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Early Detection Saves Lives: Updates on Cancer Screening

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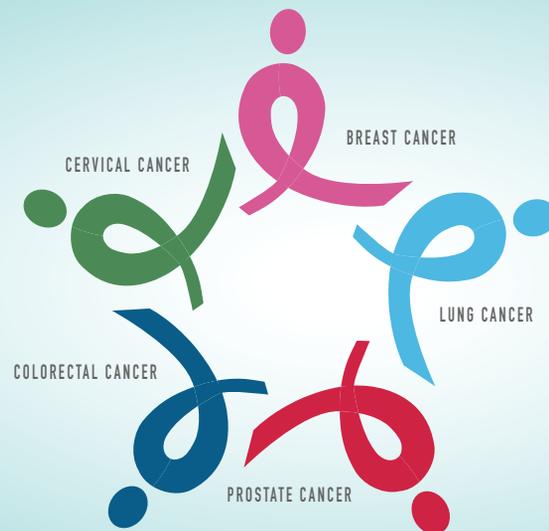
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Pharmacists Optimizing Cancer Care®

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Looking Back, Looking Ahead



Early Detection Saves Lives: Updates on Cancer Screening



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Overall cancer mortality has decreased by 25% from 1990 to 2015 in the United States, which can be attributed to greater awareness of cancer screening in the general population.¹ The American Cancer Society (ACS) and the U.S. Preventive Services Task Force (USPSTF) provide cancer screening recommendations each year, with the aim of increasing the likelihood of benefits and limiting the harms from screening. The annual report updates previous recommendations, provides data on cancer screening rates, and discusses issues related to early cancer detection. Through early detection by screening, death rates have been reduced in cancers of the breast, uterine cervix, colon, rectum, prostate, and lung.

Breast Cancer Screening

Female breast cancer death rates have been decreasing since 1989 in the United States through early detection by mammography.² The goal of screening mammograms is to detect breast cancer early, but this comes with risks because there may be false-positive findings. Providers have debated what age is appropriate for the initiation of a mammography. In 2015, experts offered more guidance on this issue and provided their recommendations in the updated ACS breast cancer screening guidelines. The recommended primary screening exam for average-risk women is an annual mammography starting at age 45. The risk among women aged 40–44 years was lower and more similar to the risk among women in their late 30s, leading the ACS to not make any direct recommendations for screening in this population. Therefore, women aged 40–44 years are encouraged to choose whether to screen earlier than age 45. Women aged 55 or older have the option to transition to biennial screening or continue screening annually. Mammography screening should continue as long as the patient's overall health is good and life expectancy is 10 years or longer. In addition to the discussion on screening mammograms, breast

exams—either self-exams or exams from a medical provider—are no longer recommended by the ACS because research did not show any clear benefit.³

Cervical Cancer Screening

Cervical cancer incidence and mortality rates have markedly decreased over the decades in the United States, with most of the reduction attributed to screening with the Pap test. The number of deaths declined from 2.8 to 2.3 deaths per 100,000 women from 2000 to 2015.⁴ Vaccination and routine cervical cancer screening are essential in preventing this disease: approximately 70% of human papillomavirus (HPV)-related cancer cases can be prevented with vaccination. The Advisory Committee on Immunization Practices (ACIP) revised its HPV vaccine schedule in 2016 from a three-dose schedule to a two-dose schedule for patients younger than 15 years. The change was prompted after antibody responses for the two-dose schedule were shown to be noninferior to those for young women who received all three doses. In addition, the U.S. Food and Drug Administration approved the use of the HPV vaccine in men and women up to age 45; however, no changes in guidelines have been made, and insurance plans may not cover the vaccine administration after age 26.⁵

In 2018, the USPSTF updated its recommendation to offer three screening options for women. Women aged 30–65 years may choose the following screening strategies: Pap-only testing every 3 years, high-risk HPV-only testing every 5 years, or co-testing every 5 years. This differs from recommendations by the American College of Obstetricians and Gynecologists and the American Society for Colposcopy and Cervical Pathology for co-testing every 5 years, with alternative options of Pap-only or HPV-only testing every 3 years. The new recommendation by the USPSTF was implemented after its review of randomized and observational studies. It was noted that both co-testing and high-risk HPV testing offer similar cancer detection rates: each prevents one additional cancer per 1,000 women screened as opposed to Pap-only testing.⁵ The USPSTF continues to recommend triennial cervical cytology for

women aged 21 to 29 years.⁴ The most critical aspect of screening is getting all women screened—regardless of which method is used.

