

# HOPA NEWS

Pharmacists Optimizing Cancer Care®

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## Pharmacists' Impact on Tobacco Cessation Initiatives at WVU Medicine

==== page 3 ====

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Pharmacists Optimizing Cancer Care®

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## Pharmacists' Impact on Tobacco Cessation Initiatives at WVU Medicine



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Although the smoking rate among the general U.S. population decreased from 20.9% in 2005 to 14% in 2017, the smoking rate among people with cancer remains elevated.<sup>1,2</sup> This disparity was recently highlighted by the National Cancer Institute (NCI) Cancer Moonshot in an effort to increase cessation resources for the cancer population.

The NCI initiative, known as the Cancer Center Cessation Initiative (C3I), has offered funding to a total of 42 cancer centers across the nation for the creation or expansion of smoking-cessation treatment programs. To support the overarching mission of ensuring that every cancer patient who smokes is provided with adequate cessation support, each C3I participating site is required to develop a plan to continue cessation efforts after the conclusion of the 2-year funding period.<sup>2</sup> Sustainability is an important aspect of the C3I because the initiative also draws attention to the fact that historically, less than half of all patients diagnosed with cancer were engaged in a conversation regarding cessation, treated with cessation medications, or referred elsewhere for cessation support.<sup>2</sup>

Yet another disparity in smoking rates is seen in certain regions of the United States (for example, in Appalachia and the state of West Virginia). According to the Centers for Disease Control and

Prevention, 26% of West Virginians smoked in 2017, the highest percentage in any state and 12% above the national average.<sup>1</sup> Furthermore, in 2016 West Virginia had the second highest rate of smokeless tobacco use: 8.5%.<sup>3</sup> Recognition of these statistics, which may be associated with a deficiency in care, has allowed WVU Medicine to independently capitalize on the intentions of the C3I through internal initiatives to increase tobacco cessation among all patients, including patients with cancer.

Our efforts to improve access to tobacco cessation resources began when the West Virginia Hospital Association Honors Program established “increased access to tobacco cessation” as a requirement for designation as a Silver Honors facility in 2018. This requirement fueled the administrative support needed to enact meaningful change at our hospital and across the entire WVU Medicine system. To tackle this issue, we wanted to leverage our electronic medical record (EMR) to refer patients to our state’s Quit Line, provide tobacco-cessation medications, and provide eventual outpatient referral to tobacco-cessation clinics. Our EMR vendor pointed us to similar programs in other academic medical centers, which we emulated in our program.

Identification of a physician champion in the early stages was critical in order to vet the program and then engage physicians as the project progressed. We found ours in Samantha Minc, a vascular surgeon in our Heart and Vascular Institute (HVI). While the information technology (IT) team was busy in spring 2018 with building the program in the EMR, Dr. Minc helped us decide which services to include in the program pilot and develop education for providers. Education was provided by service line and included information on the program workflow, tobacco-cessation options, and outpatient referral opportunities. The IT team’s work building the program was completed in early summer 2018. The program was rolled out initially to services located in the HVI, then to our academic medicine services, and finally system-wide during the summer. Our program relies on a Best Practice Alert

(BPA), which alerts the provider that a patient was designated a smoker during the nursing staff's initial assessment for inpatient admissions. This alert fires only after the patient has been in a nonintensive-care-unit bed for 24 hours. The BPA suggests that the provider discuss tobacco cessation and provides the mechanism for sending that referral, ordering tobacco cessation medications, and, as of early 2019, referring the patient to outpatient tobacco-cessation services.

The program has been widely accepted and used by our providers since its launch. Our BPA has fired on 45.54% of all admissions since its inception, and we are currently seeing a 13.5% referral rate to the Quit Line throughout the system. These referrals have been hindered because of administrative requirements on the Quit Line side, but we have initiated a fix that we hope will be in place by the end of the first quarter of 2019. In order to expand the program's reach beyond the inpatient stay, we have tied outpatient referral orders to both a tobacco-cessation clinic located in our Mary Babb Randolph Cancer Center (MBRCC) and a pharmacist-led group class housed in our Family Medicine Clinic.

The two smoking-cessation programs (offered at MBRCC and the Family Medicine Clinic) are similarly structured as a free 5- to 6-week tobacco-cessation support group offered to patients and caregivers alike. Both series focus on overcoming barriers to cessation, identifying and preparing for a patient-designated quit date, and providing support for sustaining cessation after the quit date has passed. Medications proven to assist with successful cessation are individualized for each participant. Classes are led by various providers, including pharmacists, all of whom have earned the Certified Tobacco Treatment Specialist (CTTS) designation.

The CTTS certification is issued by the Council for Tobacco Treatment Training Programs (CTTTP) to healthcare providers who have completed and passed an accredited training program designed to provide education about tobacco addiction and nicotine withdrawal symptoms, causes and consequences of tobacco use, and guidance on individualizing effective treatments for all forms of tobacco and nicotine use. Certification for many of these providers was obtained onsite through a program developed by the WVU School of Dentistry, one of only 20 programs in the nation to gain accreditation through CTTTP and the first dental school to join the list in 2017.<sup>4</sup>

In addition to these group therapy options, other ongoing initiatives at MBRCC are aimed at improving tobacco-cessation rates among our oncology patients. Screening for tobacco use has been

incorporated into the WVU Cancer Institute's Cellular Therapy Survivorship Clinic, a pharmacist-driven clinic at MBRCC for patients who have undergone hematopoietic cell transplantation. Patients in this clinic are continually assessed for initiation or continuation of tobacco use, and patients using any form of tobacco are encouraged to consider cessation. One of the board-certified oncology pharmacists who see patients in the survivorship clinic has also obtained CTTS training. When a patient in the clinic has been identified as being ready to tackle cessation, a separate appointment for tobacco cessation is arranged for more focused, individualized counseling and support.

Outside of the survivorship clinic, other providers in MBRCC are able to give a referral for pharmacist-led tobacco cessation services for interested patients. Patients seen for tobacco cessation are scheduled for a 45- to 60-minute initial session to identify barriers to cessation, assess prior quit attempts, and discuss pharmacotherapy options through motivational interviewing techniques. Through a collaborative practice agreement, pharmacists are able to prescribe pharmacotherapy based on the individual patient's preferences and comorbidities and then follow up with the patient as appropriate, according to their preferences and needs.

Regardless of CTTS designation, oncology pharmacists are often in an ideal position to address tobacco use. It is imperative that we as pharmacists discuss with our patients any interactions between various chemotherapies and smoking, such as the potential for decreased concentrations of bendamustine, erlotinib, irinotecan, and pomalidomide in patients who smoke.<sup>5-7</sup> In addition, screening for tobacco use is easily incorporated into initial counseling sessions for patients who are undergoing cancer treatment. Cessation counseling may be offered if the patient screens positive for tobacco use, or a referral to a local cessation clinic or support group can be given. Follow-up sessions with patients undergoing treatment can also be used to continue encouraging or monitoring cessation.

As evidenced through efforts at WVU Medicine, pharmacists play a vital role in the battle against tobacco use by implementing institutional quality improvement initiatives, seeking additional training through CTTTP, or simply starting the conversation with a cancer patient. The NCI's Cancer Moonshot C3I accented the need for increased attention, resources, and time dedicated to supporting cancer patients on their journey to cessation. This program can be a driver of change to decrease smoking rates and improve oncology outcomes in cancer centers across the nation. ●●

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## Finding Courage Through Authenticity



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When I was asked to write this article for *HOPA News*, I immediately accepted the opportunity. Possible topics flooded my mind. Would I write about well-being, work-life integration, strength-based leadership, the importance of diversity in the workplace, or humility? And then a trace of self-doubt nudged its way into my mind, creating chaos amid the excitement. Am I qualified to write this article? How would my colleagues perceive my casual storytelling writing style? And, dare I say it, am I good enough?

Our mind plays ping-pong, and internal conflict resolution is challenging. Doubts about self-worth, fear of failure, and questions about personal strength infiltrate the mind. Every. Single. Day. Our power lies in taking off our masks and showing the world our true selves. It lies in accepting who we are and recognizing that we have great talents to share. This, my friends, is authenticity. It is saying “Yes, I am good enough to ... (in my case, write this article).” I would like to share with you my journey to authenticity.

As for many, my trajectory in my pharmacy career and in life was linear. High school, undergrad degree, PharmD, residency, job, board certification, marriage, and then children. (Nonlinear kinetics seems to be prohibited when one is discussing life planning!) However, in 2015, I was experiencing a deep internal restlessness, a feeling that there was more for me in life. I tried to ignore it but found myself searching late at night for

additional certifications, training programs, and even different career options. After a year of discernment (because I stew about things), I decided to enroll in a graduate course in organizational leadership. I can’t explain why, but I thought it “would be fun!” Little did I know that the program would be transformational. I fell in love with learning and developing my leadership skills. I didn’t need more content knowledge but needed to figure out who I was. It quickly became apparent to me that I could not learn leadership skills without self-awareness and daily reflection. Graduate education allowed me to focus on myself, something I had neglected since the completion of my PharmD degree in 2003.

I graduated in December 2018, with a master of science degree in organizational leadership (MSOL). Over the past 3 years, I have experienced tremendous personal and professional growth. I am becoming the authentic leader that I desire to be. The MSOL coursework ignited in me gratitude and a love of journaling. It helped me embrace my strength as a relator and reinforced the importance of service, humility, and *agape* (the Greek word for self-sacrificing love) in the workplace. The classes gave me the confidence to accept who I am, with my imperfections and all. In many ways, the courses gave me permission to reflect and created time for reflection so I could lead authentically.

I used to think that transformational and visionary leadership was the ideal leadership style. I was wrong. Over a thousand studies have shown that there is no single preferred leadership style. The best leadership style is the one that fits with who you are. It fits with who you want to be. Every day our actions and our words influence one another. We bring our unique gifts to the workplace and share them with our

colleagues. We are great leaders who permeate the walls of our institutions and organizations.

Leading with authenticity requires self-awareness and the ability to learn from one’s own story. It involves accepting the past and adjusting for the present. Authentic leaders learn from their experiences, live their values, and practice chosen principles.<sup>1</sup> Our actions align with our words. I used to feel bad saying no to a work event because I wanted to attend a son’s soccer game. If I value family, then I must make time for my family. That may require my saying no so I can say yes to things that truly matter.

