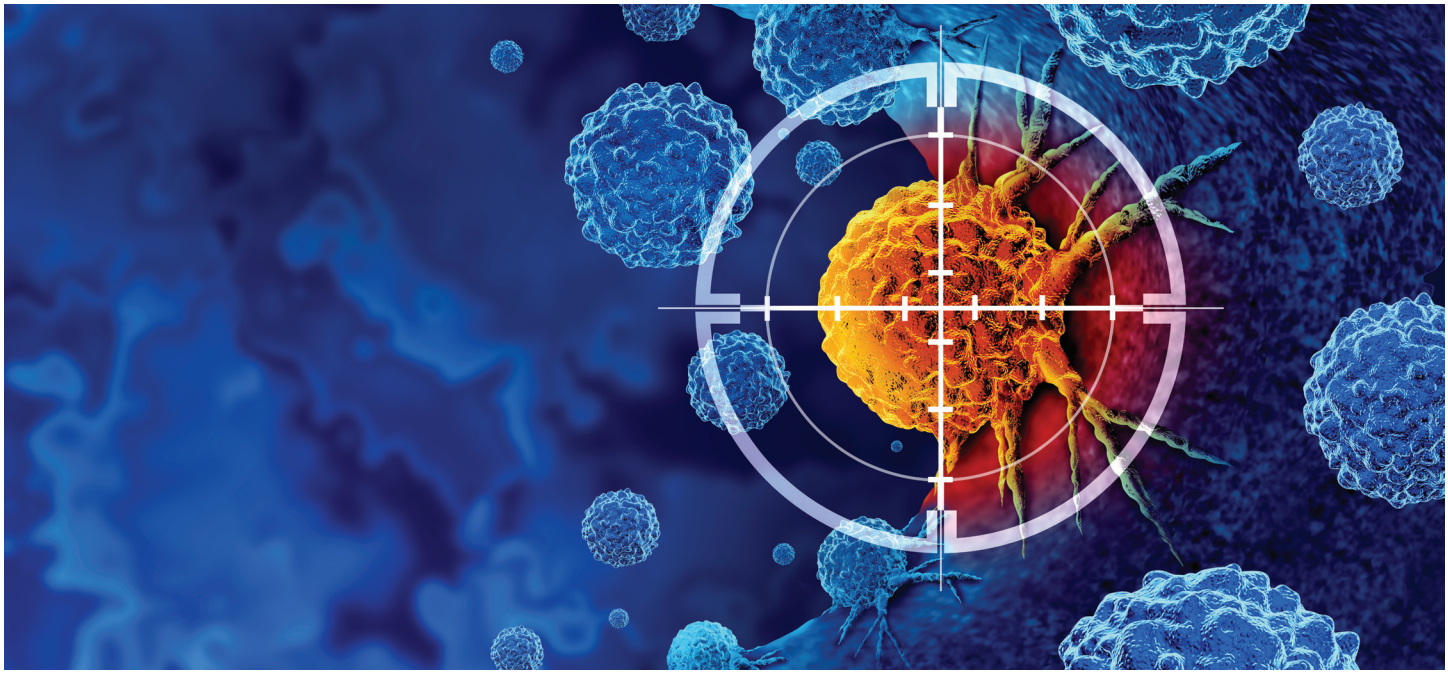

DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY: A REVIEW OF TESTING CONSIDERATIONS AND BARRIERS

By Stephanie E. Trexler, PharmD, BCOP

Fluoropyrimidines are a class of chemotherapy called antimetabolites and include the agents fluorouracil and capecitabine.

They are used widely in the treatment of solid tumor malignancies, including gastrointestinal, colorectal, breast, and head and neck cancers.

Stephanie Trexler

As with most traditional chemotherapies, fluoropyrimidines have a narrow therapeutic window. Potential toxicities include diarrhea, stomatitis, fatigue, anorexia, nausea/vomiting, myelosuppression and hand-foot syndrome.

The severity of these toxicities depends in part on the dose given and duration of treatment as well as patient-specific factors (i.e., performance status, baseline renal and hepatic function).[1]

About 30% to 40% of patients may experience any grade 3 to 4 adverse event while receiving FOLFOX, a multidrug chemotherapy regimen containing fluorouracil and oxaliplatin.[2]

Dihydropyrimidine dehydrogenase (DPD) is the first and rate-limiting enzyme involved in the catabolism of fluoropyrimidines. Many genetic variants are known in *DPYD*, the gene encoding DPD. Some variants may alter the enzymatic function of DPD, whereas some may still result in a normal phenotype.[3]

Patients carrying DPD alleles associated with decreased enzymatic function are at an increased risk for severe

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TABLE 1: DPD PHENOTYPES[3]

PHENOTYPE	ACTIVITY SCORE	GENOTYPES
DPYD normal metabolizer	2	Two normal function alleles.
DPYD intermediate metabolizer	1 or 1.5	One normal function allele plus one no function allele or one decreased function allele. Two decreased function alleles.
DPYD poor metabolizer	0 or 0.5	Two no function alleles. One no function plus one decreased function allele.

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and profound toxicities if they receive a fluoropyrimidine-based treatment.[4]

Rates of DPD deficiency vary based on a patient's self-identified biogeographical group. In general, population studies report that about 3% to 5% of cancer patients may have a partial DPD deficiency. Complete DPD deficiency is extremely rare.[5]

GENOTYPE-GUIDED DOSING RECOMMENDATIONS

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published recommendations on upfront dose adjustments for fluoropyrimidine-based treatment based on a patient's DPD phenotype. The DPD phenotype is determined by combining the activity scores (AS) of an individual's two *DPYD* variant alleles (**Table 1**).

A normal DPD metabolizer is defined with two normal function variants (*DPYD*-AS: 2).

An intermediate metabolizer carries one decreased or no function variant (*DPYD*-AS: 1 or 1.5).

Finally, a poor metabolizer carries two no function variants or a no function variant plus a decreased function variant (*DPYD*-AS: 0 or 0.5).[3]

For a *DPYD* normal metabolizer, there is no need to adjust dose or change treatment upfront (**Table 2**). *DPYD* intermediate metabolizers require an upfront dose adjustment depending on the activity score and should be closely monitored during therapy.

Those with an activity score of 1 should be initiated with a dose reduction of at least 50%; those with an activity score of 1.5 may be started at a dose reduction of 25% to 50%. If patients tolerate this initial lowered starting dose well without significant dose-limiting toxicities, their dose may be escalated in order to maintain effectiveness.

On the other hand, if individuals do not tolerate their starting dose well, the dose should be decreased further with subsequent cycles.

TABLE 2: DOSE RECOMMENDATIONS OF FLUOROPYRIMIDINES BY DPD PHENOTYPE[3]

PHENOTYPE	ACTIVITY SCORE	DOSING RECOMMENDATIONS
DPYD normal metabolizer	2	No indication to adjust dose or therapy
DPYD intermediate metabolizer	1.5	Reduce starting dose by 25% to 50%
	1	Reduce starting dose by 50%
DPYD poor metabolizer	0.5	Avoid use
	0	Avoid use

DPD deficiency greatly increases an individual's risk for severe or potentially fatal toxicities if they receive fluoropyrimidine-based treatment. CPIC provides guidance on dose modifications for those found to be *DPYD* intermediate or poor metabolizers.

Individuals with complete DPD deficiency are at a greatly increased risk for severe or even fatal toxicities if they receive fluoropyrimidine-based treatment. Therefore, CPIC guidelines strongly recommend avoiding use of these drugs and considering alternative anticancer therapies.[3]

CONSIDERATIONS FOR TESTING

Despite the potential for severe morbidity and mortality associated with DPD deficiency and dosing recommendations available, implementation of universal pretreatment *DPYD* genotyping has yet to be widely implemented. Several barriers are commonly cited, which include a limited evidence base, a cumbersome and lengthy testing process, and a lack of insurance coverage.[6]

Several studies have been published demonstrating that preemptive DPD testing improves patient safety outcomes and may reduce treatment-related costs.

A prospective, multicenter study evaluated upfront genotyping of a single *DPYD* variant, *DPYD**2A (c.1905+1G>A) in 2,038 patients. Genotype-guided dosing in individuals who were carriers of this variant (n = 22) had a lower rate of grade 3 or higher adverse events of 28% compared to 73% in historical controls (n = 48) ($p<0.001$). Average total treatment cost per patient was lower for screened patients ($3767) than nonscreened patients ($3,828).[7]

Another prospective, multicenter study screened 1,103 patients eligible for fluoropyrimidine-based therapy for four *DPYD* variants: *DPYD**2A, c.2846A>T, c.1679T>G, and c.1236A>G. Genotype-guided dosing for *DPYD**2A

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carriers had a lower relative risk for severe fluoropyrimidine-based toxicity of 1.31 (95% CI 0.63-2.73) compared to a relative risk of 2.87 (2.14-3.86) in the historical cohort, no toxicity compared with 4.30 (2.10-8.80) in c.1679T>G carriers, 2.00 (1.19-3.34) compared with 3.11 (2.25-4.28) for c.2846A>T carriers, and 1.69 (1.18-2.42) compared with 1.72 (1.22-2.42) for c.1236G>A carriers.[8]

The United States Food and Drug Administration (FDA) added labeling to fluorouracil and capecitabine package inserts warning about the potential for increased serious or fatal toxicities in patients with low or absent DPD activity.[9,10] In 2020, the European Medicines Agency (EMA) recommended that all patients be tested for DPD deficiency prior to starting cancer treatment with fluoropyrimidines.[11]

However, other national practice guidelines do not endorse universal DPD testing outright. The National Comprehensive Cancer Network (NCCN) recognizes that pre-treatment *DPYD* testing can reduce toxicity but does not recommend universal genotyping at this time as the impact of upfront dose adjustments on efficacy have not been fully elucidated.