Colorectal Cancer Screening

An accelerated decline in colorectal cancer incidence rates occurred during the past decade, which may be attributed to the increased uptake of screening and removal of precancerous lesions. In the 2018 update, the ACS lowered the age to start screening average-risk people to age 45. This new recommendation was made because of the emergence of new data that showed increasing rates of colorectal cancer in younger populations. The study found that colon and rectal cancer rates had increased by 0.5% to 2% per year from the mid-1990s through 2013 for adults aged 40–54 years. Regular colorectal cancer screening should continue through age 75 if the person is in good health and has a life expectancy of more than 10 years. Different screening options are available, and adults may choose one of the following methods: guaiac-based fecal occult blood test or fecal immunochemical test every year, multitarget stool DNA test every 3 years, flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, or CT colonography every 5 years. For adults older than 85 years, colorectal cancer screening is no longer recommended.⁶

Prostate Cancer Screening

In the United States, the lifetime risk of being diagnosed with prostate cancer is approximately 11%, with a 2.5% lifetime risk of dying. The USPSTF stated in the 2018 update that men aged 55–69 years should decide whether to undergo periodic prostate-specific antigen (PSA) screening for prostate cancer after discussion with their provider. The main difference is the update to the recommendation grade from D in the 2012 USPSTF recommendation to C in

the update. The change in recommendation grade is based on additional evidence that increased the USPSTF's certainty about the reductions in risk of dying of prostate cancer and risk of metastatic disease. Longer-term follow-up of the European Randomized Study of Screening for Prostate Cancer trial found that PSA-based screening for prostate cancer prevents 1.28 men from dying of prostate cancer for every 1,000 men screened. However, men should be advised that screening offers a small potential benefit. Studies continue to demonstrate the harms of PSA-based screening, including false-positive results, overdiagnosis, and overtreatment. The intention of the USPSTF update is to promote the importance of informed decision making prior to screening.⁷

Lung Cancer Screening

Lung cancer is the leading cause of death from cancer in men and women. This tumor type accounted for an estimated 154,050 deaths in 2018, approximately 26% of all cancer deaths in the United States. Among men, mortality rates have declined by 43% since 1990, and among women, mortality rates have declined by 17% since 2002.² In the 2013 ACS lung cancer screening guidelines, the recommendation for screening was unclear. Therefore, the ACS clarified this recommendation in the 2017 update by stating that annual screening for lung cancer with low-dose computed tomography (CT) is recommended in adults aged 55–74 years who have a 30 pack/year smoking history and currently smoke or have quit within the past 15 years.² The USPSTF has a broader age range for lung cancer screening, with recommendations for adults up to age 80 based on modeling studies.⁸

Adults should recognize the importance of cancer screenings and be reminded when they are due for them. By increasing awareness of regular screening, cancer deaths can continue to decline in the United States. ●●

REFERENCES

1. Byers T, Wender RC, Jemal A, Baskies AM, Ward EE, Brawley OW. The American Cancer Society challenge goal to reduce US cancer mortality by 50% between 1990 and 2015: results and reflections. *CA Cancer J Clin.* 2016;66:359-369.
2. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin.* 2018;68:297-316.
3. Oeffinger KC, Fontham ET, Etzioni R, et al.; American Cancer Society. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. *JAMA.* 2015;314:1599-1614.
4. U.S. Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. *JAMA.* 2018;320:674-686.
5. Zhang S, Batur P. Human papillomavirus in 2019: an update on cervical cancer prevention and screening guidelines. *Cleve Clin J Med.* 2019;86:173-178.
6. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin.* 2018;68:250-281.
7. U.S. Preventive Services Task Force, Grossman DC, Curry SJ, et al. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *JAMA.* 2018;319:1901-1913.
8. Moyer VA, U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2014;160:330-338.

Going Above and Beyond in Your Career Following Residency Training



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During the time of year when residency candidate interviews are occurring and residency match day is on the horizon, it is only fitting that residents would begin to reflect on their own personal residency experience and the role that postgraduate training has played in shaping who they are today. After being asked to reflect on my own experience as a resident, I knew I needed to start from the beginning of my career journey. By the ripe age of 7, I had established the goal to become a pharmacist when I grew up. My mom had a few female friends who were community pharmacists and who truly enjoyed their career and the quality of life they were able to have while being full-time pharmacists. I started working at a community pharmacy the day I turned 16 in an effort to gain experience in the field. I always knew I wanted to do something that would help others and have a positive impact on their lives. During my first year of pharmacy school, I transitioned my focus to hospital pharmacy and the opportunity to specialize. Throughout my oncology rotation during my postgraduate year-1 residency at UF Health Jacksonville, I fell in love with the positive and encouraging atmosphere of the UF Health Cancer Center. I then went on to complete a postgraduate year-2 (PGY-2) residency in oncology at the Medical University of South Carolina, where I was challenged daily to learn as much as possible and was engulfed in all the oncology opportunities I could find.

The experience and knowledge I gained as a resident was invaluable. Following my residency, I am still using and continuing to build on the education I obtained. I've had to learn how to create and implement policies and facilitate practice changes in the clinic, both of which are important skills I use in my practice every day. My year as a resident was one of the more challenging of my career thus far, but it also contained some of the most rewarding experiences. According to the American Society of Health-System Pharmacists, the purpose of a pharmacy residency is "to accelerate the resident's growth beyond entry-level professional competence in direct patient care and in practice management, and to further develop leadership skills that can be applied in any position and in any practice setting."¹ I can honestly say that this is exactly what my residencies did for me: they put me years ahead of where I would have been professionally without residency training. In pharmacy school you hone critical thinking skills and learn about

direct patient care and pharmacotherapy. A residency propelled me above and beyond, allowing me to develop my time management, research design, and professional communication skills, as well as providing opportunities in leadership and public speaking.