Authenticity involves an understanding of one’s purpose in life. This is not an easy task when we trudge along the linear path of life. When is the last time you stopped and asked yourself if you are living your purpose? What is your purpose? I know—it is hard to find time to reflect on such questions in the busyness of life. But making that time is crucial for me because authenticity is the foundational principle from which my leadership philosophy grows. Being authentic allows me to focus on areas of leadership that are important to me (i.e., strength-based leadership, well-being, and diversity).

How do you desire to lead? What principles and theories of leadership resonate with your authentic self?

Being a leader is hard. Over Christmas break, I watched the film *The Greatest Showman* with my boys. I can’t help thinking of authentic leadership when I hear these words from the song “This Is Me.”<sup>2</sup>

When the sharpest words wanna cut me down  
I’m gonna send a flood, gonna drown them out  
I am brave, I am bruised  
I am who I’m meant to be, this is me.

(continued on p. 7)

## Oncology Pharmacists' Role in Value- and Quality-Based Patient Care



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Over the past several years, oncology practice in the United States has moved away from a fee-for-service model to a fee-for-value model. Value-based contracts are much more prevalent now, and reimbursement is becoming more dependent on patient outcomes. This movement has changed the dynamic of oncology care across all types of practices. Often, appropriate medication management is necessary to ensure the success of a value-based arrangement. Increased pressure is being placed on all stakeholders—from practice administrators to payers—to improve medication efficiencies, especially in such areas as antineoplastics and biologics. Organizations must maintain the financial strength of their practices while concomitantly demonstrating improved patient outcomes.

Oncology pharmacists occupy an influential position in these new models because they participate both in creating medication guidelines and policies in their organizations and in evaluating high-volume and high-cost medications on the formulary. The role of pharmacists is evolving as organizations use them to improve medication adherence and reduce readmissions, a key metric in many value-based payment arrangements.

More research evaluating pharmacists' roles in improving these specific patient outcomes has been published in the area of primary care; however, oncology pharmacists are also publishing in this area. In 2018, Vulaj and colleagues published research on an assessment by three pharmacists of 200 Quality Oncology Practice Initiative (QOPI) measures on which pharmacists could potentially have an impact; of 177 measures, 67 (38%) were identified as ones with outcomes that pharmacists could influence. These measures were related mainly to optimization of medication therapy through the development and implementation of guidelines. Patient counseling and symptom management were also identified as metrics that could be completed by pharmacists.<sup>1</sup> Two HOPA members, Shannon Hough, PharmD BCOP, and Emily Mackler, PharmD BCOP, were part of this study and authored the publication.

In response to HOPA members' interest in the value and quality of care for cancer patients and in the rapidly changing landscape of oncology reimbursement and quality measurement, HOPA formed the Quality Oversight Task Force following its 2018 annual conference. The task force was charged with incorporating health-care quality and value into HOPA's strategic initiatives, specifically by attending to quality improvement; making recommendations in such areas as standards, research, and external relations; and making recommendations to HOPA's board of directors.

One of the first tasks of the group was to complete a baseline assessment of quality-focused work being done both within HOPA and in cooperation with external organizations. Committee leaders and HOPA liaisons for external relations completed the assessment. The group found that a substantial amount of work

on quality and value is being completed across 28 committees representing the four pillars of the organization. However, the group also noted that HOPA needs to do better as an organization in coordinating efforts in the areas of value and quality of care. The development of partnerships and collaborations with other oncology and pharmacy organizations in efforts related to the value and quality of care will be crucial.

Those participating in the assessment were asked several questions. In response to the question "How would you rate HOPA's engagement with or focus on the quality and value of cancer care?" only 50% of committee leaders rated it as *excellent* or *above average*. When asked "How would you rate your own knowledge and skills on the quality and value of cancer care?" more respondents rated their own knowledge as *excellent* or *above average*, but 43% of the committee leaders stated that their knowledge was only *average*. To the final question, "How would you rate our overall membership's knowledge and skills in this area?" respondents answered *excellent* (4%), *above average* (29%), *average* (61%), and *below average* (7%). The responses to this survey constitute a further call to action for HOPA and the Quality Oversight Task Force to work on new ways to increase members' knowledge, strengthen HOPA's research and advocacy efforts, and support members in their professional practices in this area.

Following the baseline assessment, the task force prioritized several action items, giving consideration to their scope, feasibility, reach to the membership, resources needed, and time to execute. One action item is to provide HOPA members with appropriate resources and tools, given the wide continuum of roles and responsibilities carried out by oncology pharmacists in their practices. HOPA members need to be able to incorporate quality measures in their documentation of everyday interventions in their standard workflow. Other action items are to help members routinely benchmark their work against metrics and to provide for them focused live education and training on evaluating quality metrics and conducting quality-based research initiatives.

The task force is currently evaluating a number of training programs provided by other organizations. One is the American Society of Clinical Oncology's Quality Training Program (QTP). The program is designed to train oncology healthcare providers in a multidisciplinary team-based setting to investigate and implement data-driven quality-improvement processes, as well as manage clinical and nonclinical processes and outcomes. The program combines coaching, peer-to-peer mentoring, and shared learning approaches with experiential learning techniques effective for solving problems related to quality of care. Several HOPA members have completed this program with their organizations, including George Carro, MS BCOP, director of oncology pharmacy services at NorthShore University HealthSystem near Chicago, IL. One of NorthShore's projects involves reducing financial toxicity for patients in the ambulatory oncology setting, with a main goal of providing education for patients and engaging in informed

discussion with them prior to making treatment decisions. The group wanted to evaluate patient-reported outcomes and the effects of high-cost therapies, such as immune checkpoint inhibitors, on the institution. Several other oncology pharmacists have participated in quality training programs in their organizations, and their experiences will be highlighted over the next year. The ASCO QTP library shares information on past projects, which can be a resource for idea generation.

HOPA's Quality Oversight Task Force continues to plan the development of specific resources and education for members. In addition, opportunities both for members to be engaged and for HOPA to build depth in this area are being assessed.

Oncology pharmacists are in a unique position to contribute significantly to quality and value metrics in the care of patients with cancer. The pharmacist's role as part of multidisciplinary teams, including providing oversight for coordination of care for individual patients in conjunction with a systemic view of medication management, is significant. Pharmacists understand the need for standardizing medication practices in order to improve efficiencies and contain costs. Our roles will continue to evolve in this area, and we must be ready to show the value of the care we provide to our patients. ●●

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## Finding Courage Through Authenticity *(continued from p. 5)*

Authenticity takes courage. It means being vulnerable, often to the unsolicited critiques of others. We've all been hurt, and it is hard to remain brave when we are faced with obstacles. But authenticity is easier when we become the same person in and out of the workplace. Happiness emerges as we take off our masks and show the world our true self. We learn to appreciate the gifts we and others bring to our workplace and organization. We know who we are and who we want to be. Authenticity is right in front of

us if we take the time to define the values that are important. My charge to you is to identify and define the values that are important to you. Then live those values.

With sincere gratitude, I thank you for reading my story. I hope that the days ahead bring you kindness, compassion, and endless opportunities. May you live a life you love and find self-acceptance and contentment. Through authenticity, may you be the person you were meant to be. ●●

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## Updates on Drug Pricing



**Sarah Nicholson, JD**  
HOPA's Health Policy Manager

For a majority of President Trump's term, he and his administration have championed lower drug prices. However, no real effort has been made to define *lower drug prices*. Is it lower list prices or lower net prices? Is it a lower out-of-pocket cost for the patient? Or something else? Below is a summary of some of the major developments in efforts to lower drug prices through various means.

### "American Patients First" Blueprint

In May 2018, the Trump Administration released "American Patients First," a blueprint that sought to identify challenges in reforming drug prices and to present opportunities for reform. Four opportunities for reform were identified: improved competition, better negotiation on drug pricing, increased incentives for lower prices, and lowering of out-of-pocket costs. Accompanying the blueprint was a formal request for information (RFI) from stakeholders and interested parties. In July 2018, HOPA submitted comments in response to the RFI. The comments covered educating patients and providers on the safety and efficacy of biosimilars and improving patients' access to biosimilars. HOPA also expressed concern about the proposed move of Medicare Part B drugs to Medicare Part D, arguing that such a move could increase patients' out-of-pocket costs, particularly for oral chemotherapy drugs. In addition, HOPA reiterated its opposition to pharmacy gag clauses (language in a pharmacy's contract with a pharmacy benefit management company that prevents pharmacists from telling consumers when cheaper prescription drug alternatives are available), which hinder patients' access to needed medications. HOPA also joined its coalition partners in signing a letter written by the Cancer Leadership Council expressing concern about this issue.

### Medicare Advantage Step Therapy

In August 2018, the Centers for Medicare and Medicaid Services announced that Medicare Advantage plans would have the option of applying step therapy for physician-administered and other Part B drugs starting in January 2019. (*Step therapy*—also called "fail

first" therapy—refers to a payer's requirement that a patient try less costly drugs as the first step in treating a disease or condition. Only after a patient tries and "fails" the treatment will the insurance company authorize payment for a more costly drug.) This change is meant to balance drug costs with the costs of providing greater access to drugs and services. HOPA joined the Cancer Leadership Council in expressing serious concerns about this plan. As cancer treatment increasingly becomes patient centered, step therapy may impede the delivery of cancer care to patients.

### Modernizing Part D and Medicare Advantage

In November 2018, the U.S. Department of Health and Human Services released a proposed rule offering changes to Medicare Advantage plans and Part D prescription drug coverage. This proposed rule is intended to "support health and drug plans' negotiation for lower drug prices and reduce out-of-pocket costs for Part C and D enrollees."<sup>1</sup> HOPA signed several letters expressing concern that changing the protected classes of drugs would harm cancer patients; the specific concern is that an increase in requirements for prior authorization and step therapy may delay proper treatment for patients.