Insurance companies base their coverage determinations on these national practice guidelines.[12] Since preemptive *DPYD* genotyping is not strongly recommended across the board, most insurance companies may not cover it, citing it to be investigational.[6]

The NIH Genetic Testing Registry website lists all commercially available DPD testing options. There are currently 88 tests listed ranging from targeted variant analysis to sequence analysis of the entire coding region.

CPIC has identified four variants that are of primary significance based on available published literature linking them to severe fluoropyrimidine toxicity. These variants are c.1905+1G>A, c.1679T>G, c.2846A>T, c.1129-5923C>G. Most tests focus on these four well-established risk variants. However, a test that includes only a subset of these variants will have reduced sensitivity.[3]

Clinicians have expressed concerns about the variety of DPD testing options available and their ability to interpret results accurately depending on variants tested in one qualitative study.

Turnaround times can vary from as short as five days to longer than four weeks. Most providers felt that a turnaround time longer than one week would be infeasible if it were to be used to guide chemotherapy dosing.[6]

CONCLUSION

DPD deficiency greatly increases an individual's risk for severe or potentially fatal toxicities if they receive fluoropyrimidine-based treatment. CPIC provides guidance on dose modifications for those found to be *DPYD* intermediate or poor metabolizers.

However, there are several barriers to universal pretreatment testing, which include the wide assortment of testing options, cost and lack of insurance coverage, and limited evidence in support of upfront testing.

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A HARD ISSUE TO HANDLE

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY: AN OVERVIEW OF CURRENT TREATMENT MODALITIES

By Jing Chien, DNP, CRNP, AOCNP

Chemotherapy-induced peripheral neuropathy (CIPN) is extremely difficult to manage in the oncology population. It rears its ugly head in cases of both curative intent, and palliative treatment in metastatic patients.

Jing Chien

In the former patient population, peripheral neuropathy greatly hinders patients' quality of life, in certain situations impeding on their ability to perform tasks involving fine motor skills such as painting, needlework or other crafts. In those whose livelihoods depends on their fine motor skills, neuropathy impacts income. In this aspect, CIPN has a tremendous impact among cancer survivors.

For metastatic patients, mitigating the severity of peripheral neuropathy can often feel like a losing battle. Chronic, debilitating neuropathic pain is often exacerbated while patients receive ongoing treatments as most systemic agents have peripheral neuropathy listed as a potential adverse effect.

The management of chemotherapy-induced peripheral neuropathy is loosely standardized as the effectiveness of available treatment options vary widely among patients.

A COMMON ISSUE

Approximately 30% to 40% of all patients who receive neurotoxic chemotherapy will develop a certain degree of peripheral neuropathy.

The leading chemotherapy agents known to cause neuropathy include vinca alkaloids, taxanes, platinums and anti-microtubular agents. Novel treatment agents

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also have the potential for neurotoxicity; these are thalidomide and proteasome inhibitors, among others.

Hence, when evaluating oncology patients for neuropathy causality and severity, it is helpful to consider both the therapeutic treatment(s) received and cumulative dosage.[1]

Peripheral neuropathy from chemotherapy results from damage to the peripheral nerves, including the motor, sensory and autonomic nerves. Depending on the type of nerve involved and severity, the manifestation can range from sensory issues such as numbness, tingling, cold sensitivity or pain.

Most patients report pain such as an unpleasant sensation, painful burning, freezing or shock-like electric sensation. Motor problems are reported in severe cases such as decreased proprioception, leading to inability to do intricate handiwork such as sewing and writing.

Complaints of the lower extremity include weakness, lack of sensation in the feet, or the sensation of walking on pebbles. These all contribute to fall risks and decreased functional ability.[1]

Certain patients are at increased risk of chemotherapy-induced peripheral neuropathy. In a study evaluation CIPN risk, it was found that age, chemotherapy type and cumulative dose of neurotoxic chemotherapies received are the most significant risk factors.[2]

Increased age, alcohol use, nonalcoholic liver disease and diabetes are influential factors likely to exacerbate CIPN symptoms.

Presently, there are no preventive treatment options and no neuroprotective medications for chemotherapy-induced neuropathy. Baseline assessment for existing neuropathy or predispositions are considered as essential preventive measures.[3]

Therefore, to minimize overall risk for the development of peripheral neuropathy, patients with peripheral nervous system disorders (spinal stenosis radiculopathy, hereditary neuropathy, diabetic poly-neuropathy) should be identified prior to chemotherapy initiation.[1]

To decrease the risk of exacerbating existing neuropathy, treating providers should take measures such as dose reduction, therapeutic agent selection or frequent follow-up to assess for peripheral nerve dysfunction throughout the course of cancer treatments.

EVALUATING CIPN

There are various evaluation tools for CIPN; none have been deemed more superior than the other.

The most utilized tool in the cancer setting by providers is the Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5, developed by the National Cancer Institute.

The CTCAE grades peripheral neuropathy on a scale of 1 to 5, from asymptomatic to most severe. Most chemotherapy-induced neuropathy is typically identified as grade 1 to 3. The latter grade signifies severe, self-care limiting.[4] At these degrees, interventions should be initiated to either limit further progression of neuropathy or alleviate symptoms.

Treatment modalities for peripheral neuropathy are varied and it is most certainly not a one size fits all approach. In the discussion of treatments, it is imperative to recognize that positive and negative symptoms of CIPN are targeted differently.

Negative symptoms such as motor weakness, loss of sensation and numbness cannot be reversed by medications. These symptoms may or may not improve with time, physical therapy and occupational therapy to target muscle, gait/balance training and motor skill training.[5]

For positive symptoms, paresthesia and dysesthesia — which are defined as the physical uncomfortable symptoms of burning and pain — the medical management varies and often requires combination medications or a trial-and-error approach.

TREATMENT OPTIONS

Of the medicines used in the treatment of CIPN, duloxetine, gabapentin and pregabalin are most commonly prescribed. Others added to the therapeutic mix include amitriptyline and venlafaxine.

It is important to note that trials investigating the use of these agents for neuropathy are primarily in the setting of diabetic peripheral neuropathy or generalized neuropathy. Few trials are specifically in the realm of chemotherapy-induced neuropathy or in the cancer population.

In a small clinical trial examining duloxetine 30mg twice daily versus pregabalin 75mg twice daily in management of CIPN in breast cancer patients, both medications were found to be well-tolerated. Both drugs prevented the progression of neuropathy and improved neuropathy symptoms from grade 3 to grade 2 after six weeks of treatment.[6]

In clinical practice and in a systemic review of randomized control trials involving duloxetine, the dosage for neuropathy can be increased to as high as 120mg daily. In studies comparing duloxetine to placebo, the former consistently showed improvements in neuropathic pain.

In comparison of duloxetine with pregabalin or amitriptyline, the medications' efficacies varied among the different trials which suggests that there are individual variations and factors involved in neuropathy pain relief.

Duloxetine has higher affinity for 5-HT and NE reuptake inhibition versus amitriptyline, a TCA, therefore, it has the added benefit of addressing emotional symptoms along with pain in cancer patients.[7]

COMBINATION THERAPY

In patients showing partial response to monotherapy despite upward titration to the maximum dosage of one drug, it is clinically acceptable to consider combination therapy in these difficult cases. Combination therapy typically consists of duloxetine with amitriptyline or pregabalin.

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However, combination therapy may or may not be more efficacious.

The COMBO-DN (Combination vs. Monotherapy of pregabalin and duloxetine in Diabetic Neurotherapy) study, a randomized, double-blind multinational trial found no statistical significance in pain reduction among combination therapy versus monotherapy when comparing the duloxetine 60mg/day plus pregabalin 300mg/day cohort with monotherapy duloxetine 120mg/day or pregabalin 600mg/day groups.[8]

Clinically, we up-titrate one agent before adding on a second medication. If no significant improvement is found, then tapering off the unbeneficial medication is appropriate.

▲ **PREGABALIN:** Pregabalin's efficacy in neuropathic pain is due to its ability to modify neurotransmitter release. Pregabalin does not bind to plasma protein, nor is it metabolized by the liver. This makes it a better agent for combating neuropathic pain than gabapentin as it reduces drug-drug interaction in all patients, especially in cancer patients who are more likely to have polypharmacy for malignancy and symptom management.

In a trial evaluating pregabalin for diabetic neuropathy, cancer pain and back pain, pregabalin was found to be 80% effective in all patients at the six-week mark. The treating dosages were between 150mg to 600mg/day; average dosing was roughly 250mg/day. Most patients reported 30% to 80% reduction in their pain.[9]

While pregabalin overall has positive data to support its use, gabapentin, the older antiepileptic that regulates calcium influx and neurotransmitter release, does not have the same positive data across the board.

▲ **GABAPENTIN:** Studies investigating gabapentin for CIPN are conflicting. In a multi-institutional, double-blind, placebo-controlled, crossover design study of 115 patients, comparing gabapentin at a targeted dose of 2,700mg/day with placebo, the study failed to demonstrate statistical significance favoring gabapentin over the placebo in treatment of CIPN. The study did find gabapentin was overall well-tolerated. The greatest side effects were fatigue and drowsiness.[10]

For the sake of patients suffering from CIPN, it will take clinician persistence to continue trying various medications and reach beyond the data to pull in complementary alternative medicines in hopes of offering relief.

Gabapentin has demonstrated effectiveness in treatment of nerve pain caused by tumor infiltration or compression of the nervous structure when used in conjunction with opioids at 600mg to 1,800mg daily dosing.[11] Clinically, gabapentin is typically started as first line response to patients complaining of peripheral neuropathy symptoms, particularly CIPN. It is then often first titrated upwards to 1,800mg/day dosing before rotation to pregabalin.

However, when choosing between the two medications as first line, pregabalin should be considered over gabapentin.