After securing a PGY-2 residency, the next phase is to find a job postresidency, and my mentors and preceptors assisted me a great deal during the decision-making process. One of the best pieces of advice I received was to interview at more than one place and keep an open mind. I thought I knew what type of position I wanted and where I wanted to practice; however, that opinion changed during my on-site interviews. I accepted my first postresidency position at Baptist Health Lexington in Lexington, KY, where I remain today. I was one of two oncology specialists hired throughout Baptist Health System in Kentucky, which consists of eight hospitals. I was the first oncology pharmacy specialist at Baptist Health Lexington and was given the opportunity to develop my own position in the Cancer Center's medical oncology clinic, gynecologic oncology clinic, and outpatient infusion center. The majority of my time is spent in the outpatient clinic and infusion center; however, I am the liaison between the pharmacy department and the inpatient oncology unit. In our medical oncology clinic and gynecological cancer clinic, we average approximately 100 outpatient visits per day, and in the infusion center we average about 63 patient infusion visits per day. We treat both benign and malignant hematology, oncology, and gynecological cancers. Because we care for patients with a variety of disease states on any given day, each day brings something new.

The most satisfying part of my job is my interaction with patients. I get to know my patients personally during their journey fighting cancer, which allows me to better serve them on an individual basis. Our patients are grateful for everything we do, and they express that gratitude to the entire staff. I have also had the opportunity to initiate the expansion of pharmacy services in the clinics by becoming a readily available resource for the entire staff. Over time, I have become even more involved with the education of our patients and now have separate appointments with patients to discuss their cancer treatment and what to expect throughout their treatment process.

Over the last 6 years, my role has changed numerous times in order to fulfill the needs of our clinic and the patients we serve. My residency training provided me the necessary tools and skills to establish innovative programs and incorporate pharmacy services throughout the Cancer Center. I developed oncology competencies for the staff pharmacists to ensure that they were

(continued on p. 26)

Working to Keep the Lights On in the Era of High-Cost Antineoplastic Treatment: Strategies for Managing Inpatient Drug Administration



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The cost of cancer care has never been higher, and as the U.S. Food and Drug Administration (FDA) continues to approve new drugs, those costs climb higher still. Between August 2018 and July 2019, the FDA approved 17 new antineoplastic therapies.¹ The costs associated with adult cancer treatment in the United States continue to be significant, totaling approximately \$87.2 billion in 2012.² New targeted antineoplastic agents are priced at \$6,000–\$12,000 per month, or approximately \$70,000–\$140,000 annually, with immunotherapy costs even higher.³ Drug acquisition costs are the biggest source of spending in the pharmacy department and can account for approximately 80% of the total budget.⁴ Under a diagnosis-related group payment structure and with these new approvals, total inpatient drug spending is increasing and contributing to rising total hospital expenditures. Independent of the increasing cost of treatment, institutions are working with higher operating costs and changing reimbursement models while also being challenged to provide high-quality, consistent patient care at the lowest possible expense.⁵

Given these staggering statistics, it is imperative to implement cost-saving strategies, maximize reimbursement through use of drug discounts (i.e., federal 340B outpatient drug discount pricing) and avoid diagnosis-related group inpatient reimbursement.⁶ The American Society of Health-System Pharmacists has recommended guidelines for medication management strategies that cover three areas:⁷

- pharmacy-directed activities, such as purchasing, inventory management, and waste reduction
- interdisciplinary activities
- reimbursement and charging strategies.

A survey of 281 cancer institutions confirmed that one strategy includes administering antineoplastic treatment in the outpatient clinic setting. A growing number of published articles on the implementation of such changes by single institutions document the achievement of remarkable cost savings. One study described the implementation of a policy limiting inpatient administration of antineoplastic medication that resulted in decreased numbers of inpatient admissions and associated drug cost savings of approximately \$160,000 annually.⁸ Another report demonstrated drug

cost savings of nearly \$2 million and a cumulative cost savings for a health system of approximately \$3.3 million in a 2-year period.⁹ Shifting the administration of these agents to the outpatient setting benefits both the treating institution and the patient because of pricing structures.

Another cost-saving strategy includes the use of Pharmacy and Therapeutics (P&T) committees to restrict medication usage to specific areas of administration, specialties, or patient populations. One report described the development of a standardized review process with a request form for the use of outpatient-restricted medications.¹⁰ Another institution developed a High-Cost Medication Review Committee, describing a standard process for inpatient high-cost medication approval. This committee was composed of a multidisciplinary team that reviewed inpatient requests based on clinical efficacy and appropriateness, with an expectation that a decision is made within 48 hours. Through the establishment of the review committee, the institution reported a cost savings of approximately \$490,000 annually.¹¹

At our institution, we have implemented a number of these strategies. For example, we routinely transition our chemotherapy regimens to the outpatient setting. Complex hematologic regimens such as R-ICE, R-EPOCH, HyperCVAD, and HIDAC are routinely administered in the outpatient setting. We consistently administer both autologous and allogeneic preparative regimens in the outpatient setting. Our approach has been successful because we have clear guidelines for patients who are receiving outpatient administration, including adequate patient

caregiver support, requirements for proximity to the outpatient infusion center, and a triage line that is available for questions and support. Our outpatient infusion clinic is open 7 days a week and is open until 7 pm on weekdays and 2 pm on weekends. We also use tools such as ambulatory infusion pumps and have in place policies regarding approved line access for outpatient administration of chemotherapy via an ambulatory pump.