The House and the Senate began hearings on drug pricing during the last week of January 2019. The House Oversight Committee, chaired by Rep. Elijah Cummings (D-MD), is "investigating the actions of drug companies in raising prescription drug prices in the United States, as well as the effects of these actions on federal and state budgets and on American families."<sup>2</sup> The Senate Finance Committee, chaired by Sen. Chuck Grassley (R-IA), is holding hearings to identify and address the many reasons for high drug prices. Senator Grassley believes that pharmaceutical companies' lack of transparency about drug prices is where the investigation should begin. Grassley and Sen. Ron Wyden (D-OR), ranking member of the Senate Finance Committee, introduced the Right Rebate Act of 2018 to close a "loophole" in Medicaid that allows pharmaceutical companies to misclassify drugs for purposes of the Medicaid drug rebate program. This misclassification has resulted in Medicaid's payment of higher costs for certain drugs. HOPA continues to monitor these hearings. ●●

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## Gamifant (emapalumab-lzsg): The One and Only



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### Background

Hemophagocytic lymphohistiocytosis (HLH) is a disease characterized by abnormal activation of the immune system and impaired cytotoxic function, resulting in hemophagocytosis, hypercytokinemia, and hyperinflammation. Cytokines released by activated macrophages, including interferon gamma (IFN gamma), interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF) alpha, infiltrate body tissues, leading to progressive tissue damage and multi-organ failure.<sup>1</sup> HLH is classified as either primary HLH, which is a heterogeneous autosomal recessive disorder, or secondary HLH, caused by infection, rheumatic disease, or malignancy. Primary HLH occurs in 1:30,000–1:50,000 live births and commonly presents before the age of 1 year (70%–80% of cases).<sup>2</sup> Clinically, both primary and secondary HLH look very similar and may be equally severe. Symptoms manifest as prolonged fever, splenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia. Major complications include severe infection, hepatitis, multi-organ failure syndrome, and central nervous system disease.<sup>2</sup> If left untreated, HLH is fatal.<sup>1</sup>

### Developmental Process and Clinical Data

Preliminary data from animal models suggest that hyperactivity of CD8+ T cells and subsequent elevations in IFN gamma are responsible for the hypercytokinemia and activated lymphocytes that cause HLH complications.<sup>3,4</sup> Investigators discovered that mice with high circulating levels of IFN gamma had clinical and laboratory features similar to those of human HLH disease. When treated with anti-IFN gamma antibody, the abnormalities resolved, and life span was prolonged.<sup>4</sup> The robust role of IFN gamma in the pathogenesis of HLH disease, as well as promising results from animal studies, provided a rationale for developing a targeted therapy to neutralize IFN gamma action while minimizing systemic adverse effects of treatment. In November 2018, the U.S. Food and Drug Administration (FDA) approved emapalumab-lzsg, a fully human immunoglobulin G1 (IgG1) anti-IFN gamma monoclonal antibody, for the treatment of pediatric and adult patients with primary HLH who have refractory, recurrent, or progressive disease or intolerance to conventional HLH therapy.<sup>5</sup> Prior to the market introduction of emapalumab, no medications for this disease had been approved by the FDA. The standard of care for primary HLH is protocol HLH-94, an etoposide- and dexamethasone-based

treatment regimen, followed by continuation therapy and eventually hematopoietic stem cell transplantation (HSCT).<sup>2,6</sup> A combination of corticosteroids and T cell-directed agents, such as cyclosporine, alemtuzumab, or antithymoglobulin, may also be incorporated into treatment regimens.<sup>7</sup> Despite efforts to improve the HLH-94 protocol, overall probability of survival in patients with primary HLH remains low, with mortality rates approaching 40%–50%.<sup>6,8,9</sup> Further, myelosuppression and immunosuppression induced by T cell-directed therapies are major limitations to treatment.<sup>2</sup> Emapalumab is one of the first significant medical advancements for primary HLH induction therapy in more than 20 years.<sup>10</sup>

Emapalumab gained FDA approval following a pivotal phase 2/3 multicenter open-label single-arm clinical trial (NCT01818492) of 34 patients 18 years of age or younger (median age: 1 year; range 0.1–13 years). The patients had a diagnosis of primary HLH

**“Emapalumab is one of the most significant improvements in the treatment of primary HLH in more than 20 years and provides an opportunity to improve outcomes for patients with this devastating disease.”**

based on genetic confirmation, family history, or the presence of five or more of the eight HLH-2004 diagnostic criteria: fever; splenomegaly; cytopenias affecting 2 of 3 lineages in the peripheral blood; hypertriglyceridemia and/or hyperfibrinogenemia; hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy; low or absent NK-cell activity; ferritin levels of 500 mcg/L or higher; and soluble CD25 levels of 2,400 U/mL or higher.<sup>6,11</sup> Twenty-seven of the included patients (79%) had previously failed conventional HLH therapy, while seven were treatment naïve. It is important to note that the FDA approved emapalumab solely for patients who had failed standard therapy. Emapalumab was administered intrave-

nously twice weekly, or every 3 days, at a starting dose of 1 mg/kg. Subsequent doses were titrated to a maximum of 10 mg/kg on the basis of clinical and laboratory results. Of note, 44% of patients remained at a dose of 1 mg/kg. All patients received 5–10 mg/m<sup>2</sup>/day of dexamethasone concurrently. Treatment duration was 4–8 weeks but could be extended to allogeneic HSCT, if needed. The primary efficacy endpoint was overall response rate (ORR), defined as normalization or at least 50% improvement from baseline of fever, splenomegaly, cytopenias, hyperferritinemia, fibrinogen and/or D-Dimer levels, and central nervous system abnormalities, with no sustained worsening of soluble CD25 serum levels. At the end of treatment, ORR for the subset of patients failing conventional therapy was 63% (95% confidence interval [CI]: 42%–81%,  $p = .0134$ ), which exceeded the investigators' estimated null hypothesis of 40%. Median time to response was 8 days (95% CI: 7–14), and the majority of patients (70.4%) proceeded to HSCT. In an analysis of all treated patients ( $n = 34$ ), ORR was 64.7% (95% CI: 46%–80%,  $p = .0031$ ).

At the end of the trial, patients had the option to enroll in an open-label extension study (NCT0269899) in which outcomes were evaluated for 1 year post HSCT or after the last dose of emapalumab. Twenty-two patients were included in this analysis.<sup>1</sup> In addition to clinical efficacy and safety outcomes, the study evaluated immunogenicity and pharmacodynamics. One patient (3%) developed treatment-emergent antitherapeutic antibodies (ATA) within the first 9 weeks of emapalumab exposure. Fortunately, the ATAs did not appear to alter the medication's safety or efficacy profile. In regard to pharmacodynamics, emapalumab caused reductions in both serum IFN gamma and serum levels of an IFN gamma-induced chemokine, CXCL9.<sup>2,11</sup>

## Safety

Safety data from the pivotal phase 2/3 trial (NCT01818492) suggest that emapalumab is generally well tolerated, with the most common adverse effects being infection (56%), hypertension (41%), mild to moderate infusion-related reactions (27%), and pyrexia (24%).<sup>11</sup> One-third of the infusion-related reactions occurred during the first dose. Despite general tolerability, two patients experienced fatal adverse reactions resulting from septic shock and gastrointestinal hemorrhage. One patient withdrew from the trial because of disseminated histoplasmosis, which resolved with treatment. Suppression of IFN gamma increases risk for serious or fatal infections in patients receiving emapalumab. The most concerning pathogens are primarily intracellular and include mycobacteria, herpes zoster virus, and histoplasma capsulatum. All patients treated with emapalumab should receive prophylaxis for herpes zoster, *Pneumocystis jirovecii*, and fungal infections. Live vaccines and live attenuated vaccines should be avoided.<sup>11</sup>

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## Future Directions

Despite promising efficacy and safety data supporting the use of emapalumab for primary HLH, many questions regarding long-term outcomes remain unanswered. An ongoing international multicenter extension of the pivotal phase 2/3 clinical trial (NCT02069899) aims to provide additional information regarding the long-term efficacy, safety, tolerability, and pharmacokinetic profile of emapalumab.<sup>1,12</sup> The study's estimated completion date is September 2020. It is also unclear whether continuous blockade of IFN gamma will be required for sustained response, given that cytokine production occurs downstream from T cells.<sup>2</sup>

The role of emapalumab in secondary HLH is still unknown. Ongoing clinical trials in this population are limited to a phase 2 open-label single-arm multicenter study in Italy including pediatric patients (younger than 18 years old) with systemic juvenile idiopathic arthritis who developed macrophage activation syndrome or secondary HLH.<sup>13</sup>

## Conclusions

Emapalumab, a fully human IgG1 anti-IFN gamma monoclonal antibody, meets an unmet medical need for pediatric and adult patients with primary HLH who have refractory, recurrent, or progressive disease or intolerance to conventional HLH therapy. Although emapalumab is generally well tolerated, patients should be carefully monitored for serious infections and infusion-related reactions. Ongoing clinical trials aim to provide more information regarding long-term outcomes and emapalumab's role in the treatment of secondary HLH. Emapalumab is one of the most significant improvements in the treatment of primary HLH in more than 20 years and provides an opportunity to improve outcomes for patients with this devastating disease. ●●

## Tips for Navigating the Publication Process



**Lisa M. Holle, PharmD BCOP FHOPA**  
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UConn School of Pharmacy  
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Preparing a first manuscript for publication in a peer-reviewed journal can be daunting, but it is important for the advancement of health care and science and also for one's own professional development.<sup>1</sup> As you near the end of your PGY2 residency, consider the following tips for navigating the publication process now, but also during your future career.

### Authorship

One often confusing component of manuscript development is authorship. Authorship confers credit, responsibility, and accountability, but it also has important academic, social, and financial implications. Thus, understanding the qualifications of an author and the different types of authorship is important. Because some unfortunate examples of inaccurate authorship have surfaced in the news over the years, ethical guidelines for authorship have emerged. The International Committee of Medical Journal Editors (ICMJE) recommends that authorship is based on four criteria, and most journals require these criteria for authorship. Each author must have (1) substantially contributed to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; *and* (2) drafted the work or critically revised the work for important intellectual content; *and* (3) approved the final version for publication; *and* (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.<sup>2</sup> In addition to these four criteria, all authors should be aware of the contributions by, and have confidence in, their co-authors. In contrast, a contributor is someone who has met fewer than four of the authorship criteria; for example, this might be someone who supervised part of the research or provided writing, editing, or proofreading assistance. Contributors should be acknowledged for their work, and this is typically done in the Acknowledgments section.