▲ **DULOXETINE:** Duloxetine can used in combination therapy with pregabalin for patients with significant neuropathy at the 60mg/day dosing. If neuropathy pain continues to be refractory, amitriptyline and venlafaxine can be considered in these cases. However, the latter agents have failed to demonstrate superior results. In one study comparing venlafaxine and duloxetine for chemotherapy-induced peripheral neuropathy, both were deemed effective in treatment of cranial, motor and sensory issues but ultimately duloxetine was proven to be superior.[12]

▲ **AMITRIPTYLINE:** In a 14-week randomized, cross over study comparing three doses of amitriptyline (10mg, 25mg and 50mg/nightly) versus duloxetine (20mg, 40mg and 60mg/daily), both agents were equal, demonstrating a greater than 30% reduction in pain.[13]

Clinically, amitriptyline is secondary to duloxetine given duloxetine's superior safety profile. Safety is in a concern when utilizing multiple agents. It is imperative to check with the pharmacist for safe dosing and other polypharmacy concerns when layering on multiple agents for mood, pain and neuropathy as they can increase the chance for serotonin syndrome.

▲ **METHADONE:** Methadone, a synthetic opioid, offers another potential option in difficult-to-treat neuropathic pain. Methadone has not yet been studied in CIPN. However, a pilot study was submitted in March 2023 to explore methadone in this setting.[14]

Methadone has a rapid onset and long half-life, while lacking active metabolites. Methadone has an affinity for both opioid receptors and N-methyl-D-aspartate (NMDA) receptors, a modulator of neuropathic pain.

A little over half of a 13-person retrospective case study showed methadone as an effective agent for chronic neuropathic pain. It is important to note that among those 13 patients, all patients were also taking coanalgesics, another opioid, anti-inflammatory, antidepressants or anticonvulsants.[15]

This retrospective study is representative of what is seen clinically. In patients with severe CIPN or cancer-related neuropathy who have failed all other treatment modalities, methadone can be trialed at 2.5mg or 5mg BID. Upward titrating would depend on tolerability. There is potential for cardiac arrhythmias due to prolonged QTc interval. Frequent follow-up is essential with baseline and repeat EKGs.

Opioids are not typically offered to patients who present with CIPN. Systemic

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review of 31 trials examining opioid use for peripheral neuropathy did not yield any conclusive recommendation. While the majority of the studies showed opioids to be efficacious in treatment of nerve pain, the trials themselves were short duration, less than 12 weeks, small sample size and possibly inherently biased.[16]

The side effects and risk of opioid use must be evaluated and discussed with patients. The most significant ones are constipation, gastrointestinal upset, possible sedation and the risk of physical dependency. The pros and cons must be discussed, and a mutual decision should be made to safely trial opioids for CIPN if diminished quality of life deems it necessary.

COMPLEMENTARY ALTERNATIVE MEDICINE

When all prescriptive agents seem to have failed, complementary alternative medicine (CAM) is a viable option. Many of these options do lack strong scientific rationales as randomized control studies have not been conducted.

Of the various CAM methods available for CIPN, cannabis medicine, acupuncture and scrambler therapy are more well-known and often advised in the cancer population.

▲ **CANNABIS:** There are many cannabis medicine products available, and the choice can often be overwhelming. Medically certified patients can seek out products specifically for neuropathy with varying ratios of THC and/or CBD concentrations. Products vary by state and dispensary. The science behind acupuncture is also not well-established, however, it seems to work on endorphin release and inflammatory response.

▲ **ACUPUNCTURE:** In a very small trial, 10 acupuncture sessions over the course of 10 weeks in bortezomib-induced peripheral neuropathy patients showed statistically significant improvement in numbness, tingling, cold sensitivity, and discomfort.[17] Insurance reimbursement and finding an experienced provider are two barriers to acupuncture therapy.

▲ **SCRAMBLER THERAPY:** Calmare or scrambler therapy works by placing one electrode proximal and one electrode distal to the site of pain. A signal of 0.9 volts to 4.9 volts is sent every 5 to 15 minutes until tolerated strength was reached. Each treatment session lasts roughly an hour and for several days consecutively.[18]

Varied small studies have been conducted on evaluation of scrambler therapy for neuropathic pain. Results are varied. In terms of CIPN, two studies showed promising results.

One pilot study involved 37 patients with CIPN who received 30 minutes of scrambler therapy for 10 consecutive days. Results demonstrated a 53% reduction in pain, 44% reduction in tingling and 37% reduction in numbness.[19]

A trial involving 39 cancer patients with CIPN and cancer pain syndromes also demonstrated a 30% reduction in overall pain following an average of 10 days of scrambler treatment.[20]

The greatest barrier for patients interested in this therapy is access to a provider. Secondly, cost may be a significant burden as it is unlikely for scrambler therapy to be a covered procedure under insurance.

CONCLUSION

Chemotherapy-induced peripheral neuropathy is exceptionally difficult to treat. It can cause debilitating and unrelenting symptoms for both cancer survivors and metastatic patients. At best, it is an irritating sensation that will not let patients forget their cancer journey.

At worst, CIPN reduces quality of life, greatly impacting activities of daily living. The presence of burning pain, sensory loss and temperature sensitivity are often compounded with chronic cancer-related pain elsewhere in the body.

Hence, the desire is great among clinicians, both palliative care providers and oncologists to find an effective medical management for CIPN.

The unfortunate reality is that CIPN treatment is not one size fit all. There are guidelines, but no concrete pathway.

For the sake of suffering patients, it will take clinician persistence to continue trying various medications as mentioned above and reach beyond the data to pull in complementary alternative medicines in hopes of offering relief.

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OPDUALAG: A NOVEL DUAL IMMUNOTHERAPY TREATMENT OPTION FOR ADVANCED MELANOMA

By Hardeep Phull, MD

In the past year, there has been an exciting development targeting a novel immunotherapy pathway in front-line advanced (unresectable or metastatic) melanoma.


Hardeep Phull

On top of targeting the traditional programmed cell death protein-1 (PD-1) pathway with nivolumab, additional dual inhibition of Lymphocyte activation gene-3 (LAG-3) via relatlimab-rmbw can provide a synergistic immunotherapy blockade.

The dual product, known as **Opdualag™** (nivolumab/relatlimab-rmbw), provides a new weapon in an oncologist's armamentarium for the treatment of advanced melanoma.

LAG-3 was first discovered as a cell surface molecule on T cells and numerous immune cells, exhibiting overall inhibitory effects on T-cell function including reducing activation and proliferation as well as cytokine secretion, with approximately 100 times more affinity for MHC-II than CD4.[1] It was also found to have distinct ligands from other checkpoints such as PD-1 or CTLA-4 (cytotoxic T-lymphocyte-associated protein 4).[2]

Anti-LAG-3 antibodies like relatlimab-rmbw can bind to LAG-3, thereby inhibiting its interaction with MHC-II and reducing the inhibition of the LAG-3 pathway on T cell inhibition which had previously allowed tumor cells to evade immune detection.[3]

By blocking PD-1 via nivolumab and LAG-3 via relatlimab-rmbw, the novel dual checkpoint blockade offered by Opdualag can cause re-activation of the T-cell response and eventual tumor death.[3]

RELATIVITY-047 TRIAL

To investigate the efficacy and safety of Opdualag in the clinical setting, a phase 2-3 double-blind, randomized clinical trial, known as Relativity-047, was conducted globally.[4]

Patients with treatment-naïve metastatic or unresectable melanoma were randomized 1:1 to intravenous Opdualag (nivolumab 480mg + relatlimab-rmbw 160mg) every four weeks as compared to intravenous nivolumab monotherapy 480mg every four weeks. The 714 patients were then evaluated for progression-free survival (PFS), overall response rate (ORR), overall survival (OS), and other endpoints.

Of note, though this trial sought to investigate the study drug in treatment naïve patients with advanced melanoma, those with prior adjuvant or neoadjuvant therapies including BRAF targeted medications were eligible if the prior therapy was completed at least six months before the date of disease recurrence.

Moreover, certain characteristics were minimally represented in Relativity-047 including mucosal melanoma (uveal melanoma was excluded), untreated brain metastases, and patients with treated M1d disease.

Through blinded independent central review, PFS was reported for the intention to treat population as 10.1 months with Opdualag, with a hazard ratio of 0.75 (p=0.006), when compared to 4.6 months with nivolumab.[4] The 24-month PFS was 38% vs. 31%, and the 36-month PFS was 31% vs. 27%, in the experimental arm as compared to the nivolumab arm.

Forrest plot analysis of various subgroups showed a clear trend towards Opdualag, including age, sex, melanoma subtype, LDH level, tumor burden, BRAF mutation status and metastasis stage. Interestingly, PD-L1 expression did not show a clear correlation with response though >1% of LAG-3 expression did favor the Opdualag arm.[4]

There were several post-hoc analyses which were also reported in this study, that were not powered for but were nonetheless interesting.[5] OS was not reached for the study group as compared to 33.2 months for nivolumab alone. At 36 months, OS was 54% vs. 48% and at 48 months, it was 52% vs. 42%, respectively. Overall response rate was 44% in the study arm as compared to 34% in the nivolumab-only arm, though duration of response was not reached for both arms.

Melanoma specific survival (MSS) was not reached for the study group vs. 46.7 months for nivolumab. The most common other deaths were sepsis, myocardial infarction, stroke, pneumonia and respiratory insufficiency.

PFS-2 (a parameter measuring time from randomization to progression after the next line of therapy) was 28.4 months in the Opdualag group as compared to 20.1 months for nivolumab. Indeed, when evaluating subsequent therapies received in both arms of this study, a reassuring pattern emerged.