Formulary management is a key element to our cost-containing strategy. Our Hematology/Oncology/Bone Marrow Transplant (H/O/BMT) P&T Subcommittee, a multidisciplinary team with hematologists and oncologists serving as voting members, reviews all new drug approvals for clinical efficacy while also evaluating them for cost. Our formulary categorizations include

- addition to formulary without restriction
- addition to formulary with restrictions
- nonformulary not stocked
- nonformulary not allowed.

“Shifting the administration of [neoplastic] agents to the outpatient setting benefits both the treating institution and the patient because of pricing structures.”

This formulary status is reflected in our electronic medical record for medications that are restricted to use in the outpatient setting; a best-practice advisory alert appears upon the entry of outpatient restricted medications. When a medication has been categorized as high cost or restricted to outpatients, we note this on the maintained list that is readily accessible to our team.

If a medication that is restricted to outpatient administration is requested in the inpatient setting, our clinical pharmacist enters the request through an electronic High-Cost Log. Information required in the request includes indication, literature supporting use, potential alternative therapies, and the reason for inpatient administration. This log electronically notifies the cancer care leadership team of the request. The administrator then sends a request, including information about the patient's case and supporting literature, to the H/O/BMT P&T Subcommittee for a vote within 48 hours. If the request is approved by the subcommittee, the administrator approves the electronic log request, thereby notifying our supply chain team to order the medication. After the medication has been ordered, the supply chain team updates the electronic request, and this is communicated to the clinical team pharmacist. This log must be used each time a dose is requested. If the request is denied, the requesting provider is notified, and the patient does not receive the requested medication as an inpatient. This log was initiated in January 2019 and has

been used to process 228 requests in the first 11 months following its initiation. The log has also been instrumental in tracking trends and has resulted in the creation of an approved utilization policy for rituximab. In addition, this approach allows our purchasing team to maintain the minimum amount of stock of these high-cost therapies, making us good stewards of the pharmacy budget.

Engagement of our physician colleagues through our H/O/BMT P&T Subcommittee has been essential to our success. By using evidence-based studies and drug assessment data to review each new medication, we define our utilization up front. We routinely report back and discuss methods for cost reduction, supported by evidence-based research, to propose changes. We also identify physician champions for specific initiatives. Despite these electronic standardizations, the success of our high-cost management program is owed in large part to the activities of our clinical pharmacy team. Their active daily involvement and enforcement of the guidelines has been crucial to the success of these efforts.

By using the outpatient administration process outlined above, formulary management, technological tools, and partnership with the multidisciplinary team, we minimize cost to the institution while continuing to deliver consistent and high-quality patient care. Each of these strategies, if implemented, can be helpful to other institutions seeking to minimize their overall inpatient drug costs. ●●

REFERENCES

1. American Association for Cancer Research. AACR Cancer Progress Report 2019. Available at https://www.cancerprogressreport.org/Documents/AACR_CPR_2019.pdf. Accessed November 27, 2019.
2. Soni A. Top five most costly conditions among adults age 18 and older, 2012: estimates for the U.S. civilian non-institutionalized population. Statistical Brief #471. Agency for Healthcare Research and Quality. April 2015. Available at www.meps.ahrq.gov/mepsweb/data_files/publications/st471/stat471.pdf. Accessed November 27, 2019.
3. Kantarjian HM, Fojo T, Mathisen M, Zwelling LA. Cancer drugs in the United States: justum pretium—the just price. *J Clin Oncol*. 2013;31:3600-3604.
4. NORC at the University of Chicago. Trends in hospital inpatient drug costs: issues and challenges. Final report. October 11, 2016. Available at www.aha.org/content/16/aha-fah-rx-report.pdf. Accessed November 27, 2019.
5. Barr TR, Towle EL. Oncology practice trends from the National Practice Benchmark. *J Oncol Pract*. 2014;10:407-410.
6. Warren A, Shankar A. Oncology transactions and the 340B drug pricing program. *J Oncol Pract*. 2013;9:89-91.
7. ASHP Expert Panel on Medication Cost Management. ASHP guidelines on medication cost management strategies for hospitals and health systems. *Am J Health-Syst Pharm*. 2008;65:1368-1384.
8. Foster AE, Reeves DJ. Inpatient antineoplastic medication administration and associated drug costs: Institution of a hospital policy limiting inpatient administration. *P T*. 2017;42:388-393.
9. McBride A, Campen CJ, Camamo J, et al. Implementation of a pharmacy-managed program for the transition of chemotherapy to the outpatient setting. *Am J Health Syst Pharm*. 2018;75:e246-e258.
10. Lau KM, Derry K, Dalton A, Martino J. Outcomes of inpatient administration of restricted antineoplastic medications at a large academic medical institution. *P T*. 2019;44:481-485.
11. Durvasula R, Kelly J, Schleyer A, Anawalt BD, Somani S, Dellit TH. Standardized review and approval process for high-cost medication use promotes value-based care in a large academic medical system. *Am Health Drug Benefits*. 2018;11:65-73.