The order of authors listed in a manuscript submission can also be confusing, especially to first-time authors. There are four types of authors: first author, senior author, co-author, and corresponding author. The first or lead author (sometimes called the principal author) is typically the person who has performed most of the research, prepared the majority of the first draft of the manuscript, or both.<sup>3,4</sup> Ultimately, this first author is responsible for the integrity of the work and for ensuring that all other authors meet the requirements of authorship. The senior author is often the research mentor, such as a residency program mentor or the principal investigator of the study. The senior author provides oversight and guidance and directs the work, ensuring the scientific accuracy of its methodology, analysis, and conclusions. Often, the senior author is listed last in the list of authors. Co-authors are all other

authors whose contributions are not at the same level as those of the first or senior author; they are often listed in order of their relative contribution to the research or manuscript development. The corresponding author is the author who is responsible for communicating with the journal editors and readers and is often the author responsible for submitting the manuscript. Typically, the corresponding author is either the first author or the senior author. It is important that the corresponding author expects to remain at the institution listed at the time of the manuscript submission so that he or she can easily be contacted after publication, which in some instances can occur up to a year after the manuscript has been accepted for publication. Because of this, the corresponding author is often the senior author for those first authors who are in a training program.

Authorship disputes among collaborators can occur. In some cases disputes arise because success and promotions in some positions may depend on a successful publication record or because authors feel that their contributions have not been fully recognized. To avoid these disputes, which can be tricky, it is best to decide at the beginning of the project who will work on specific tasks. During this discussion, authorship can be determined on the basis of the ethical guidance and the definitions of authorship; the order of authorship should be apparent when the weight of the assigned tasks is considered. Outlining this in advance can prevent disputes; however, if contributions change throughout the project, then communicating these changes and how they relate to authorship can prevent the occurrence of disputes later on.

### Manuscript Placement

Another important part of the publication process is determining which journal will be the best place for your manuscript. One of the most common reasons for manuscript rejection is that the manuscript doesn't fit the goals and scope of the journal. A first step is to collect a list of journals publishing research similar to yours. As part of your research project development or identification of a manuscript topic, you likely performed a literature search for similar research or topics. Reviewing the journals where these articles were published can help you arrive at a list of journals to consider with your preceptor or co-authors. Journal search tools available online can be helpful, but they are often geared toward journals associated with a particular publisher. After creating a list, you should then review each journal's goals and scope, often found in the "About Us" or "Guide to Authors" section. By doing this you can ascertain whether your manuscript will meet the expectations for publication in that journal.

Once you have narrowed the list of journals for which your manuscript is likely to be a good fit, identifying the target journal may rely on other factors, such as PubMed indexing, the journal's impact factor, and the cost for publication.

It is desirable to have your article be indexed and its content searchable. If a journal is not indexed in the U.S. National Library

of Medicine's PubMed database, it may not be searchable using the PubMed search tool. A journal's "About Us" section may indicate whether the journal is indexed in PubMed, or you can search the journal list on PubMed.

The impact factor of the journal is also an important consideration. This metric is based on how often articles published in the journal have been cited in other articles. The higher the impact factor, the more frequently the journal was cited by other authors, and therefore the more prestigious the journal. However, with higher prestige comes competitiveness; thus it is important to consider the time and effort required to submit a manuscript to a journal with a high impact factor and the likelihood of its acceptance, based on the quality and scientific value of the manuscript and the publication experience of the authors. Often articles written by first-time authors are more likely to be accepted by journals with lower impact factors.<sup>5</sup>

Finally, some journals have a fee associated with submission or publication (or both). This is more common with journals that are online-only publications. Before you select a journal, it is

worthwhile to read the "Guide to Authors" to determine whether fees are associated with a manuscript's submission or publication.

### Manuscript Submission

After you have selected the target journal, be sure to reread the "Guide to Authors" and follow the instructions for manuscript preparation. This will prevent your receiving an outright rejection or negative comments from peer reviewers for nonadherence to the guidelines. Next, read as many related articles in the journal as possible. This will help you draft your own manuscript, knowing what writing style the editors and peer reviewers deem appropriate and what novel and interesting work is suited for publication. Working closely with all authors throughout the process and ensuring that each has a substantial role in contributing to and approving the final draft is essential.

I wish you the best of luck as you wrap up your PGY2 year and fruitful results for your future publication submissions! ●●

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## A Pharmacist-Delivered Tobacco Intervention Program in an Ambulatory Oncology Clinic



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Smoking cessation is a crucial aspect of care for patients with a cancer diagnosis. The American Cancer Society reports that more than 30% of all cancer-related deaths and more than 70% of all lung cancer-related deaths are associated with tobacco use.<sup>1</sup> Tobacco cessation among oncology patients not only provides general health benefits but also prevents tumor progression, decreases the risk for secondary tumors, and reduces complications from therapy.<sup>2</sup> The importance of tobacco-cessation programs in oncology care is endorsed by major professional organizations like the American Society of Clinical Oncology and the National Comprehensive Cancer Network. Multiple studies have shown the effectiveness of pharmacist-delivered tobacco-cessation programs. However, only a few studies have evaluated this model in the population of oncology patients.

In 2018 Kimmel and colleagues conducted a prospective pilot study with a historical comparator arm in order to assess the impact of a pharmacist-delivered tobacco intervention program in an ambulatory oncology setting.<sup>3</sup> Prior to the implementation of the tobacco intervention program in the oncology clinic at the University of Illinois Hospital, patients were referred to the Tobacco Treatment Center. However, high numbers of oncology patients were failing to keep their appointments at the Tobacco Treatment Center. The authors were hoping to increase the number of interventions by providing tobacco-cessation services in conjunction with other oncology clinic appointments.

Patients included in the study were divided into prospective and retrospective arms, with 12 patients in each. Patients in the prospective arm received tobacco-cessation services from oncology pharmacists at the time of their anticancer therapy visits. Patients were included if they had a cancer diagnosis, were receiving intravenous anticancer therapy at the time of enrollment, had self-identified as smokers, and had expressed interest in quitting. Patients in the retrospective arm received interventions at the Tobacco Treatment Center, a pharmacist-run clinic. Patients were included if they had a cancer diagnosis, were at least 18 years old, and had received tobacco interventions at the Tobacco Treatment Center after January 1, 2000. At the initial visit, patients in the prospective group received “Deciding How to Quit: A Smoker’s Guide,” a brochure published by the American Cancer Society, and were asked to complete the Fagerström Test for Nicotine Dependence. Oncology pharmacists conducting the visit provided behavior counseling, pharmacologic interventions, or both, according to the patient’s specific needs. Subsequent meeting frequency was determined by the participant’s cancer treatment schedule, and the number of visits was based on

the participant’s individual needs. At each visit with the pharmacist, Smokerlyzer breath tests were administered to measure carbon monoxide levels. Patients were asked to complete a 12-item questionnaire to assess their satisfaction with the program at their last visit or 3 months after enrollment. The tobacco intervention program used in the oncology clinic was based on the model established at the Tobacco Treatment Center. Thus, patients in the retrospective group received similar interventions.

Of the 24 patients included in the study, 67% were women, and 88% were African American. The most common cancer types were breast cancer (33%), head and neck cancer (21%), and non-small-cell lung cancer (17%). The average number of visits with a pharmacist was similar for the groups: 3.3 in the prospective group and 3 in the retrospective group. More patients in the prospective arm (77%) initiated tobacco intervention treatment within 6 months of their diagnosis, compared with patients in the retrospective arm (17%). Carbon monoxide levels consistent with those of a non-smoker were recorded in 4 of 11 patients (36%) in the prospective group and in 3 of 12 patients (25%) in the retrospective group. Pharmacologic interventions were prescribed for 10 patients in the prospective arm and for 8 patients in the retrospective arm. Commonly used agents were nicotine-replacement therapies and varenicline. Only 4 patients in the prospective arm completed the satisfaction survey; the average score was 4.625 on a 5-point Likert scale for general satisfaction.

This study was originally designed as a prospective randomized trial, with patients being randomized to receive pharmacist interventions at the oncology clinic versus physician intervention or referral to the Tobacco Treatment Center. However, the protocol was amended because of low accrual. Most patients declined study participation because of a desire to receive the tobacco-cessation therapy in the oncology clinic, which highlights the necessity of offering these services in the oncology-clinic setting. The authors observed a slight increase in quitting rates with introduction of the program in the oncology clinic (36% vs. 25% in the prospective and retrospective arms, respectively). Another advantage of embedding tobacco-cessation services in the oncology clinic is the opportunity to begin interventions soon after the cancer diagnosis. In this study, a higher percentage of patients received early intervention in the prospective arm. Finally, oncology pharmacists are uniquely equipped to use their knowledge of cancer therapies and associated toxicities to tailor tobacco-cessation interventions to the needs of patients with malignancies.

Although this study had a small sample size, it demonstrates the feasibility and potential advantages of implementing pharmacist-driven tobacco-cessation programs in an ambulatory oncology setting. The delivery of smoking-cessation interventions is one way that pharmacists can have a significant impact on oncology patient outcomes and survivorship. ●●

(continued on p. 23)

# GROUNDBREAKING EFFICACY



**AN UNPRECEDENTED**  
**18.9 vs 10.2**  
months median PFS vs erlotinib/gefitinib  
in the FLAURA study

Hazard ratio=0.46 (95% CI: 0.37, 0.57),  $P<0.0001$



Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSE (n=279; 80 mg orally, once daily) or EGFR TKI comparator (n=277; gefitinib 250 mg or erlotinib 150 mg orally, once daily). Crossover was allowed for patients in the EGFR TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was PFS based on investigator assessment (according to RECIST v.1.1). Secondary endpoints included OS, ORR, and DOR.<sup>1,2</sup>

## INDICATION

TAGRISSE is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

## SELECT SAFETY INFORMATION

- There are no contraindications for TAGRISSE
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1 142 TAGRISSE-treated patients; 0.4% of cases were fatal. Withhold TAGRISSE and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSE if ILD is confirmed
- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSE-treated patients. Of the 1 142 TAGRISSE-treated patients in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported.



# WITH FIRST-LINE TAGRISSO®

**OS**

**Overall survival data were not mature at the time of the final PFS analysis<sup>1</sup>**

- There were 58 deaths with TAGRISSO (21%; n=279), and 83 deaths in the EGFR TKI comparator arm (30%; n=277)<sup>2</sup>

**NCCN  
PREFERRED**

**Osimertinib (TAGRISSO) is the only National Comprehensive Cancer Network® (NCCN®) preferred first-line therapy option in metastatic EGFRm NSCLC. This preferred designation is based on efficacy, safety, and evidence.<sup>3\*</sup>**

\*The NCCN Guidelines do not endorse specific testing modalities or techniques for biomarker tests.