In particular, patients in the study group had evidence of response to future checkpoint blockade and PFS benefit, namely with nivolumab/ipilimumab, and BRAF/MEK oral oncolytics. These subsequent responses were far lower in the nivolumab-only arm, but there was nonetheless still a response to checkpoint blockade in both arms, suggesting the potential ability to preserve subsequent efficacy of immunotherapy use in second-line settings.[5]

Lastly, regarding safety, the most common immune-mediated adverse events in the study arm included hypothyroidism/thyroiditis, rash and

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OPDUALAG

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diarrhea/colitis.[4] When evaluating grade 3 or 4 toxicities, 18.9% of Opdualag patients experienced these, as compared to 9.7% in the nivolumab arm.

The notable grade 3 or 4 adverse effects which were higher with the dual immunotherapy included fatigue, arthralgia, hepatitis, myocarditis and adrenal insufficiency.[4]

Interestingly, the incidence of grade 3 or 4 diarrhea/colitis was higher in the nivolumab arm. In any case, a majority of the toxicities resolved in both arms.[4] There were four treatment-related deaths in the study arm as compared to two in the nivolumab-only arm.[5]

OUTSTANDING SAFETY PROFILE

The major potential strength of the new treatment option in Opdualag includes the outstanding safety profile without compromising efficacy.

Indeed, fewer than 20% of patients who received relatlimab-rmbw–nivolumab reported serious grade 3 or 4 side effects,[4] compared historically with nearly 55% of patients who were reported to have these adverse events with the original investigation (reported in CheckMate 067) of dual nivolumab/ipilimumab immunotherapy.[6]

In that trial, 16% of patients in the nivolumab-only arm and 27% in the ipilimumab-only arm had grade 3 or 4 toxicity. Nevertheless, in that classic trial, the combination of nivolumab/ipilimumab generated robust response rates of nearly 58% and after nearly six years of follow-up, an impressive and durable median survival benefit of more than 60 months has emerged as compared to monotherapy.[7]

Though cross trial comparison is not a valid method of comparing treatments, the above long-term, historical experience and effectiveness of nivolumab/ipilimumab does call into question how Opdualag will fit into the treatment paradigm for advanced melanoma.

For instance, many experts regard nivolumab/ipilimumab to be the superior "benchmark to which other regimens should be compared," including from a practice experience standpoint such as settings in which there are untreated brain metastases, liver metastases, high LDH, bulky disease or post-adjuvant anti-PD-1 treatment failure.[7]

Meanwhile, for desmoplastic melanoma or autoimmune disease, it is thought that monotherapy may be safer.

Therefore, it could be conjectured that the combination of nivolumab/relatlimab-rmbw may be a "compromise" option for patients in between the above scenarios in which a robust response is desired without major impact on safety. This is further supported by recently published data demonstrating a similar health-related quality of life with Opdualag when compared to nivolumab monotherapy.[8]

The PFS-2 endpoint in Relativity-047 also portends a promising response to subsequent treatment, which potentially could allow Opdualag to play a major role in treatment sequencing. Moreover, as adjuvant BRAF/MEK inhibition was not approved at the time of CheckMate 067 enrollment and there was evidence that prior inhibition of this pathway could be associated with decrease subsequent response with checkpoint blockade, Relativity-047 did demonstrate that there can still be a response in this patient population.[4]

In summary, after two years of follow-up, Opdualag continues to demonstrate consistent benefit in PFS, PFS-2, ORR, OS, and MSS. Patients on this novel dual immunotherapy regimen have sustained benefit beyond progression, including observed efficacy on subsequent second-line therapy.

Importantly, the adverse events expected with nivolumab/relatlimab-rmbw are consistent with the data and manageable overall. Future investigation will be crucial to compare the true efficacy of Opdualag as compared to nivolumab/ipilimumab and other agents including combinations with oncolytics such as BRAF/MEK inhibitors, as well as the ideal sequencing of therapy. Optimally, head-to-head comparisons in the same, controlled trial should be conducted to make valid comparisons between these therapeutic agents.

Indeed, clinical trials are underway to better understand the role of biomarkers such as LAG-3, inclusion of patients with untreated brain metastases, and treatment in the neoadjuvant and adjuvant settings.

Nevertheless, Opdualag provides a new weapon in the arsenal of immunotherapy treatment choices for advanced melanoma in the first-line setting which previously was limited to anti-PD1 monotherapy or dual immunotherapy with nivolumab/ipilimumab.

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BPA WORLDWIDE™

ENGAGEMENT, JOB SATISFACTION HELP DRIVE EFFECTIVE ONCOLOGY EDUCATION PROGRAMS

By Liam King, BSc, BPharmSci, MPharm, MMedRes, PhD candidate in Pharmacy

The healthcare landscape in Australia has suffered from a workforce shortage in recent years due to a reduction in skilled worker migration and healthcare worker burnout as a result of the COVID-19 pandemic.

With reduced workers to fill essential roles, healthcare organizations must focus on employee engagement and job satisfaction to promote staff retention.

Liam King

All organizations should strive to promote employee engagement as people are frequently regarded as an organization's most valuable asset, when managed and engaged properly.

Engaged employees consistently strive for excellence in their roles,[1] with research demonstrating a significant correlation between employee engagement and employee performance in healthcare settings.[2]

Several drivers that promote employee engagement have been identified with appropriate remuneration often being the primary focus. However, the literature points to various factors that lead to high employee engagement including empowerment, leadership, career development opportunities, training and development, and performance management.[3]

EMPOWERMENT

By definition, empowerment is the act or process of giving someone more control over their own life or situation they are in.[4] Within the workplace, research has further broken empowerment into a combination of psychological and structural empowerment.[5]

Access to resources, support, opportunities and information have been identified as aspects of structural empowerment, while meaning, choice, competence and impact are seen as determinants of psychological empowerment.[5] The use of effective education programs can positively impact several of these factors.

Structural empowerment in the form of educational programs not only grants employees access to information but also acts as a resource platform. Group settings are utilized to conduct programs, which aid participants in building connections with their coworkers, and in turn, create a support network.

The strength of this network is further enhanced by the involvement of experienced and senior members of the organization functioning as facilitators.

The involvement of senior team members also highlights additional opportunities for participants to develop their skills should they remain with the organization.

From a psychological perspective, the improvement of an employee's competence should be seen as one of the primary goals of educational programs, with organizations often viewing competence as a means of delivering gold-standard service.

However, as noted, the development of competence in a role also promotes employee empowerment, while a lack of competence can have a negative impact on engagement.

Past literature has suggested that a lack of competence can lead to poorly performed tasks and end results that are not as expected, which may cause employees to feel unmotivated to continue to perform in their role.[6]

LEADERSHIP

The link between leadership styles and employee engagement is well documented throughout the literature.

Leadership styles such as transformational leadership and transactional leadership have been shown to have positive associations with engagement, whereas passive-avoidant leadership leads to negative impacts.[7]

Therefore, leaders within the workplace must be aware of the leadership style they are portraying to ensure a positive influence on employee engagement.

Education programs can be a prime opportunity for effective leadership to be displayed, while presenting leadership opportunities to team members outside of the typical managerial structure.

Literature indicates that empowering others to lead is a characteristic of effective leadership.[8] This suggests that educational initiatives that concentrate on enhancing employees' leadership abilities will yield more significant outcomes when compared to programs that focus exclusively on improving technical skills or knowledge.

CAREER DEVELOPMENT OPPORTUNITIES

Organizations that provide career development opportunities tend to have highly engaged workers and, as a result, retain talented employees.[9] Effective programs encompass both skill and knowledge development and the opportunity to apply them. Therefore, it is important for organizations to develop structured career progression frameworks to complement educational activities.

Encouraging career development also has been found to significantly contribute to employee engagement more than support provided by training initiatives alone.[10] Therefore, education

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programs should be seen as more than just training exercises.

TRAINING AND DEVELOPMENT

To some degree, all organizations utilize training and development to enable key tasks to be carried out by their employees. However, effective training and development also can increase employee engagement.

At its core, training aims to develop an employee's competence within their role and as previously highlighted, competence leads to psychological empowerment and ultimately increased employee engagement.[3]

Training also allows employees to learn new skills that may generate interest in aspects of their role which they have previously not explored and result in the employee becoming more engaged within the workplace.[3]

While training and development have a positive correlation with employee engagement, several considerations need to be made to ensure the optimal training and development activities.

Firstly, prior to the development of a training activity, an analysis should be conducted to identify gaps within an organization and ensure it is applicable to the workforce.[11]

Next, activities should align with the individual employee's needs, and employees should be actively involved in these activities.[12]

Finally, organizations need to ensure the provision of suitable resources to allow employees to utilize the new skills they have acquired and training should be continually evaluated and adapted as needed.[11]

PERFORMANCE MANAGEMENT

When effectively applied, performance management helps create and sustain high levels of employee engagement.[13] Mone et al., suggest that effective performance management should include five key components:[14]

TABLE 1: COMPONENTS OF AN ONCOLOGY EDUCATION PROGRAM ADDRESSING DRIVERS OF ENGAGEMENT FOR ATTENDEES

DRIVER OF ENGAGEMENT	PROGRAM COMPONENT
Empowerment	Enhances knowledge
	Creates a support network of other oncology pharmacists
	Develops competencies for pharmacists for self-assessments
	Introduces cancer care course delivered in a face-to-face manner to enhance network development
Leadership	Demonstrates the focus that organizational leaders place on education and employee development
	Develops a culture of mentorship through relationship-building with the facilitators
Career development opportunities	Highlights organization's oncology pharmacist career framework to promote career development opportunities
	Provides employees with an opportunity to further develop their skills and advance their career
Training	Provides attendees with the knowledge to carry out their role as an oncology pharmacist
	Introduces attendees to a variety of resources to assist them in the role as an oncology pharmacist
	Utilizes interactive/case -based sessions to ensure attendees are actively involved
Performance management	Provides employees with an achievable goal to set during performance reviews if they want to develop in the area of oncology

- Setting performance and development goals;
- Providing ongoing feedback and recognition;
- Managing employee development;
- Conducting mid-year and year-end appraisals; and
- Building a climate of trust and empowerment.