Pharmacists' Influence on Immunization in Cancer Patients: Increasing Vaccination Rates and Reducing Mortality from Preventable Diseases



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Immunizations prevent approximately 2–3 million deaths each year and have proven to be a safe and cost effective use of health-care dollars.¹ Measured in light of the federal government's Healthy People 2020 goals, vaccination rates among adults and children are still substandard.² As trusted and accessible members of the health-care profession, pharmacists play a key role in heightening patients' participation in immunizations.³ A meta-analysis by Isenor and colleagues found that patient vaccination rates increased when pharmacists were involved in the immunization process in any capacity: as patient educators, as facilitators of others in the delivery of vaccines to patients, and as administrators of vaccines in the pharmacy.⁴ Every state in the United States now allows for pharmacist-provided immunization in some capacity.⁵ The types of vaccinations allowed and the age of patients that pharmacists can vaccinate differ based on state regulations. HOPA's Quality Oversight Committee, of which I am a member, would like to highlight some successes and potential areas of development for hematology/oncology pharmacists in meeting this essential quality metric for patients with cancer.

Influenza Vaccination

Less than 50% of patients undergoing cancer treatment receive the recommended seasonal influenza vaccine.⁶ Studies have shown varying results in patients' ability to mount serologic responses to influenza vaccinations while they are receiving chemotherapy. A recent population-based study of more than 26,000 Canadian patients with cancer who underwent influenza testing found the influenza vaccine to be effective.⁷ Immunization was associated with reduced hospitalization in patients with laboratory-confirmed influenza. Vaccine effectiveness was higher in patients with solid-tumor versus hematologic malignancies (25% vs. 8%, $p = .015$). No difference was found in influenza vaccine efficacy in patients receiving chemotherapy versus those who were not receiving therapy (14% vs. 22%, $p = .38$).⁷ Because this trial increased the evidence of influenza vaccine effectiveness in patients with cancer, it is important to identify opportunities to improve vaccination rates. A quality improvement project at Massachusetts General Hospital Cancer Center sought to better a 40% influenza vaccination rate in patients receiving parenteral antineoplastic therapy in its clinic.⁸ During a 1-month period, with the oversight of board-certified oncology pharmacists, pharmacy students reviewed the immunization history of 617 patients who were receiving parenteral chemotherapy. One hundred twenty-four patients were interviewed to verify their influenza vaccination status, and 33 patients received the vaccine. With the effort of pharmacists-in-training, influenza

vaccination rates at Massachusetts General Hospital Cancer Center increased to 60.5%.⁸

Post-Hematopoietic Cell Transplant Revaccination

Hematopoietic cell transplant (HCT) patients 6–24 months post-transplant should be immunized against pathogens such as *pneumococcus*, *Haemophilus influenza*, Herpes zoster, *meningococcus*, hepatitis A and B, diphtheria/tetanus toxoids and acellular pertussis, polio, and measles-mumps-rubella.⁹ Hematology/oncology pharmacists play a critical role in ensuring that appropriate vaccination schedules are maintained, with consideration of clinical factors such as active graft-versus-host disease, use of immunosuppressive therapies, and recent administration of chemotherapy or B-cell-depleting treatments.¹⁰ A pharmacist-directed quality improvement pilot project to standardize the timing of HCT vaccinations post-transplant was conducted at Saint Luke's Mountain States Tumor Institute in Boise, ID. Over a 4-month period, a total of 12 patients were given 64 post-transplant vaccinations by an immunization-certified pharmacist. Providers expressed satisfaction with the pharmacy service, and patients experienced shorter wait times and an overall improvement in care. Pharmacists' involvement in this vaccination clinic also decreased potential immunization errors and omissions for HCT patients.¹¹

Human Papillomavirus (HPV) Vaccination

HPV is a sexually transmitted infection that results in approximately 44,000 new cases of HPV-associated cancers (cervical, oropharyngeal, and penile cancers) each year.¹² Common types of HPV (strains 16 and 18) can be prevented with immunization prior to sexual activity. The Advisory Committee on Immunization Practices recommends that the three-dose HPV vaccination series be routinely recommended at age 11 or 12 years.¹³ Data from the 2018 National Immunization Survey—Teen, a report on more than 18,000 adolescents, showed that only 50% of youth have received the HPV vaccine series. Sixty-eight percent of adolescents received one or more HPV vaccine doses.¹⁴ These survey numbers are well below the Healthy People 2020 goal of 80% HPV vaccination for teens.² Pharmacist-led vaccine clinics are an innovative way to increase HPV immunization and reduce the incidence of HPV-associated cancers. Many states, however, allow pharmacists' administration of HPV vaccines only in adult women ages 18 or older. Some states require a physician-specific collaborative practice agreement with the pharmacist, or an HPV vaccine prescription, in order for patients to be vaccinated.¹⁵ Although laws about HPV administration currently vary among states, survey results show that 79% of physicians and 81% of parents approve of pharmacist-guided HPV vaccinations.¹⁶ A pilot of pharmacy-located HPV vaccination clinics was recently conducted at pharmacies in North Carolina, Michigan, Iowa, Kentucky, and Oregon. Barriers to expansion of this pharmacy vaccination

program included third-party billing reimbursement practices and clinics' limited affiliation with primary care and specialty clinics (and therefore a decrease in the number of referrals for vaccination).¹⁷ Opportunity exists for hematology/oncology pharmacists to increase legislators' and the public's awareness of pharmacist-provided HPV vaccination services for this preventable disease.