## SELECT SAFETY INFORMATION

Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia

- Cardiomyopathy occurred in 2.6% of the 1 142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF)  $\geq 10\%$  from baseline and to  $< 50\%$  LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1 142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Most common adverse reactions ( $\geq 20\%$ ) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

Abbreviations: CNS, central nervous system; DOR, duration of response; EGFRm, epidermal growth factor receptor mutation-positive; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, Overall Survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TKI, tyrosine kinase inhibitor.

**REFERENCES: 1.** TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. **2.** Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378(2):113-125. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC V.3.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed January 22, 2019. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. To view the most recent and complete version of the guideline, go online to [NCCN.org](http://NCCN.org).

**Please see Brief Summary of Prescribing Information on adjacent pages.**

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**TAGRISSO®**  
osimertinib

## TAGRISSO® (osimertinib) tablets, for oral use

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

### INDICATIONS AND USAGE

#### First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see *Dosage and Administration (2.1) in the full Prescribing Information*].

### DOSAGE AND ADMINISTRATION

#### Patient Selection

Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens [see *Clinical Studies (14) in the full Prescribing Information*]. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.

Information on FDA-approved tests for the detection of EGFR mutations is available at <http://www.fda.gov/companiondiagnostics>.

#### Recommended Dosage Regimen

The recommended dosage of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

#### Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink.

If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 30 mL).

#### Dosage Modifications

##### Adverse Reactions

**Table 1. Recommended Dosage Modifications for TAGRISSO**

Target Organ	Adverse Reaction <sup>a</sup>	Dosage Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue TAGRISSO.
Cardiac	QTc <sup>†</sup> interval greater than 500 msec on at least 2 separate ECGs <sup>b</sup>	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose.
	QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Permanently discontinue TAGRISSO.
	Symptomatic congestive heart failure	Permanently discontinue TAGRISSO.
Other	Adverse reaction of Grade 3 or greater severity	Withhold TAGRISSO for up to 3 weeks.
	If improvement to Grade 0-2 within 3 weeks	Resume at 80 mg or 40 mg daily.
	If no improvement within 3 weeks	Permanently discontinue TAGRISSO.

<sup>a</sup> Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).

<sup>b</sup> ECGs = Electrocardiograms

<sup>†</sup> QTc = QT interval corrected for heart rate

### Drug Interactions

#### Strong CYP3A4 Inducers

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when co-administering with a strong CYP3A4 inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer [see *Drug Interactions (7) and Clinical Pharmacology (12.3) in the full Prescribing Information*].

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

#### Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal.

Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed [see *Dosage and Administration (2.4) and Adverse Reactions (6) in the full Prescribing Information*].

#### QTc Interval Prolongation

Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1142 patients treated with TAGRISSO in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec [see *Clinical Pharmacology (12.2) in the full Prescribing Information*]. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the

QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia [see *Dosage and Administration (2.4) in the full Prescribing Information*].

#### Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal.

A decline in left ventricular ejection fraction (LVEF)  $\geq$  10% from baseline and to less than 50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment.

Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO [see *Dosage and Administration (2.4) in the full Prescribing Information*].

#### Keratitis

Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

#### Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended clinical dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5 times those observed at the recommended dose of 80 mg once daily. Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose [see *Use in Specific Populations (8.1, 8.3) in the full Prescribing Information*].

### ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling: Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions (5.1) in the full Prescribing Information*]

QTc Interval Prolongation [see *Warnings and Precautions (5.2) in the full Prescribing Information*]

Cardiomyopathy [see *Warnings and Precautions (5.3) in the full Prescribing Information*]

Keratitis [see *Warnings and Precautions (5.4) in the full Prescribing Information*]

#### 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 section reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) [see *Warnings and Precautions (5) in the full Prescribing Information*].

The data described below reflect exposure to TAGRISSO (80 mg daily) in 558 patients with EGFR mutation-positive, metastatic NSCLC in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.

#### Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months.

The most common adverse reactions ( $\geq$ 20%) in patients treated with TAGRISSO were diarrhea (58%), rash (58%), dry skin (36%), nail toxicity (35%), stomatitis (29%), and decreased appetite (20%). Serious adverse reactions were reported in 4% of patients treated with TAGRISSO; the most common serious adverse reactions ( $\geq$ 1%) were pneumonia (2.9%), ILD/pneumonitis (2.1%), and pulmonary embolism (1.8%). Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (4.3%), diarrhea (2.5%), and lymphopenia (1.1%). Adverse reactions leading to permanent discontinuation occurred in 13% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3.9%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in FLAURA. FLAURA was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TAGRISSO, or for the control arm, for any adverse reaction listed in Tables 2 and 3.

**Table 2. Adverse Reactions Occurring in  $\geq$ 10% of Patients Receiving TAGRISSO in FLAURA\***

Adverse Reaction	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
<b>Gastrointestinal Disorders</b>				
Diarrhea <sup>a</sup>	58	2.2	57	2.5
Stomatitis	29	0.7	20	0.4
Nausea	14	0	19	0
Constipation	15	0	13	0
Vomiting	11	0	11	1.4

**Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA\* (cont'd)**

Adverse Reaction	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
<b>Skin Disorders</b>				
Rash <sup>b</sup>	58	1.1	78	6.9
Dry skin <sup>c</sup>	36	0.4	36	1.1
Nail toxicity <sup>d</sup>	35	0.4	33	0.7
Pruritus <sup>e</sup>	17	0.4	17	0
<b>Metabolism and Nutrition Disorders</b>				
Decreased appetite	20	2.5	19	1.8
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Cough	17	0	15	0.4
Dyspnea	13	0.4	7	1.4
<b>Neurologic Disorders</b>				
Headache	12	0.4	7	0
<b>Cardiac Disorders</b>				
Prolonged QT Interval <sup>f</sup>	10	2.2	4	0.7
<b>General Disorders and Administration Site Conditions</b>				
Fatigue <sup>g</sup>	21	1.4	15	1.4
Pyrexia	10	0	4	0.4
<b>Infection and Infestation Disorders</b>				
Upper Respiratory Tract Infection	10	0	7	0

\* NCI CTCAE v4.0

<sup>a</sup> One grade 5 (fatal) event was reported (diarrhea) for EGFR TKI comparator

<sup>b</sup> Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion.

<sup>c</sup> Includes dry skin, skin fissures, xerosis, eczema, xeroderma.

<sup>d</sup> Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasia, onycholysis, onychomadesis, onychomalacia, paronychia.

<sup>e</sup> Includes pruritus, pruritus generalized, eyelid pruritus.

<sup>f</sup> The frequency of "Prolonged QT Interval" represents reported adverse events in the FLAURA study. Frequencies of QTc intervals of >500 ms or >60 ms are presented in Section 5.2.

<sup>g</sup> Includes fatigue, asthenia.

**Table 3. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in FLAURA**

Laboratory Abnormality <sup>a,b</sup>	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)
<b>Hematology</b>				
Lymphopenia	63	5.6	36	4.2
Anemia	59	0.7	47	0.4
Thrombocytopenia	51	0.7	12	0.4
Neutropenia	41	3.0	10	0
<b>Chemistry</b>				
Hyperglycemia <sup>c</sup>	37	0	31	0.5
Hypermagnesemia	30	0.7	11	0.4
Hyponatremia	26	1.1	27	1.5
Increased AST	22	1.1	43	4.1
Increased ALT	21	0.7	52	8
Hypokalemia	16	0.4	22	1.1
Hyperbilirubinemia	14	0	29	1.1

<sup>a</sup> NCI CTCAE v4.0

<sup>b</sup> Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 256 - 268)

<sup>c</sup> Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TAGRISSO (179) and EGFR comparator (191)

## DRUG INTERACTIONS

### Effect of Other Drugs on Osimertinib

#### Strong CYP3A Inducers

Co-administering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone [see *Clinical Pharmacology* (12.3) in the full Prescribing Information]. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid co-administering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when co-administering with a strong CYP3A4 inducer if concurrent use is unavoidable [see *Dosage and Administration* (2.4) in the full Prescribing Information]. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

### Effect of Osimertinib on Other Drugs

Co-administering TAGRISSO with a breast cancer resistant protein (BCRP) or P-glycoprotein (P-gp) substrate increased the exposure of the substrate compared to administering it alone [see *Clinical Pharmacology* (12.3) in the full Prescribing Information]. Increased BCRP or P-gp substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the BCRP or P-gp substrate, unless otherwise instructed in its approved labeling, when co-administered with TAGRISSO.

### Drugs That Prolong the QTc Interval

The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid concomitant administration of drugs known to prolong the QTc interval with known risk of Torsades de pointes. If not feasible to avoid concomitant administration of such drugs, conduct periodic ECG monitoring [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3) in the full Prescribing Information].

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Risk Summary

Based on data from animal studies and its mechanism of action [see *Clinical Pharmacology* (12.1) in the full Prescribing Information], TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical 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% to 4% and 15% to 20%, respectively.

#### Data

##### Animal Data

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1 times the AUC observed at the recommended clinical dose of 80 mg once daily), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

### Lactation

#### Risk Summary

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death [see *Use in Specific Populations* (8.1) in the full Prescribing Information]. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

### Females and Males of Reproductive Potential

#### Pregnancy Testing

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

#### Contraception

TAGRISSO can cause fetal harm when administered to pregnant women [see *Use in Specific Populations* (8.1) in the full Prescribing Information].

#### Females

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose [see *Use in Specific Populations* (8.1) in the full Prescribing Information].

#### Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO [see *Nonclinical Toxicology* (13.1) in the full Prescribing Information].

#### Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible [see *Nonclinical Toxicology* (13.1) in the full Prescribing Information].

### Pediatric Use

The safety and effectiveness of TAGRISSO in pediatric patients have not been established.

### Geriatric Use

Forty-three percent (43%) of the 1142 patients in FLAURA (n=279), AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and AURA1, (n=173) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (13.4% versus 9.3%) and more frequent dose modifications for adverse reactions (13.4% versus 7.6%) in patients 65 years or older as compared to those younger than 65 years.

### Renal Impairment

No dose adjustment is recommended in patients with creatinine clearance (CL<sub>cr</sub>) 15 - 89 mL/min, as estimated by Cockcroft-Gault. There is no recommended dose of TAGRISSO for patients with end-stage renal disease (CL<sub>cr</sub> < 15 mL/min) [see *Clinical Pharmacology* (12.3) in the full Prescribing Information].