While generally regarded as separate to education, effective education programs can aid both the organization and individual in the performance management process and assist both parties in attaining diverse organization and workplace goals.[15]

APPLICATION

In recent years, our organization identified of a lack of process standardization and practice gaps in our oncology service across our facilities nationally, despite most pharmacy and oncology practice guidelines and standards having national coverage within Australia.

This demonstrated the need for the development of an appropriate education program that focused on promoting standard processes and providing support and resources for employees to follow these processes. However, we also saw this as an opportunity to impact employee engagement by focusing on the factors mentioned above.

Due to the availability of theoretical-based education through organizations such as the Clinical Oncology Society of Australia (COSA) and the Society of Hospital Pharmacists of Australia (SHPA), our program focused more on the practicalities of how to fulfill the role of an oncology pharmacist within our organization as a supplement to the learning provided by these organizations.

The content was also tailored to ensure it addressed key factors that promoted staff engagement. While the program was targeted at pharmacists

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and technicians new to the area of cancer care, the program was also designed to provide opportunities for senior pharmacists to act as facilitators.

Table 1 and **Table 2** outline components of our program that address the drivers of employee engagement that have been discussed for both the attendees (junior employees) and facilitators (senior/experienced employees) respectively.

Before undertaking a formal competency assessment, newly hired oncology pharmacists and technicians must enhance their skills through relevant training sessions. This training aims to equip the employees with the required knowledge and skills, which is then assessed during the formal competency assessment.

The assessment serves as a crucial performance appraisal tool, providing employees with a clear understanding of the expected level of competency in their field.

As an organization, we intend to track the impact of the education program in promoting staff retention within the oncology service line and the program's contribution to the improvement of the pharmacy service in this sector.

We also aim to extend the program to develop activities geared specifically toward our senior oncology pharmacists to drive excellence within the service line and increase the number of mentors for our junior employees.

In conclusion, organizations should recognize education programs as a crucial means to enhance the abilities of their workforce and foster employee engagement.

It is imperative to carefully evaluate the education content and delivery methods to achieve optimal learning outcomes and maintain employee engagement.

TABLE 2: COMPONENTS OF AN ONCOLOGY EDUCATION PROGRAM ADDRESSING DRIVERS OF ENGAGEMENT FOR FACILITATORS

DRIVER OF ENGAGEMENT	PROGRAM COMPONENT
Empowerment	Provides opportunity to take on new responsibilities as a mentor
	Delivers course in a face-to-face manner to enhance network development
Leadership	Provides opportunity to take part in a leadership role as a facilitator
	Develops a culture of mentorship through building connections with the attendees
Career development opportunities	Highlights the organization's oncology pharmacist career framework, including progression opportunities for experienced pharmacists
	Provides opportunity for experienced pharmacists to contribute lead education activities outside of formal educational roles
Training	Provides training on facilitating educational activities and enhance mentoring skills
Performance management	Allows experienced team members to set a goal to facilitate the education activities

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FOOD AND DRUG ADMINISTRATION ANNOUNCES THE APPROVAL OF 10 NEW ORAL ONCOLYTICS


Derek Gyori


Kirollos Hanna

By Derek Gyori, PharmD, BCOP, & Kirollos Hanna, PharmD, BCPS, BCOP

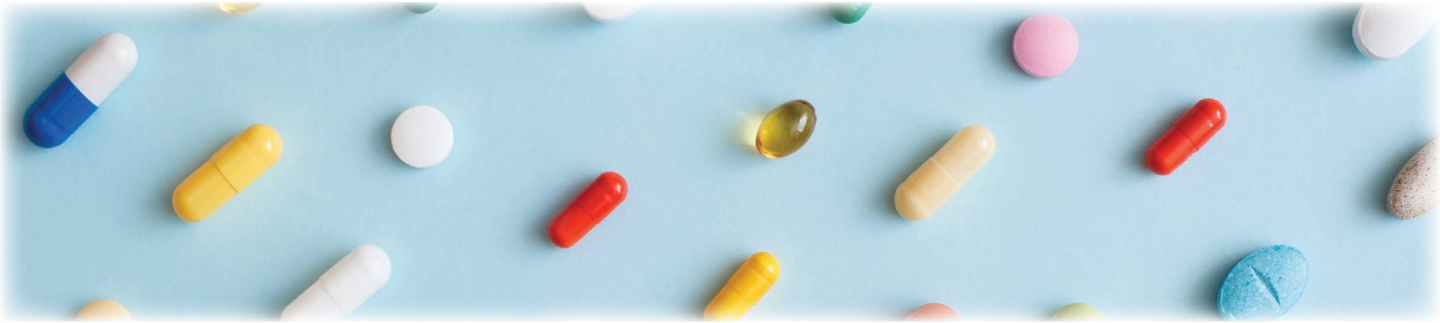
The U.S. Food and Drug Administration (FDA) approved 10 oral oncology agents from January 21 through August 11, 2023. In the chart below and on the following four pages, the asterisk (*) represents a new indication for a previously approved therapy.

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
Jaypirca™ (pirtobrutinib)[1-3]	1/27/2023	• Mantle Cell Lymphoma, R/R • 200mg orally once daily until disease progression or unacceptable toxicity	**BRUIN** • N=120 • ORR: 50% (95% CI: 41, 59) with CR of 13% • DOR: 8.3 months (95% CI: 5.7, NE) • DOR Rate at six months: 65.3% (95% CI: 49.8, 77.1)	• ≥15%: Fatigue, musculoskeletal pain, diarrhea, edema, dyspnea, pneumonia and bruising • Grade 3/4 Lab Abnormalities ≥10%: Decreased neutrophil counts, lymphocyte counts and platelet counts • Warnings/precautions: Infections, hemorrhage, cytopenias, atrial fibrillation and flutter, and second primary malignancies	• Available as 50mg and 100mg tablets • Administer with or without food • Consider prophylaxis (including vaccinations and antimicrobial prophylaxis) in patients who are at increased risk for infections, including opportunistic infections • Consider risk versus benefit of withholding pirtobrutinib three to seven days prior to and after surgery
ORSERDU™ (elacestrant)[1,4-5]	1/27/2023	• Breast cancer, advanced or metastatic, ER-positive, HER2-negative, ESR1-mutated (postmenopausal patients or males) • 345mg once daily until disease progression or unacceptable toxicity	**EMERALD** • N=478 ESR1+ mutation • n=228 PFS: 3.8 months (95% CI: 2.2, 7.3) elacestrant vs. 1.9 months (95% CI: 1.9, 2.1) fulvestrant or aromatase inhibitor • HR: 0.55 [95% CI: 0.39, 0.77], two-sided p-value=0.0005	• ≥10%: Musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush and dyspepsia	• Available as 86mg and 345mg tablets • Administer with food (to reduce nausea and vomiting)

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
Verzenio® (abemaciclib)[1,6-8]	3/3/2023*	• Breast cancer, early, high risk, HR-positive, HER2-negative, node-positive • 150mg taken twice daily with tamoxifen or an aromatase inhibitor until completion of two years of treatment or until disease recurrence or unacceptable toxicity	**monarchE** **Cohort 1** • N=5120 [91%] • IDFS HR 0.653 (95% CI: 0.567, 0.753) • IDFS at 48 months: Abemaciclib plus standard endocrine therapy – 85.5% (95% CI: 83.8, 87.0) versus standard endocrine therapy alone – 78.6% (95% CI: 76.7, 80.4) • OS data for Cohort 1 is still immature **Cohort 2** • More deaths were observed with abemaciclib plus standard endocrine therapy compared to standard endocrine therapy alone (10/253 vs. 5/264)	• ≥20%: Diarrhea, infections, neutropenia, fatigue, leukopenia, nausea, anemia and headache • Severe diarrhea associated with dehydration and infection can occur. Most patients experienced diarrhea during the initial month of abemaciclib; the median time to onset of the first diarrhea event was six to eight days	• High Risk (Cohort 1) is defined as having either ≥4 pALN (pathologic axillary lymph nodes) or 1-3 pALN and either tumor grade 3 or a tumor size ≥50mm • Cohort 2 was defined as not eligible for cohort 1 and must have had 1-3 pALN and tumor Ki-67 score ≥20% • This approval removes the requirement of Ki-67 score >20% • Available as 50mg, 100mg and 150mg tablets • Administer with or without food • Abemaciclib is associated with moderate to high emetic potential. Antiemetics may be warranted
Tafinlar® **+ Mekinist®** (dabrafenib + trametinib)[1,9-12]	3/16/2023*	• Low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy • Dosing is based on body weight in pediatric patients • Dabrafenib is administered orally twice daily and trametinib is administered orally once daily • Administered until disease progression or unacceptable toxicity	**Study CDRB436G2201** • N=110 • Randomized 2:1 to dabrafenib plus trametinib (D+T) or carboplatin plus vincristine (C+V) ORR • D+T: 46.6% (95% CI: 34.8, 58.6) versus C+T: 10.8% (95% CI: 3.0, 25.4) (p= <0.001) DOR • D+T: 23.7 months (95% CI: 14.5, not estimable) versus C+T: not estimable (95% CI: 6.6, not estimable) PFS • D+T: 20.1 months (95% CI: 12.8, not estimable) versus C+T: 7.4 months (95% CI: 3.6, 11.8) (HR=0.31 [95% CI: 0.17, 0.55]; p= <0.001) • OS results at the interim analysis did not reach statistical significance	• >20%: Pyrexia, rash, headache, vomiting, musculoskeletal pain, fatigue, dry skin, diarrhea, nausea, epistaxis and other bleeding events, abdominal pain and dermatitis acneiform	• Capsules and tablets are available. Tablets can be used to create an oral suspension. • Administer dabrafenib at least one hour before or two hours after a meal; doses should be administered ~12 hours apart at approximately the same time each day • Administer the once-daily trametinib dose with the morning or evening dose of dabrafenib • Secondary prophylaxis with antipyretics may be required when resuming dabrafenib following a severe febrile drug reaction