Conclusion

Nationally, vaccination rates continue to be a high-priority quality metric among multiple stakeholders, including public health,

payer, and medical organizations. Improvements in these metrics are dependent on changes at local practice sites and organizations led by individuals who are responsible for clinical operations and are providing direct care for patients. Pharmacists and pharmacists-in-training are in a prime position to make a substantial impact in these metrics at local practices and organizations. By receiving appropriate vaccination training, augmenting documentation of vaccine doses in the electronic health record, and collaborating with local providers and clinics, pharmacists can contribute significantly to thwarting preventable infections and cancers. ●●

REFERENCES

- World Health Organization (WHO). Immunization. Available at <https://www.who.int/topics/immunization/en/>. Accessed December 2, 2019.
- Centers for Disease Control and Prevention. Division for Heart Disease and Stroke Prevention. Healthy People 2020. Washington, DC. Available at <https://www.cdc.gov/dhdsp/hp2020.htm>. Accessed December 2, 2019.
- American Society of Health-System Pharmacists Council on Professional Affairs. ASHP guidelines on the pharmacist's role in immunization. *Am J Health Syst Pharm*. 2003;60:1371-1377.
- Isenor JE, Edwards NT, Alia TA, et al. Impact of pharmacists as immunizers on vaccination rates: a systematic review and meta-analysis. *Vaccine*. 2016;34:5708-5723.
- Immunization Action Coalition. State Information. States Authorizing Pharmacists to Vaccinate. Available at <https://www.immunize.org/laws/pharm.asp>. Accessed December 2, 2019.
- Loulergue P, Mir O, Alexandre J, et al. Low influenza vaccination rate among patients receiving chemotherapy for cancer. *Ann Oncol*. 2008;19:1658.
- Blanchette PS, Chung H, Pritchard KI, et al. Influenza vaccine effectiveness among patients with cancer: a population-based study using health administrative and laboratory testing data from Ontario, Canada. *J Clin Oncol*. 2019;37:2795-2804.
- Kim EB, Zangardi M, Rostamjad L, et al. Impact of a student pharmacist-directed pilot intervention on influenza vaccination documentation and administration rates in older adults receiving parenteral anticancer therapy. *J Clin Oncol*. 2019;37(27_suppl):abstract 71.
- Centers for Disease Control and Prevention. Vaccine Recommendations and Guidelines of the ACIP [Advisory Committee on Immunization Practices]. Available at <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html>. Accessed December 2, 2019.
- Clemmons AB, Alexander M, DeGregory K, et al. The hematopoietic cell transplant pharmacist: roles, responsibilities, and recommendations from the ASBMT Pharmacy Special Interest Group. *Biol Blood Marrow Transplant*. 2018;24:914-922.
- Pence S, Mancini R. Pharmacist-run vaccination and medication management service for patients after bone marrow transplant. *J Hematol Oncol Pharm*. 2015;5:8-11.
- Centers for Disease Control and Prevention. HPV and Cancer. Available at <https://www.cdc.gov/cancer/hpv/index.htm>. Accessed December 2, 2019.
- Meites E, Szilagyi PG, Chesson HW, et al. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2019;68:698-702.
- Walker TY, Elam-Evans LD, Yankey D, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years—United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68:718-723.
- Brewer NT, Chung JK, Baker HM, et al. Pharmacist authority to provide HPV vaccine: novel partners in cervical cancer prevention. *Gynecol Oncol*. 2014;132:S3-8.
- Shah PD, Calo WA, Marciniak MW, et al. Support for pharmacist-provided HPV vaccination: national surveys of US physicians and parents. *Cancer Epidemiol Biomarkers Prev*. 2018;27:970-978.
- Calo WA, Shah PD, Gilkey MB, et al. Implementing pharmacy-located HPV vaccination: findings from pilot projects in five U.S. states. *Hum Vaccin Immunother*. 2019;15:1831-1838.

Selinexor: A Nuclear Export Inhibitor for Treating Relapsed or Refractory Multiple Myeloma



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Despite significant advances in therapy for multiple myeloma (MM) in recent years, it continues to be an incurable hematologic malignancy. MM primarily affects the elderly, with a median age of diagnosis of 69 and an estimate of 32,000 new diagnoses in 2019.¹ MM is characterized by uncontrolled proliferation of clonal plasma cells. Treatment generally includes an induction regimen, autologous transplant for eligible patients, and maintenance therapy. Although transplant gives patients the best chance for overall survival, all patients are expected ultimately to relapse. In the relapse setting, agents include proteasome inhibitors (bortezomib, carfilzomib, ixazomib), immunomodulatory agents (thalidomide, lenalidomide, pomalidomide), alkylating agents (cyclophosphamide, bendamustine), and/or monoclonal antibodies (daratumumab, elotuzumab).^{1,2} Daratumumab is an anti-CD38 monoclonal antibody approved for use in newly diagnosed patients and relapsed or refractory patients.³ Elotuzumab is a SLAMF7-directed monoclonal antibody approved for use in the relapsed setting.⁴ Despite these treatments, development of resistance continues.