### Hepatic Impairment

No dose adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh A and B or total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment (total bilirubin between 3 to 10 times ULN and any AST) [see *Clinical Pharmacology* (12.3) in the full Prescribing Information].

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# Drug-Drug Interactions Between HIV Medications and Chemotherapy Agents



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Human immunodeficiency virus (HIV) continues to affect millions of Americans and others around the globe. At the end of 2015, an estimated 1.1 million persons 13 years of age or older were living with HIV infection in the United States.<sup>1</sup> In 2016, the number of new HIV diagnoses in the United States was 39,782, and the number of deaths was 6,160.<sup>2</sup> Both of these numbers have decreased substantially and continue to decline following the introduction of antiretroviral therapy (ART). HIV has become a chronic disease state for those dependent on lifelong use of ART.

Patients living with HIV have a significantly increased risk of developing some cancers compared to similar patients without HIV.<sup>3,4</sup> Patients who are diagnosed with both HIV and cancer present a challenging treatment scenario. Cancer treatment can supersede the treatment of other diseases because of its urgency and the poor prognosis that often accompanies the disease. Patients taking ART and being treated with chemotherapy are at risk for drug-drug interactions (DDIs). Management strategies to consider when the risk of DDIs is present include selecting an alternative chemotherapy or ART or temporarily discontinuing the ART. Temporarily withholding ART is the less desirable clinical plan, but risks and benefits must be considered in each scenario. For example, if a patient with HIV is taking ARTs that have potential DDIs and is diagnosed with a curable cancer, then all attempts should be made to achieve appropriate treatment of the cancer. If concomitant treatment with an interacting ART and chemotherapy is necessary, dose adjustments to either therapy may be warranted in order to increase the chance of cure and minimize toxicity.

Several classes of medications can be used in combination as ART. They are listed and their potential for DDIs is summarized in

**Table 1.** Protease inhibitors (PIs), integrase inhibitors (except raltegravir), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), and cobicistat in particular have a higher likelihood of DDIs because of their cytochrome P450 3A4 (CYP3A4) metabolism. Dolutegravir, raltegravir, and maraviroc have fewer DDIs and could be alternatives.<sup>27,28,30</sup> Oral chemotherapy agents are more prone to DDIs with ART. More than half of the oral chemotherapy agents (mostly tyrosine kinase inhibitors) are substrates of CYP3A. In addition, patients being treated with chemotherapy are sometimes concomitantly taking acid-suppressive therapy. Patients taking rilpivirine and atazanavir should avoid concomitant use of proton pump inhibitors.<sup>16,17</sup>

Risks for additive toxicities are also present with any concomitant medication use. Neurotoxicity (specifically neuropathy, with didanosine and stavudine) can occur, and the use of didanosine and stavudine with platinum agents, taxanes, vinca alkaloids, and proteasome inhibitors should be avoided, if possible.<sup>6,9,32</sup> Zidovudine use should be avoided with concomitant myelosuppressive chemotherapy because of its attendant risk of severe neutropenia.<sup>10</sup> The use of didanosine, stavudine, zidovudine, and maraviroc can lead to hepatotoxicity; therefore chemotherapy that can also cause hepatotoxicity or be metabolized by the liver should be used with caution.<sup>6,9,10,30,33</sup> QT prolongation with protease inhibitors (ritonavir, atazanavir, saquinavir) and rilpivirine is of concern.<sup>16,17,23,24</sup> Concomitant QT-prolonging chemotherapy and supportive care should be avoided in order to circumvent the potential for arrhythmias and death.

In conclusion, because of the paucity of data studying DDIs between ART and chemotherapy, pharmacists should be vigilant about the possibility of DDIs when concomitant therapy is given. Consideration should also be given to the supportive care medications that may be needed in patients being treated with chemotherapy and ART. Pharmacotherapy in these patients should be individualized, and communication and collaboration with various specialties should be constant throughout treatments.

**Table 1. Summary of Potential Interactions with Antiretroviral Therapy<sup>5-31</sup>**

ART	Route of Elimination*	CYP450 and Transporter Effects			Other Relevant Drug Interactions
		Substrate*	Inhibitor*	Inducer*	
<b>Nucleoside reverse-transcriptase inhibitors</b>					
Abacavir	Renal, ADH, UGT	None	None	None	
Didanosine	Renal, purine nucleoside phosphorylase	None	None	None	Didanosine may decrease quinolone concentration.
Emtricitabine	Renal	None	None	None	
Lamivudine	Renal	None	None	None	
Stavudine	Renal	None	None	None	Doxorubicin may decrease stavudine.
Zidovudine	UGT2B7	None	None	None	Doxorubicin may decrease zidovudine. Atovaquone increases zidovudine.

**Table 1. Summary of Potential Interactions with Antiretroviral Therapy<sup>5-31</sup> (continued)**

ART	Route of Elimination*	CYP450 and Transporter Effects			Other Relevant Drug Interactions
		Substrate*	Inhibitor*	Inducer*	
<b>Nucleotide reverse-transcriptase inhibitors</b>					
Tenofovir	Renal	PGP, BCRP	CYP1A2	None	
<b>Non-nucleoside reverse-transcriptase inhibitors</b>					
Doravirine	<b>CYP3A4</b>	<b>CYP3A4</b>	None	None	Enzalutamide decreases doravirine (use is contraindicated).
Efavirenz	<b>CYP3A4</b>	<b>CYP2B6, CYP3A, UGT2B7</b>	CYP2C9, CYP2C19, CYP3A4	CYP2B6, CYP3A4	Efavirenz decreases itraconazole, posaconazole, and voriconazole. Voriconazole increases efavirenz.
Etravirine	<b>CYP3A4</b>	<b>CYP2C9, CYP2C19, CYP3A, UGT</b>	CYP2C9, CYP2C19, PGP	CYP2B6, CYP3A	Etravirine decreases itraconazole. Etravirine increases voriconazole. Fluconazole, itraconazole, posaconazole, and voriconazole increase etravirine. Dexamethasone decreases etravirine.
Nevirapine	CYP2B6, <b>CYP3A4</b> , UGT	CYP2B6, <b>CYP3A4</b> , UGT	None	CYP2B6, CYP3A4	Fluconazole increases nevirapine. Nevirapine decreases itraconazole.
Rilpivirine	<b>CYP3A</b>	<b>CYP3A</b>	None	None	Fluconazole, itraconazole, posaconazole, and voriconazole may increase rilpivirine. Dexamethasone decreases rilpivirine.
<b>Protease inhibitors</b>					
Atazanavir	<b>CYP3A4</b> , PGP	<b>CYP3A4</b> , PGP	CYP2C8, <b>CYP3A</b> , MRP2, <b>UGT1A1</b>	None	Atazanavir increases irinotecan (use is contraindicated). Atazanavir increases itraconazole. Atazanavir decreases voriconazole. Voriconazole decreases atazanavir.
Darunavir	<b>CYP3A4</b>	<b>CYP3A4</b>	<b>CYP3A4</b>	None	Darunavir increases itraconazole. Itraconazole and posaconazole increase darunavir. Darunavir decreases voriconazole. Darunavir increases dasatinib, nilotinib, and vinca alkaloids.
Fosamprenavir or amprenavir	CYP2D6, CYP2C9, <b>CYP3A4</b> , PGP, UGT	CYP2D6, CYP2C9, <b>CYP3A4</b> , PGP, UGT	<b>CYP3A</b>	CYP3A4, PGP	Fosamprenavir increases itraconazole. Dexamethasone may decrease fosamprenavir.
Indinavir	<b>CYP3A4</b> , PGP, MRP2, UGT	<b>CYP3A4</b> , PGP, MRP2, UGT	CYP2D6, <b>CYP3A</b> , UGT1A1	None	Itraconazole increases indinavir.
Lopinavir	<b>CYP3A</b> , MRP2	<b>CYP3A</b> , MRP2	<b>CYP3A</b> , UGT1A1	None	Lopinavir increases itraconazole and isavuconazonium. Lopinavir decreases voriconazole. Lopinavir may decrease atovaquone. Glucocorticoids decreases lopinavir. Lopinavir increases glucocorticoids. Lopinavir increases dasatinib, nilotinib, and vinca alkaloids. Lopinavir increases venetoclax and ibrutinib (avoid use).
Nelfinavir	CYP2C9, <b>CYP2C19</b> , CYP2D6, <b>CYP3A</b>	CYP2C9, <b>CYP2C19</b> , CYP2D6, <b>CYP3A</b>	CYP2D6, <b>CYP3A</b>	CYP2C9, CYP3A4, PGP	

(continued)

**Table 1. Summary of Potential Interactions with Antiretroviral Therapy<sup>5-31</sup> (continued)**

ART	Route of Elimination*	CYP450 and Transporter Effects			Other Relevant Drug Interactions
		Substrate*	Inhibitor*	Inducer*	
Ritonavir	CYP2D6, <b>CYP3A</b> , PGP, MRP2	CYP2D6, <b>CYP3A</b> , PGP, MRP2	CYP2D6, CYP2C9, <b>CYP3A</b>	CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, UGT	Ritonavir decreases voriconazole (use is contraindicated). Ritonavir increases itraconazole. Ritonavir may decrease atovaquone. Ritonavir increases glucocorticoids. Ritonavir increases dasatinib, nilotinib, and vinca alkaloids. Ritonavir increases venetoclax and ibrutinib (avoid use).
Saquinavir	<b>CYP3A4</b> , PGP, MRP2	<b>CYP3A4</b> , PGP, MRP2	CYP2D6, CYP2C9, <b>CYP3A</b> , PGP, MRP2, UGT1A1	None	Glucocorticoids decrease saquinavir. Saquinavir increases glucocorticoids. Saquinavir increases dasatinib and sunitinib (use is contraindicated).
Tipranavir	<b>CYP3A</b> , PGP, UGT	<b>CYP3A</b> , PGP, UGT	<b>CYP2D6</b> , <b>CYP3A4</b> , PGP	CYP1A2, CYP2C9, CYP2C19	
<b>Integrase inhibitors</b>					
Bictegravir	CYP3A, UGT1A1	CYP3A, UGT1A1	OCT2 and MATE1	None	
Dolutegravir	CYP3A4, BCRP, PGP, <b>UGT1A1</b> , UGT1A3, UGT1A9	CYP3A4, BCRP, PGP, <b>UGT1A1</b> , UGT1A3, UGT1A9	OCT2	None	
Raltegravir	UGT1A1	UGT1A1	None	None	
<b>Fusion inhibitors</b>					
Enfuvirtide	Catabolism	None	None	None	
<b>CCR5 inhibitors</b>					
Maraviroc	<b>CYP3A4</b> , PGP, OATP1B, MRP2	<b>CYP3A4</b> , PGP, OATP1B, MRP2	None	None	

Note. Drug-drug interactions are taken from prescribing information. Other possible drug-drug interactions could exist beyond those covered in these resources.  
 ADH = alcohol dehydrogenase; ART = antiretroviral therapy; CYP = cytochrome P450; MATE1 = multidrug and toxin extrusion transporter 1; MRP2 = multidrug resistance protein 2; OATP = organic anion-transporting polypeptide; OCT2 = organic cation transporter 2; PGP = P-glycoprotein; UGT = uridine 5'-diphospho-glucuronosyltransferase.  
**\*Boldface type** indicates a major substrate, inhibitor, or inducer.