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
LYNPARZA® (olaparib)[1,13-14]	5/31/2023*	• mCRPC, BRCAm • 300mg by mouth twice daily (with abiraterone and prednisone/ prednisolone)	**PROpel Exploratory Subgroup Analysis in patients with BRCAm** • n= 85 Median rPFS that was not reached in the olaparib with abiraterone arm compared to 8 months (95% CI: 6, 15) for those receiving placebo with abiraterone (HR 0.24 [95% CI: 0.12, 0.45]) • OS HR: 0.30 (95% CI: 0.15, 0.59) **ITT Population without BRCAm** • rPFS HR: 0.77 (95% CI: 0.63, 0.96) • OS HR: 0.92 (95% CI: 0.74, 1.14)	• ≥10%: Anemia, fatigue, nausea, diarrhea, decreased appetite, lymphopenia, dizziness and abdominal pain	• Administered with or without food • Patients should also receive a GnRH analog concurrently or should have had a prior bilateral orchiectomy
TALZENNA® (talazoparib)[1,15-16]	6/20/2023	• HRR gene-mutated mCRPC • 0.5mg taken orally once daily in combination with enzalutamide until disease progression or unacceptable toxicity	**TALAPRO-2** N=399 with HRR gene-mutated mCRPC • rPFS: Talazoparib group median was not reached vs Placebo group 13.8 months (HR 0.45; 95% CI: 0.33, 0.61; p<0.0001)	• ≥10%: Decreased hemoglobin, decreased neutrophils, decreased lymphocytes, fatigue, decreased platelets, decreased calcium, nausea, decreased appetite, decreased sodium, decreased phosphate, fractures, decreased magnesium, dizziness, increased bilirubin, decreased potassium and dysgeusia	• Available as 0.1mg, 0.25mg, 0.35mg and 0.5mg capsules • Administer with or without food • Patients should also receive a GnRH analog concurrently or should have had bilateral orchiectomy



DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
VANFLYTA® (quizartinib)[1,17-18]	7/20/2023	**Newly diagnosed acute myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)-positive** • Induction: 35.4mg once daily on days 8 to 21 of the 28-day induction cycle • Consolidation: 35.4mg once daily on days 6 to 19 of each 28-day consolidation cycle up to four cycles **Maintenance** • C1: 26.5mg once daily on days 1 to 14 of cycle if QTcF is ≤450 msec. Increase to 53mg once daily on days 15 to 28 of a 28-day maintenance cycle if QTcF remains ≤450 msec. Maintain a dose of 26.5mg once daily if QTcF >500 msec was observed during induction or consolidation • C2: 26.5mg or 53mg (as determined in maintenance cycle 1) once daily on days 1 to 28 of each 28-day maintenance cycle for up to 36 cycles	**QuANTUM-First** • N=539 • Randomized (1:1) to receive quizartinib (n=268) or placebo (n=271) with induction and consolidation therapy and as maintenance monotherapy • OS HR: 0.78; 95% CI: 0.62, 0.98; 2-sided p=0.0324 • CR Rate: Quizartinib - 55% (95% CI: 48.7, 60.9) with a median duration of 38.6 months (95% CI: 21.9, NE) versus Placebo - 55% (95% CI: 49.2, 61.4) with a median duration of 12.4 months (95% CI: 8.8, 22.7)	• ≥20%: Febrile neutropenia, neutropenia, pyrexia, diarrhea, hypokalemia, nausea, headache, rash, vomiting, stomatitis and constipation	• Available as 17.7mg, 26.5mg tablets • Administer with or without food at approximately the same time each day • BBW for QT prolongation, torsades de pointes and cardiac arrest • Do not initiate treatment with quizartinib if the QTc interval is >450 msec • Correct electrolyte abnormalities prior to initiation of treatment • Available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), called the VANFLYTA REMS
LONSURF® (trifluridine and tipiracil)[1,19-20]	8/2/2023*	• mCRC • 5mg/m2 orally twice daily with food on days 1 through 5 and days 8 through 12 of each 28-day cycle (in combination with bevacizumab)	**SUNLIGHT** • N=492 • OS: Lonsurf+ Bevacizumab 10.8 months (95% CI: 9.4, 11.8) versus Lonsurf alone 7.5 months (95% CI: 6.3, 8.6) (Hazard ratio 0.61; 95% CI: 0.49, 0.77; 1-sided p<0.001) • PFS: Lonsurf+ Bevacizumab 5.5 months (95% CI: 4.5, 5.9) versus Lonsurf alone 2.4 months (95% CI: 2.1, 3.2) (HR 0.44; 95% CI: 0.36, 0.54; 1-sided p<0.001)	• ≥20%: Neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased AST, increased ALT, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain and decreased appetite	• Available as trifluridine 15mg/ tipiracil 6.14mg, trifluridine 20mg/ tipiracil 8.19mg tablets • Manufacturer recommends rounding each dose to the nearest 5mg increment • Administer with food • Antiemetics are recommended to prevent nausea and vomiting • Obtain blood counts prior to starting each cycle and on day 15 of each cycle • Do not initiate a cycle until ANC ≥1,500/mm3 or febrile neutropenia is resolved, platelets are ≥75,000/mm3, and/or grade 3 or 4 nonhematologic reactions

DRUG	APPROVAL DATE	INDICATION & DOSING	CLINICAL TRIAL OUTCOMES	ADVERSE EFFECTS	CLINICAL PEARLS
GAVRETO® (pralsetinib)[1,21-23]	8/9/2023*	• RET fusion-positive NSCLC • 400mg orally once daily until disease progression or unacceptable toxicity	**ARROW** **Treatment Naïve** • n= 107 •ORR: 78% (95% CI: 68, 85) • DOR: 13.4 months (95% CI: 9.4, 23.1) **Previously Treated** • n= 130 • ORR: 63% (95% CI: 54, 71) • DOR: 38.8 months (95% CI: 14.8, not estimable)	• ≥ 25%: Musculoskeletal pain, constipation, hypertension, diarrhea, fatigue, edema, pyrexia and cough	• Take on an empty stomach (no food intake for at least two hours before and at least one hour after taking pralsetinib) • Optimize BP prior to initiating treatment; do not initiate pralsetinib in patients with uncontrolled hypertension • Withhold pralsetinib for at least five days prior to elective surgery; do not administer for at least two weeks following major surgery and until adequate wound healing has occurred
AKEEGA™ (niraparib and abiraterone)[1,24-25]	8/11/2023	• Deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer • 200mg niraparib/ 1,000mg abiraterone acetate orally once daily in combination with 10mg prednisone daily until disease progression or unacceptable toxicity	**MAGNITUDE** • N=423 • rPFS: 16.6 months vs 10.9 months (HR 0.53; 95% CI 0.36, 0.79; p=0.0014) • OS: median of 30.4 vs 28.6 months (HR 0.79; 95% CI: 0.55, 1.12) • No benefit was observed in mCRPC patients without an HRR gene mutation	• ≥20%: Decreased hemoglobin, decreased lymphocytes, decreased white blood cells, musculoskeletal pain, fatigue, decreased platelets, increased alkaline phosphatase, constipation, hypertension, nausea, decreased neutrophils, increased creatinine, increased potassium, decreased potassium and increased AST	• Anticipated availability is currently unknown • Administer on an empty stomach, at least one hour before and two hours after food • Control hypertension and correct hypokalemia prior to and during niraparib/abiraterone acetate treatment • Ensure patients are recovered from hematologic toxicity from previous treatments before initiation

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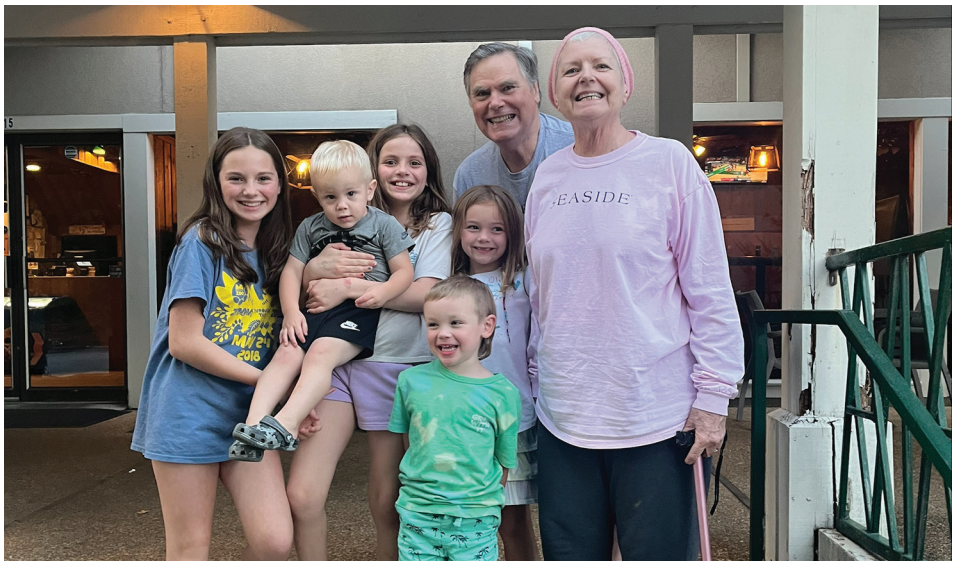
KNOWING TOO MUCH, YET UNDERSTANDING TOO LITTLE

TRANSITIONING FROM HEALTHCARE PROVIDER TO CAREGIVER OFFERS UNIQUE INSIGHT INTO THE PATIENT'S OVERWHELMING CANCER JOURNEY

By Kristin Hutchinson, PharmD, BCOP, CSP



Helen and Brian Hutchinson, the author's parents, smile during a recent visit with their grandchildren.