A cell has various proteins moving in and out of the nucleus to and from the cytoplasm. Exportin-1 (XPO-1) is a karyopherin, a family of proteins that transport molecules between the nucleus and cytoplasm.^{5,6} In normal cells, XPO-1 is essential in maintaining homeostatic levels of proteins and messenger RNAs (mRNAs).⁶ These proteins include tumor suppressor proteins (TSPs) and oncogenic mRNAs. Overexpression of XPO-1 in cancer cells inactivates TSPs by excluding them from the nucleus.⁶ In addition, this overexpression leads to increased transport of oncogenic mRNAs to the cytoplasm where translation and oncogenic protein production occurs.⁷ XPO-1 is highly expressed in patients with MM, particularly in patients resistant to bortezomib.⁸ Furthermore, high expression of XPO-1 is associated with a poor prognosis.⁸

Clinical Trial

Selinexor (Xpovio) is an oral small-molecule nuclear export inhibitor that targets XPO-1 and is approved for use in patients who have received at least two proteasome inhibitors, two immunomodulatory agents, and an anti-CD38 monoclonal antibody.⁹ Selinexor inhibits XPO-mediated nuclear export of TSPs and oncogenic mRNAs, resulting in G1/G2 arrest and apoptosis.¹⁰

Selinexor received accelerated approval in combination with dexamethasone following its evaluation in the STORM trial. STORM was a multicenter single-arm open-label study of patients with relapsed or refractory MM. STORM part 2 included 122 patients who had previously received three or more antimyeloma treatment regimens. Patients who were enrolled

had to be documented as refractory (not intolerable) to at least three treatment regimens—including an alkylating agent, glucocorticoids, bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab—and to their last line of therapy.⁹ Of the 122 patients, 83 patients had relapsed or refractory MM that was documented as being refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab.⁹ These patients were dosed with selinexor 80 mg and dexamethasone 20 mg on days 1 and 3 of each week.^{9,11} The major efficacy outcome was overall response rate (ORR). The accelerated approval granted for selinexor was based on this prespecified subgroup of 83 patients who were documented as pentarefractory because the benefit-risk ratio appeared greater in this more heavily pretreated population compared to the overall trial population.⁹ Median time to first response was 4 weeks, and median duration of treatment was nearly 4 months.^{9,11}

Safety

Many people in the relapsed or refractory MM population struggle with side effects from previous therapy, particularly peripheral neuropathy. Selinexor is not associated with any peripheral neuropathy, making it a particularly attractive option for these patients. Selinexor does have side effects that can be managed with dose reductions and supportive therapies.

The overall incidence of nausea was 72%, with 10% of patients experiencing grade 3 or 4 nausea.^{9,11} It is important to take prophylactic measures with a 5-HT₃ antagonist because the median time of onset for nausea is 3 days, and for vomiting, 5 days.⁹ If nausea continues, an additional anti-nausea agent should be added, such as an NK-1 receptor antagonist like rolapitant. Fosaprepitant and aprepitant should be avoided, given the significant interaction with high-dose dexamethasone, which can cause additional side effects, including hyperglycemia and edema. Another successful anti-nausea agent is olanzapine, an atypical antipsychotic, which can be initiated at low doses, 2.5–5 mg daily, and can be increased to up to 10 mg daily. If patients experience grade 3 nausea despite these interventions, the dose should be interrupted and the medication restarted at the next dose level after nausea has decreased to grade 1 or better.⁹

Thrombocytopenia is a common side effect of selinexor used in relapsed or refractory MM patients. Any-grade thrombocytopenia was 74%, with 61% of those patients having grade 3 or 4.^{9,11} Median time to onset is 22 days, with bleeding occurring in 23% of patients.^{9,11} Platelet counts should be monitored at baseline and throughout therapy. If the platelet count drops to <75,000/mcL, selinexor should be reduced by one dose level. If bleeding is present, selinexor should be withheld and restarted at the next dose level.⁹ Many MM patients starting therapy may have grade 2 or higher thrombocytopenia due to their disease. It's important to distinguish these patients from the cases addressed

in the dose-modification guidelines. Dose modifications contained in the package insert pertain to platelet counts *while* the patient is on therapy, not at the start of therapy. Any patient who starts treatment with a platelet count of <75,000/mcL should begin treatment at the full dose to receive the maximum benefit. Before dose modifications are made for patients with a low platelet count while on therapy, a conversation about risk versus benefit and the extent of the patient's disease should be held with the oncologist.

An atypical side effect of this oral targeted agent is hyponatremia. Median time to onset is 8 days; thus it is important to monitor sodium levels at baseline and during treatment. It is important to correct sodium levels for concurrent hyperglycemia.⁹ Hyponatremia should be treated per institutional guidelines. Some patients may benefit from taking 1 gram of sodium three times per day to maintain appropriate sodium levels while they are on therapy.

Other reported side effects (all grades) include fatigue (73%), anemia (59%), anorexia (53%), weight decrease (47%), diarrhea (44%), constipation (25%), and upper respiratory tract infections (21%).⁹

The rate of treatment discontinuation because of adverse events was 27%.⁹ Fifty-three percent of patients had a reduction in selinexor dose, and 65% had a dose interruption.⁹ It is therefore common for patients to require a dose reduction or interruption (or both) while on therapy. It is important to note, however, that patients benefit most from therapy when they start at the full dose. Because their disease is pentarefractory and is progressing

rapidly, full doses of selinexor will provide the best chance for the patient to achieve a response. If the patient experiences side effects, the dose can be adjusted for better tolerability.