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## A Pharmacist-Delivered Tobacco Intervention Program *(continued from p. 15)*

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## Drug Interactions Between Chemotherapy and Antiretrovirals: Making a Difference Behind the Scenes

*This account was written by an anonymous HOPA member. If you are interested in submitting your own story about patient care, please respond to the Patient Stories survey created by HOPA's 2018–2019 Patient Outreach Committee and available at <https://www.surveymonkey.com/r/HOPAs>. The goal of the survey is to highlight the wonderful work done by oncology pharmacists on a daily basis.*

A few years ago, when I was a new clinician practicing on the inpatient lymphoma service at a large academic medical center, a question that I didn't have an answer for was posed to me: How should one deal with drug interactions between antiretroviral (ARV) agents used to treat HIV/AIDS and the chemotherapeutic agents needed to treat lymphoma?

The result of this question—and a proposal by two physician colleagues—was a collaborative program that lasted for 2 years and helped change the way we triaged patients who had concomitant diagnoses of HIV and lymphoma. The initial proposal was simple: develop a systematic approach to treating these patients.

At the time, very few studies or guidance was available on exactly what to do in these situations. With the limited information available, we drew up a chart of known interactions and how each could be managed. For the most part, the interactions involved either a potential increase in the concentration of the chemotherapeutic agent or an additive effect of QTc prolongation with the use of prophylactic medications or anti-emetics. At the start of the pilot project, our primary focus was the possible increase in the concentration of chemotherapeutic medications and the risk of increased side effects.

Because most of the chemotherapy was administered with curative intent, we decided that if a feasible alternative for an ARV regimen was available when a patient required interacting chemotherapy, then the ARV agent would be changed. If an alternative ARV regimen was not available, the chemotherapy would proceed, but additional monitoring would be implemented. If neither of these options was feasible, then a dose reduction of chemotherapy would be considered as a last resort.

Pharmacists and nurses in the chemotherapy infusion center were educated and provided a list of interactions. The observation

of an interaction triggered a call to the clinical pharmacist on the inpatient service (me) so that I could review the interaction and discuss options with the attending physician of record.

For all new patients with concomitant diagnoses of HIV and lymphoma, a consultation with the infectious disease/HIV attending physician collaborating on the project was automatically triggered, as was a thorough review of medications by the clinical pharmacist. A checklist—which included appropriate screening laboratory tests as well as targeted drug interactions to watch for—was also implemented for both consultations.

Over the course of the following 18 months, about a third of the patients screened had changes made to the ARV agents they were receiving, and others underwent additional monitoring for possible side effects. No chemotherapy dose reductions were needed. None of the patients experienced adverse effects that would be considered additive toxicity from the combination of chemotherapy agents and ARV agents.

Reflecting as a clinician on the interventions is interesting. I can share no heartwarming stories of patients coming back to hug us, thank us for changing their ARV medications, or congratulate us on following more closely their HIV-related labs and possible side effects. In fact, most patients probably didn't give much

thought to the changes after they got used to the new ARV medication regimen. What matters is that those small changes possibly prevented adverse events and made the patients' already difficult journey through cancer treatment a little easier.

Although I subsequently left that position and moved to another state, the program evolved and continued in some form after my departure. The biggest lessons learned were the importance of collaborating with physician colleagues and making an interdisciplinary effort to combat drug interactions. Simple changes, we learned, can make a big impact. The program itself was not complicated and did not require any additional financial resources—only the time and energy of those involved. The possible prevention of side effects—as well as the close follow-up of all patients involved—was well worth the additional effort. ●●

**“What matters is that those small changes possibly prevented adverse events and made the patients' already difficult journey through cancer treatment a little easier.”**



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## Updates in the Management of Hepatocellular Carcinoma



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### Overview of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is associated with a high mortality rate and limited treatment options. The American Cancer Society estimates that in 2019, more than 42,000 individuals will be diagnosed with HCC, and nearly 32,000 individuals will succumb to the disease.<sup>1</sup> Despite an overall decline in cancer-related deaths in the United States, mortality rates due to liver cancer have increased and rank as the fifth leading cause of cancer-related death.<sup>2</sup> Chronic hepatitis B and C infections and alcohol consumption are the leading risk factors for the development of HCC in the United States.<sup>3,4</sup> Screening is recommended for individuals at high risk of developing HCC, and patients with early-stage disease may undergo surgical resection, ablation, transarterial chemoembolization, radiation therapy, or liver transplantation.<sup>5,6</sup> Patients diagnosed with late-stage or metastatic disease have limited treatment options. Prior to 2018, sorafenib was the only U.S. Food and Drug Administration (FDA)-approved targeted therapy for the initial treatment of unresectable HCC; nivolumab and regorafenib were approved in 2017 as second-line options following treatment with sorafenib.<sup>7-9</sup> The unmet need to improve outcomes for patients with advanced and metastatic HCC is clear. For this reason it is important to review recent FDA approvals and ongoing clinical trials of unique combination therapies for HCC.

### Cabozantinib (Cabometyx)

On January 14, 2019, the FDA approved cabozantinib (Cabometyx) as second-line therapy for advanced HCC following initial sorafenib therapy.<sup>10</sup> Cabozantinib is a multitargeted tyrosine kinase inhibitor with activity against vascular endothelial growth factor (VEGF) receptors 1-3, FLT-3, KIT, MET, RET, and others. The approval followed the results of the randomized double-blind placebo-controlled phase 3 CELESTIAL trial.<sup>11</sup> Eligible patients were required to have had prior treatment with sorafenib, progressive disease after one or two prior therapies, Child-Pugh Class A liver function, Eastern Cooperative Oncology Group performance score (ECOG PS) of 1 or less, and adequate hematologic and renal function measures. Patients were randomized (2:1) to receive either cabozantinib 60 mg once daily or matching placebo until the disease progressed or an intolerable level of adverse effects was

reached. The primary endpoint of the study was overall survival (OS); secondary endpoints were progression-free survival (PFS) and objective response rate (ORR).

Cabozantinib was given to 467 patients, and 237 patients received placebo; baseline demographic and clinical characteristics between the groups were balanced.<sup>11</sup> Among patients treated with cabozantinib, the median OS was 10.2 months, and the median OS with placebo was 8 months (hazard ratio [HR] 0.76;  $p = .005$ ). The median PFS was significantly longer with cabozantinib (5.2 months; 95% confidence interval [CI]: 4–5.5) compared to placebo (1.9 months) with an HR for disease progression or death of 0.44 (95% CI: 0.36–0.52;  $p < .001$ ). The ORR was also significantly higher with cabozantinib (4% vs. <1%;  $p = .009$ ). The most common side effects (20% or more) in the cabozantinib arm were diarrhea (54%), decreased appetite (48%), palmar-plantar erythrodysesthesia (46%), fatigue (45%), nausea (31%), hypertension (29%), vomiting (26%), asthenia (22%), and elevated values in liver function tests (17%–22%). Grade 3–4 adverse effects occurred in 68% of cabozantinib-treated patients, with 62% of patients requiring dose reductions because of adverse effects.<sup>10,11</sup>

The FDA-recommended starting dose of cabozantinib for HCC is 60 mg once daily taken on an empty stomach (1 hour before or 2 hours after a meal).<sup>10</sup>

### Lenvatinib (Lenvima)

On August 16, 2018, the FDA approved lenvatinib (Lenvima), a multitargeted tyrosine kinase inhibitor of VEGF, as first-line treatment of patients with HCC.<sup>12</sup> Approval was based on the international multicenter randomized open-label phase 3 noninferiority REFLECT trial conducted with 954 patients who had previously untreated metastatic or unresectable HCC.<sup>13</sup> Adult patients with Child-Pugh Class A and Barcelona Clinic Liver Cancer Stage C or B HCC who were ineligible for local liver-directed therapy, had an ECOG PS of 1 or lower, had received no prior systemic therapy for HCC, and had at least one measurable target lesion according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) assessment of HCC were randomized (1:1) to receive lenvatinib (12 mg for baseline body weight of 60 kg or greater or 8 mg for baseline body weight less than 60 kg) orally once daily or sorafenib 400 mg orally twice daily until radiological disease progression or unacceptable toxicity levels.