My mother's cancer diagnosis illustrated the complexity of the healthcare system to me in a way that years working in healthcare never could.

I was aware that patient confusion, health literacy, complex services, challenges with technology and communication and denial can be obstacles for patients. The potential consequences of these barriers became clear when I balanced being an experienced oncology pharmacist with viewing the system as the daughter of a cancer patient.

Kristin Hutchinson

I knew it was cancer before she made the appointment.

When my mother complained of early satiety and irregularity last fall, it seemed as though my own gut seized up. Whether in solidarity, fear or empathy was irrelevant — I advised her to get a second opinion, since the GI specialist she had seen recommended continuing the regimen that had offered her no relief.

I have spent the last eight years working full time in oncology as a clinical pharmacist. I realize when the only tool you have is a hammer, everything looks like a nail. But in my mother's case, it wasn't the environment contributing to my alarm. It wasn't logic or nerves or histrionics. I hoped I was wrong, but somehow, I knew that I wasn't.

At some point over these last few years, after the self-diagnostic fear dwindled and my language inadvertently became littered with acronyms, I realized that I love working in this field. The collaborative care that seemed unattainable from behind a drugstore counter exists, and I feel fortunate to be a part of it.

The complexity of cancer is reflected in the variety of services developed in pursuit of better outcomes. Patients here are treated as individuals, rather than cases. Goals of therapy may include words like, "curative" or "palliative," as well as phrases like "drug holiday for beach trip," or "attend daughter's wedding."

Range of goals aside, technological improvements have yielded new treatments and broadened our understanding of how cancer progresses. Consequently, multidisciplinary teams have expanded to include specialists in research, surgery, genetics, radiation, chemotherapy, nutrition, emotional well-being, financial counseling and social support, among others.

A LIMITED PERSPECTIVE

As a team member, I had only seen the health system machinery work from the inside. I have had patients express how confusing navigating cancer treatment is, and I recall sympathizing. Most people, after all, do not routinely mix chemotherapy in a biological safety cabinet, or attend tumor board meetings.

I naively imagined the machine propelling them through their treatment journey using the EMR as a guide. Staff provided patients with a printed schedule for clarity. Patient portal access streamlined communication. Patients received a binder with the relevant information. They were encouraged to call with questions.

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When I asked my mother what the oncologist had said, her response was a bewildered, "It's cancer …" She had forgotten to ask about having me on speakerphone.

I was able to ascertain from the paperwork provided – education on paclitaxel and carboplatin – that they suspected ovarian, fallopian tube or primary peritoneal cancer strongly enough to have a treatment plan drafted and an appointment in the infusion room scheduled days later.

My dad's excited, "He says it's treatable!" made my heart sink. Between context clues, I gathered that my mother's overwhelm prevented her from processing the details. My dad was patently optimistic.

Knowing that emotions can muddy communication in an already challenging situation, I prepared mentally before calling to ask the doctor to please repeat everything he told my parents.

His plan was guideline-based. The prognosis was concerning, but uncertain. It was different enough from my parents' version that I insisted on being present for future visits. I updated my mom's appointments on my calendar.

A COMPLICATION ARISES

Three weeks after diagnosis and Day 8 of her first chemotherapy cycle, my dad called to tell me Mom was unable to get out of bed. He asked if we should call the doctor.

As I raced to their house, I called her oncologist to report that I was taking her to the hospital. Once there, it was evident that chemo toxicity was not the most urgent issue: she had a GI blockage. The CT scan suggested metastases.

The consulting general surgeon told us Mom was not a surgical candidate given her blood counts. The surgical oncologist was hopeful that the blockage could be removed during debulking surgery, though she would not be eligible for months. The only option was to remain admitted while the single chemotherapy treatment she had received cleared the blockage.

My brother, a marine engineer, was off the coast of Hawaii. He and I decided to tell our parents that he was trying to maintain his "favorite child" status in taking a red-eye to Atlanta, rather than admit that I had asked him to cut his hitch short.

Fortunately, the inpatient support plan worked. Mom was discharged almost two weeks later, recovered enough to undergo Cycle 2 on schedule.

During her hospitalization, she started daily total parenteral nutrition (TPN). Consequently, at discharge, she was referred to a home health service, a home infusion pharmacy and a nutritionist who would review labs and manage the TPN formula.

PREPARING TO GO HOME

Mom had a consult with a palliative care physician, who coordinated a referral for outpatient services.

And that was only the beginning:

- She would need physical therapy.
- Before advancing her diet, she needed guidance from the nutritionist at the cancer center.
- Did she want to wear a wig?
- We had a transport chair, but she needed a walker.
- We missed the genetic counselor's appointment during her admission. It needed to be rescheduled.
- She would need a hospital bed on the main level of her home for a few weeks.
- She eventually needed clearance from cardiology before surgery, but that would be months away.

The paperwork provided at discharge alternated between medical jargon and legalese. I understood about half of it. We added it to her binder after I saved contact information for palliative care, home health, the infusion pharmacy, nutrition and the surgical oncologist to my phone.

My aunt was tasked with securing a hospital bed. My brother and my dad made space in the living room and cleaned the refrigerator for the weekly TPN delivery. My husband and brother moved furniture to accommodate the bed. A social worker advised me on the discharge process; and with her guidance, I updated home health with her discharge date and coordinated the continuous IV pump teaching. The infusion pharmacy was next, to arrange delivery.

Mom arrived home midday, followed by TPN bags and our home health nurse. We arranged supplies on a cart: alcohol swabs, syringes, tubing, heparin and saline flushes, batteries for the pump, and nursing supplies. My brother extended his visit an extra two weeks, and we adapted to having Mom home.

THE STARS ALIGN

Had I had known my family would face this exact challenge a decade ago, I couldn't have orchestrated a better situation to support my parents.

Working in oncology was never the plan. Living in my hometown was never the plan. I traded retail pharmacy for oncology infusion in 2014, crediting the dramatic shift to a new city, a bossy sister-in-law, and sleep deprivation that only a new mother can appreciate. It was practically accidental, and easily the best career decision I have ever made.

When an intriguing position presented years later, my husband encouraged me to apply, despite it necessitating a move away from his family and toward mine.

Between my proximity and sterile compounding experience, there was no question I would be preparing Mom's TPN. For two to three months, Mom bookended my daily routine.

Every evening, I drove the three miles to their house to prep and administer, check medications, and monitor changes before driving home.

In the morning, I returned to disconnect and flush, and kiss her beanie-clad head before starting my workday.

Home health drew labs on Mondays, and the nutritionist evaluated them Tuesdays. I called the infusion pharmacy on Wednesdays to request supplies for

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the Friday deliveries. Thursdays were reserved for appointments. Physical therapy came on Fridays if she felt well. Palliative care calls slowed as bad days became predictable.

Around Cycle 4, it became clear that she was not weaning off TPN quickly enough to undergo debulking surgery as originally planned. Mom remained reluctant to eat. The TPN had stabilized her, but the goal was to discontinue.

I requested a nutrition consult but the dietician frustrated my mother. "I don't want calorie and protein recommendations. I want to know what foods are safe. I want a list," Mom said. After eating daily, the TPN remained unchanged, as though the directive to discontinue was lost.

It took an office visit, trial and error, and guidance from a third nutritionist/friend to establish a discontinuation plan. It would require two more cycles of chemotherapy.

CLEARED FOR SURGERY

With our plan for TPN discontinuation enacted, we focused on surgery. Pre-op office visits with Cardiology, Medical and Surgical Oncology were scheduled. We informed home health, physical therapy, and palliative care. I moved her prescriptions to a local independent pharmacy that offers delivery.

After recovering from surgery, she would have frequent monitoring, since additional surgery and/or chemo was often necessary a couple of years later.

Mom clarified: "So. Two years?"

Dr. Davis smiled kindly, suggesting, "Let's get through this one before we talk about the next."

Debulking surgery went as planned. The blockage was removed and intestine successfully reattached. Pathology determined it was ovarian. A suspicious lesion near the diaphragm remained, too risky to remove. Our genetic counselor detailed unremarkable next-generation sequencing results. The oncologist showed us somatic mutation studies listing only a TP53 mutation.

My experience reminds me to be deliberate with messaging, engaged in patient assessments, observant in my interactions, gentle with my wording, and grateful for the opportunity to help my patients.

The good news was, she had no known heritable mutations; the bad news was, she had no known targetable mutations. Options were to follow NCCN guidelines with maintenance therapy, or monitor. Mom opted for maintenance, which the health-system specialty pharmacy will fulfill.

A PAINFUL CONVERSATION

Last month, about seven months into my mom's journey and after she recovered from surgery, I received a screenshot from my dad while I was working in my home office. A Wikipedia page defining "palliative" flashed, followed by a text. "Goals of therapy: palliative. I don't like what I'm reading. This sounds serious."

I messaged my team that I was taking lunch and placed the call I had been dreading. Despite the surgeon's expectation of relapse, the oncologist's description of maintenance therapy's role, and Mom's enrollment in palliative care services, my dad had been unable to process what we all had understood for months.

I recommended he have an honest conversation with Mom. I said we are running a marathon, not a sprint. I told him she has choice and autonomy in any future treatment. I reminded him to appreciate these good days. I hung up the phone, hating that I was the person relaying this message, and uncertain whether I hoped he had heard me, or hoped he hadn't.

To date, communication with providers is good. My parents use the portal and ask questions. Barriers are minimal. My family's new normal is cohesive, routine, and busy — just like before — with more high fives for platelet counts; more focus on each other; more awareness of time.

LESSONS LEARNED

Caregiving for me was a natural progression, and speaking the language and knowing the system benefited me in that role. When my mom said that she would not have survived without my involvement, I realized the impact of that benefit in advocating for her.

Admittedly, not everyone with cancer has as dramatic a story as my mother. The complexity of her case contributed to potential gaps, to be sure; but it also wasn't our first – or even our second – experience working through a cancer diagnosis.

My father survived colon cancer over 25 years ago, and my mother beat breast cancer just two years before her ovarian cancer diagnosis.

My parents are familiar with the healthcare system. Their church and community provide emotional, spiritual, and logistical support, often alongside a gourmet meal. They have a daughter who works in oncology and lives down the street. They have very distinct advantages and still a world of uncertainty.

Many patients navigate their cancer journey alone, lacking the resources to identify and overcome barriers to communication.

My experience reminds me to be deliberate with messaging, engaged in patient assessments, observant in my interactions, gentle with my wording, and grateful for the opportunity to help my patients.

▲ **Kristin Hutchinson**, PharmD, BCOP, CSP, is an oncology clinical pharmacist working in the specialty pharmacy setting in Atlanta, Georgia.

THE POLITICS OF ONCOLOGY: WHY WE MUST GET MORE INVOLVED IN HEALTHCARE LEGISLATION

Governmental policy and the politics that drive it play a major role in the practice of medicine — particularly oncology — forcing us, as healthcare professionals, into new, unexpected roles as advocates and gatekeepers.

In a perfect world, our focus would be on the oaths we took when we first became doctors, nurses and pharmacists: to practice medicine with integrity, humility and compassion, and always put the needs of our patients first. No one ever said anything about unraveling the Gordian Knot of healthcare red tape created by government bureaucracy.


Michael Reff

Policy now pervades almost all aspects of oncology, from how our clinical team members can treat our patients, how prescriptions can be filled, how much the patient must pay for their medicine and how much the practice receives for their treatment.

Take, for example, the Ethics in Patient Referrals Act, more commonly known as the Stark Law, which prohibits physicians and healthcare professionals from "self-referring" patients to facilities in which they have a vested interest.

The act, originally designed to prevent abuse of the Medicare system, has been revised numerous times in its 31-year history.

In an FAQ released on May 19, The Centers for Medicare & Medicaid Services stated that physician practices (i.e., medically integrated pharmacies or MIPs) would no longer be able to rely on the ancillary service exception to fill Part D prescriptions being mailed to the beneficiary's home.

The FAQ further stipulated that Medicare beneficiaries could get medications through the Part D plan's network of mail-order pharmacies, many of which are owned by Pharmacy Benefit Managers (PBMs).

And while most MIPs only mail a small percentage of Part D prescriptions to their patients — several NCODA members estimated the numbers at around 5% — this revision can represent a major hardship on the very population it is designed to protect.

In the past, MIPs could ship out prescriptions to patients who, due to mobility or proximity issues, were unable to pick up their oral oncolytics at the practice or pharmacy. Now, their only option is to either travel to the practice pharmacy, or have the prescription mailed to them by a pharmacy their healthcare team has no control over.

The problems with PBM-owned mail-order pharmacies have been well-documented by NCODA and others. Prescription waste and abandonment rates surge under this system, as do logistical errors and patient frustration, and speed to therapy decreases. And, at the end of the day, it's the patient's health that suffers.

On the other hand, some laws are in desperate need of clarification. Such is the case with the 340B program. Created by Congress as a resource for health facilities serving patients in need, the 340B program requires pharmaceutical manufacturers participating in the Medicaid program to supply discounted drugs to "safety net" providers, including community health centers and other institutions serving low-income populations.

While well-intentioned, the program has suffered from a lack of transparency, oversight and accountability. Under a "child site" loophole, some hospitals have used savings from the discounted drugs to expand into wealthier, more profitable communities.

At other times, however, oncology issues can only be solved by requesting the government to step in; such is the case with alternative funding programs (AFPs). With AFPs, health plan sponsors exclude some or all specialty medication from coverage, labeling them as nonessential health benefits, though the Affordable Care Act stipulated their inclusion.

Without coverage, patients' out-of-pocket spending on these medications no longer counts toward their annual deductible or out-of-pocket maximum. Plan sponsors then direct patients to pharmaceutical manufacturer programs or charitable foundations for assistance. It's time for Congress to ban AFPs.

Congressional action also is needed on other issues. Washington must come up with policies and strategies that will ensure the availability of essential medications, especially anticancer drugs.

And more work is needed to stem financial toxicity for patients.

Healthcare professionals must get more involved in the political arena. We must stand together and educate and encourage our representatives about needed legislative reform.

I encourage our membership and the broader oncology community to leverage NCODA's resource suite, including our Oncology Legislation Tracker, informative town hall webinars, and educational handouts on relevant oncology/policy issues to stay engaged on relevant topics that impact the patients we serve.

Michael J. Reff, RPh, MBA
Executive Director & Founder | NCODA

BE THE MATCH®

NCODA MEMBER STEPS UP

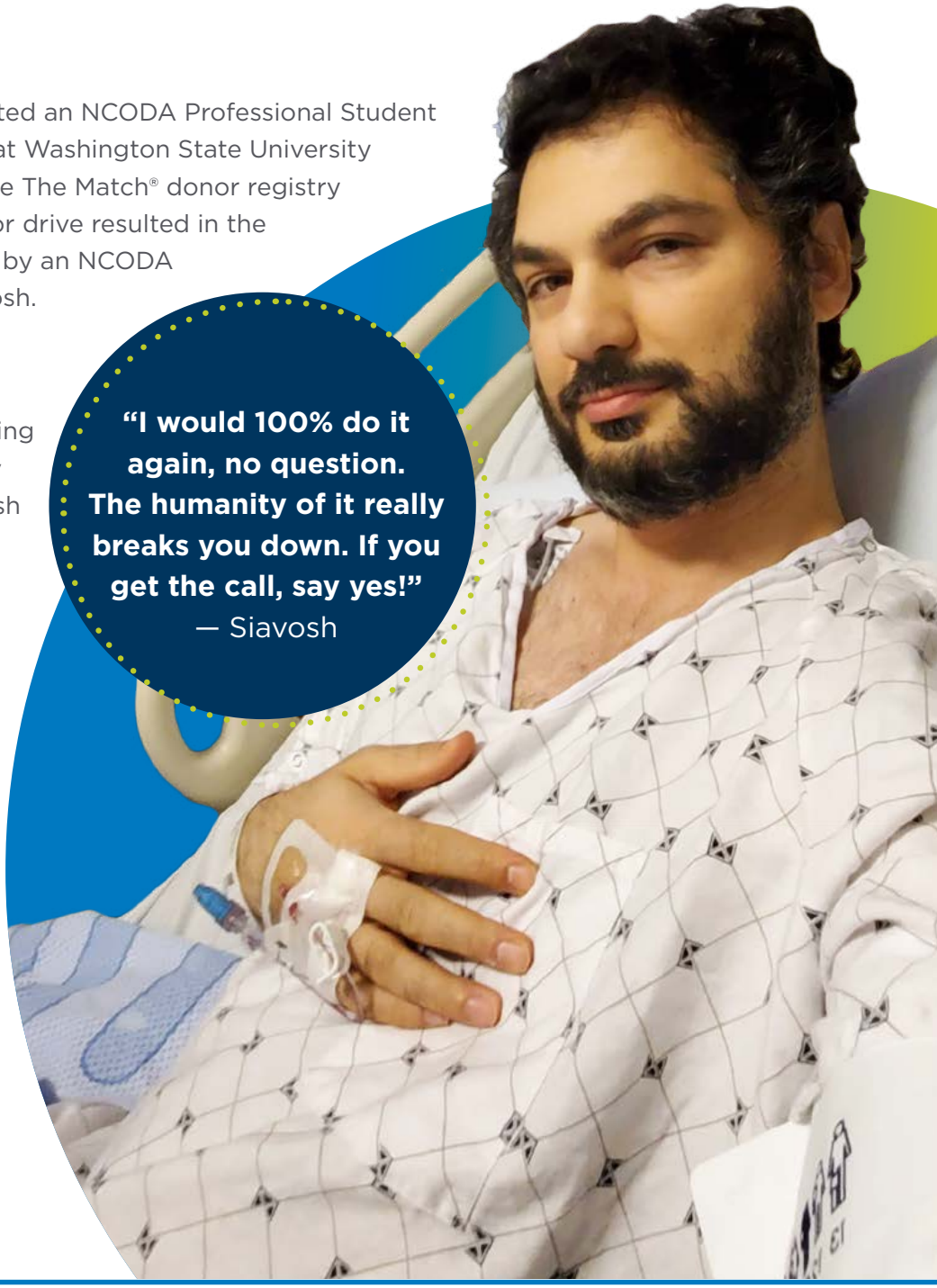
TO GIVE SOMEONE A SECOND CHANCE AT LIFE

SIAVOSH'S STORY:

In 2018, Siavosh and his wife Alanda started an NCODA Professional Student Organization (PSO) chapter on campus at Washington State University (WSU). All PSO chapters participate in Be The Match® donor registry recruitment drives. WSU's first PSO donor drive resulted in the collection of the most swabs nationwide by an NCODA chapter! This included a swab from Siavosh.

Two years later, Siavosh got a call from Be The Match that he was a match for a 15-year-old female patient. Despite juggling pharmacy rotations, his wife's pregnancy and research for his PhD program, Siavosh said it was a no-brainer to say 'yes' to donating blood stem cells. He knew they were having a daughter, so he couldn't help but think about his recipient's parents. Siavosh's own mom was also a cancer survivor and her life had been saved by a liver transplant, so he knew what it was like to wait for a stranger to save your loved one's life.

A few months later, Siavosh donated blood stem cells from his bone marrow in Georgetown, D.C., giving his recipient a second chance at life.



"I would 100% do it again, no question. The humanity of it really breaks you down. If you get the call, say yes!"
— Siavosh

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Marlo Blazer, PharmD, BCOP
Director of Pharmacy, Columbus Oncology & Hematology Associates

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