Lenvatinib was noninferior but not statistically superior to sorafenib for OS (HR 0.92; 95% CI: 0.79–1.06).<sup>13</sup> Median OS was 13.6 months in the lenvatinib arm and 12.3 months in the sorafenib arm. Lenvatinib resulted in a statistically significant improvement in PFS of 7.3 months versus 3.6 months in the sorafenib arm (HR 0.64; 95% CI: 0.55–0.75;  $p < .001$ ) per mRECIST and RECIST v1.1 for HCC. The ORR was higher for the lenvatinib arm compared to the sorafenib arm (41% vs. 12% per mRECIST and 19% vs. 7% per RECIST v1.1). The most common grade 1–4 adverse reactions observed in the lenvatinib arm (20%

or more) were hypertension (45%), fatigue (44%), diarrhea (39%), decreased appetite (34%), arthralgia or myalgia (31%), decreased weight (31%), abdominal pain (30%), palmar-plantar erythrodysesthesia (27%), proteinuria (26%), dysphonia (24%), hemorrhagic events (23%), hypothyroidism (21%), and nausea (20%), compared with palmar-plantar erythrodysesthesia (52%), diarrhea (46%), fatigue (36%), hypertension (31%), abdominal pain (28%), decreased appetite (27%), rash (24%), decreased weight (22%), and arthralgia or myalgia (20%) for sorafenib.<sup>12</sup>

The recommended lenvatinib dose for patients with HCC is based on actual body weight and is 12 mg orally once daily in patients 60 kg or greater or 8 mg orally once daily in patients less than 60 kg.<sup>12</sup>

### Pembrolizumab (Keytruda)

On November 9, 2018, the FDA granted accelerated approval to pembrolizumab (Keytruda) for patients with HCC following disease progression on or after sorafenib therapy.<sup>14</sup> The KEYNOTE-224 trial, a single-arm phase 2 multicenter trial, enrolled 104 patients with HCC who were required to have disease progression on or after sorafenib or to be intolerant to sorafenib, have measurable disease, an ECOG PS of 1 or lower, and Child-Pugh Class A liver impairment. Participants received 200 mg pembrolizumab intravenously (IV) every 3 weeks for 2 years or until disease progression, unacceptable toxicity, patient withdrawal, or investigator decision.<sup>15</sup>

Pembrolizumab resulted in a confirmed independent central review–assessed ORR of 17% (95% CI: 11–26), with one complete response (CR) and 17 partial responses (PRs).<sup>15</sup> Response durations ranged from 3.1 to 16.7 months; 89% of responders had response durations of 6 months or longer, and 56% had response durations of 12 months or longer. Forty-six patients (44%) had stable disease, 34 patients (33%) had progressive disease, and 6 patients (6%) did not have a postbaseline assessment on the cutoff date and were considered not to be assessable. Adverse reactions occurring in patients with HCC were similar to those described previously with pembrolizumab; however, there were increased incidences of grade 3 or 4 ascites (8%), immune-mediated hepatitis (2.9%), elevated aspartate aminotransferase (AST) (20%), alanine aminotransferase (ALT) (9%), and hyperbilirubinemia (10%).<sup>14,15</sup>

In contrast to these findings, the results of the confirmatory trial, KEYNOTE-240, showed that the combination of pembrolizumab plus best supportive care for the treatment of patients with advanced HCC who had been previously treated with systemic therapy did not improve PFS or OS compared to the combination

placebo plus best supportive care alone, missing the coprimary endpoints. In a press release on February 19, 2019, Merck stated that “the drug’s continued approval for this indication may be contingent upon the results of confirmatory trials.”<sup>16</sup>

The HCC dosing for pembrolizumab is 200 mg IV every 3 weeks administered over 30 minutes.<sup>14</sup>

### Future Directions

Ramucirumab (Cyramza), a monoclonal antibody targeting vascular endothelial growth factor receptor 2 (VEGFR2), has demonstrated antitumor activity and a manageable adverse-effect profile in patients with advanced HCC.<sup>17</sup> The REACH trial failed to demonstrate a survival advantage for ramucirumab over placebo as second-line therapy following sorafenib treatment in 565 patients with advanced HCC.<sup>18</sup> The REACH-2 trial was a randomized double-blind phase 3 trial comparing ramucirumab 8 mg/kg every 2 weeks to placebo in patients with advanced HCC previously treated with sorafenib and an alpha-fetoprotein concentration of 400 ng/mL or greater.<sup>19</sup> The primary endpoint was OS, with PFS and ORR as secondary outcomes. Ramucirumab significantly improved OS (8.5 months vs. 7.3 months; HR 0.71;  $p = .0199$ ) and PFS (2.8 months vs. 1.6 months; HR 0.452;  $p < .0001$ ) compared to placebo. Fatigue, peripheral edema, hypertension, and decreased appetite were the most frequently reported adverse effects. Ramucirumab could provide another treatment option in the second-line setting in a biomarker-directed population.

The future of HCC management is extremely bright, and several therapeutic targets are in trial phases. COSMIC-312 (NCT03755791) is an ongoing phase 3 trial evaluating the safety and efficacy of cabozantinib in combination with atezolizumab versus sorafenib in adults with advanced HCC who have not received previous systemic anticancer therapy.<sup>20</sup> Other phase 3 trials are evaluating checkpoint inhibition such as BGB-A317 versus sorafenib as front-line treatment in unresectable HCC (NCT03412773) and SHR-1210 in combination with FOLFOX4 (5-fluorouracil, oxaliplatin, leucovorin) versus sorafenib or FOLFOX4 as first-line treatment in advanced HCC (NCT03605706).<sup>21,22</sup>

### Conclusion

HCC is associated with poor outcomes and limited treatment options. Recent FDA approvals of lenvatinib in the first-line treatment setting and cabozantinib and pembrolizumab following treatment with sorafenib provide more treatment options for patients with advanced HCC. Ongoing clinical trials of unique agents and combinations aim to shed light on improving outcomes in HCC. ●●

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#### **Investigational Drug Service: Maintaining Consistency in a Dynamic Field**

##### **Now available**

In an environment where pharmaceutical companies and their investigational products are expected to change frequently, investigational pharmacies should prepare to manage change efficiently. Dr. Krista Wolf, supervisor of the Investigational Drug Service at Oregon Health and Science University, discusses strategies for maintaining standard practices in an evolving system. Attendees will learn how to effectively manage change in order to achieve consistency and success in a changing environment.

#### **To Approve or Not to Approve: Antineoplastic Formulary Considerations**

##### **Wednesday, July 10, 2019**

1 pm EDT/Noon CDT

Knowledge of the drug approvals process for antineoplastic agents is beneficial to practitioners who are delivering cutting-edge treatment to cancer patients. Dr. Dina Benani and Dr. Celia Proctor, both affiliated with the Johns Hopkins Health System, provide insight into the drug approval processes for oncology medications in a health system while considering the economic and clinical factors and comparing the drug approval process for antineoplastic generic and biosimilar agents. Attendees will gain an awareness of the drug approval process and understand approaches to formulary drug approval using a value-based framework.

#### **Bridging the Gap: Understanding Health Literacy**

##### **Wednesday, September 4, 2019**

7 pm EDT/6 pm CDT

Understanding health literacy is integral to providing high-quality care to a wide range of patients. Dr. Rebecca Fahrenbruch will outline how pharmacists can identify health literacy levels in patients and incorporate this knowledge into the patient-pharmacist interaction. Attendees will develop a broad understanding of health literacy, review examples and strategies for creating patient information, and receive suggestions for improving health literacy in practice.

#### **Mid-Career vs. Senior Level for Careers—Changing Pathways**

##### **Wednesday, November 13, 2019**

6 pm EST/5 pm CST

Dr. Dina Dumercy McHenry is the director of pharmacy at Miami Cancer Institute of Baptist Health South Florida and has more than 15 years of experience practicing hematology/oncology in various roles. She will speak about her career path and provide resources for attendees seeking to advance their career. Attendees will develop tools for examining and developing a career path at every stage in their career.

# Board Update

## Looking Ahead to a Bright Future



**Ryan Bookout, PharmD BCOP BCPS**  
**HOPA President (2018-2019)**

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Omaha, NE



Returning to work and preparing for summer, we reflect on HOPA Ahead 2019 and the association's 15th anniversary celebrated at this year's conference in Fort Worth. During this look back, we also reflect on the overwhelming positive growth and change that HOPA has experienced in the past 15 years. Our association has grown to more than 3,000 members, and we now represent a much wider field of pharmacy practice areas and settings. As the association turns 16, we have many reasons to expect HOPA's continued growth and flourishing. One reason is that HOPA is an *inclusive* association. As we grow and evolve, we continue to embrace *all* pharmacists who participate in oncology patient care, no matter what role they play.

### A New Plan

HOPA's leaders have been hard at work revitalizing and reimagining our association's strategic plan. Many of you know that in 2015, we began the work to create a 5-year plan for the association, and that at the end of year 3, we had *completed* our work on the plan, thanks in large part to amazing leaders at every level, volunteers, members, and external partners. As we look ahead, we know that these pillars are firmly established and will provide the structure for our continued growth and success. We are honored to be part of such an amazing association and very thankful for the opportunity to launch a revitalized plan later in 2019.

### New Relationships

HOPA has been fortunate to work with many outstanding affiliate organizations. We are currently working with individuals from other professional associations, patient-facing organizations, affiliate societies in oncology and hematology fields, and our industry partners. Never before in HOPA's history has our association been involved with such a quantity or quality of partnerships. Just one example is the Value of Cancer Care Forum: Pharmacy's Call to Action that we will collaboratively host with the Academy of Managed Care Pharmacy on June 18, 2019, at the National Press Club in Washington, DC.

Our members are representing HOPA in coalitions, collaborations, and consortiums across the country and around the world. If you would like to become more involved in carrying out HOPA's

mission, we encourage you to apply for one or more of the many positions offered through our Volunteer Activity Center, or VAC.

### A New Voice on the Cancer Care Team

Last but not least, as pharmacists, we continue to expand our role on the cancer care team, working together with nurses, physicians, and other healthcare professionals. At the core of the cancer care team, though, are our patients, the people whose strength and courage, challenges and struggles, are our highest concern. We in HOPA want to do more in this area. In the year ahead, we will seek to continue the work of our Patient Outreach Committee and the partnerships it is forging with amazing organizations like the Leukemia and Lymphoma Society, the Pancreatic Cancer Action Network, and the Society for Immunotherapy of Cancer.

### Our Thanks to You

We want to thank every HOPA member for your brilliance, your determination, and your hard work. We thank you for the energy and time that you have given and continue to give to HOPA. Your devotion and volunteerism for this association is amazing and overwhelming. Your drive and ambition have pushed this association outward and upward.

Thank you for the care that you give your patients every day. Thank you for the education that you give to your patients and their families. Know that the heartfelt empathy and sympathy you share with your patients and their families are deeply appreciated.

Thank you for sharing your passion and your knowledge with your students, residents, nurses, advanced practice professionals, physicians, and peers. Thank you for being the best pharmacists taking care of our cancer patients. It is because of you that HOPA has such a bright future and is advancing pharmacy's role on the cancer care team in such meaningful ways.

Have a wonderful summer and take care of yourselves. Remember to recharge your batteries and take time for yourselves to learn, grow, reflect, and just be in the moment. We need your continued drive and motivation for HOPA, but we also want you at your best and refreshed. Go, Team! ●●



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