Currently, no drug interactions have been reported with selinexor.

How Xpovio Is Supplied

Xpovio comes in dose packs for each dose level.⁹ The starting dose is 80 mg twice weekly. The first dose reduction is 100 mg weekly, the second reduction is 80 mg weekly, and the last recommended dose reduction is 60 mg weekly.⁹ Further dose reductions are not recommended because patients would likely not benefit from therapy. All dose packs contain 20-mg tablets. Therefore, if a patient starts on a full dose of 80 mg twice weekly and requires a dose reduction, the patient can continue to use the current dose pack with instructions of how many 20-mg tablets to take before getting a new dose pack of 100-mg dosed weekly.

Future Directions

Selinexor is currently undergoing clinical trials for use in a number of other disease states, including gastrointestinal stromal tumor, soft tissue sarcomas, non-small-cell lung cancer, non-Hodgkin lymphoma, acute myeloid leukemia, breast cancer, diffuse large B-cell lymphoma, and a number of other malignancies.¹² ●●

Disclosure

Sara Moran Smith is a speaker for Karyopharm Therapeutics.

REFERENCES

- Peterson TJ, Orozco J, Buege M. Selinexor: a first-in-class nuclear export inhibitor for management of multiply relapsed multiple myeloma. *Ann Pharmacother*. December 2, 2019. doi:10.1177/1060028019892643. [Epub ahead of print]
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. Version 2.2020 (October 9, 2019). Available at https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed December 8, 2019.
- Darzalex [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2019.
- Empliciti [package insert]. Princeton, NJ: Bristol-Myers Squibb Co.; 2015.
- Das A, Wei G, Parikh K, Liu D. Selective inhibitors of nuclear export (SINE) in hematological malignancies. *Exp Hematol Oncol*. 2015;4:7.
- Sun Q, Chen X, Zhou Q, Burstein E, Yang S, Jia D. Inhibiting cancer cell hallmark features through nuclear export inhibition. *Signal Transduct Target Ther*. 2016;1:16010.
- Culjkovic-Kraljacic B, Borden KL. Aiding and abetting cancer: mRNA export and the nuclear pore. *Trends Cell Biol*. 2013;23:328-335.
- Tai YT, Landesman Y, Acharya C, et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. *Leukemia*. 2014; 28(1):155-165.
- Xpovio [package insert]. Newton, MA: Karyopharm Therapeutics Inc.; 2019
- Gandhi UH, Senapedis W, Baloglu E, et al. Clinical implications of targeting XPO1-mediated nuclear export in multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2018;18:335-345.
- Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med*. 2019;381:727-738.
- U.S. National Library of Medicine. ClinicalTrials.gov. Available at <https://www.clinicaltrials.gov/>. Accessed December 8, 2019.

Pharmacy Residents' Mental Wellness: Why and How to Prioritize Resilience in Residency



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In recent years, discussions about the overall wellness of health-care providers and the effect that it may have on patient care have dominated national professional organizations.¹ Although burnout among healthcare providers, including pharmacists, is not a new phenomenon, minimal guidance on promoting wellness has been given to new pharmacists to help them prevent burnout throughout a career.

The term *burnout* was coined in 1974 by H. J. Freudenberger to describe the effects of long-term exhaustive stress associated with one's occupation.² The characteristics include visible exhaustion and fatigue, sleeplessness, frustration, paranoia about one's colleagues, and inflexibility. In 2019, the World Health Organization (WHO) announced that burnout would be updated in the International Classification of Diseases (ICD-11) in 2022 to a syndrome "characterized by feelings of energy depletion or exhaustion, increased mental distance from one's job, or feelings of negativism or cynicism related to one's job, and reduced professional efficacy."³ Similar to Freudenberger, WHO recognizes the correlation between prolonged occupational stress and burnout.

Le and Young evaluated the stress experienced by pharmacy residents using a questionnaire that included the 10-item Perceived Stress Score (PSS10) and the Multiple Affect Adjective Checklist-Revised (MAACL-R).⁴ The PSS10 is a validated tool used to evaluate perceived stress on a scale of 0 to 40, where higher scores correlate with higher perceived stress levels. The MAACL-R is a licensed test used to evaluate the "affect of individuals; specifically depression, anxiety, hostility, and dysphoria." The PSS10 results showed a mean \pm SD perceived stress level of 19 ± 5.90 and a statistically significant correlation between elevated PSS10 scores and a work week longer than 60 hours. According to the MAACL-R results, working more than 60 hours per week was also statistically significantly correlated with depression, hostility, and dysphoria. Elevated PSS10 scores were correlated with statistical significance in relation to anxiety, depression, hostility, and dysphoria.

The increased stress on pharmacy residents can have serious adverse effects on both residents and patients. In the United

States, depression affects about 7% of the general population but affects 30% of medical residents.^{5,6} Although the data on pharmacy residents do not yet exist, given their strenuous training, it is likely that they also have an increased incidence of depression. In 2004, the aggregate suicide rate ratio among male and female physicians compared to the general population was 1.41 (95% confidence interval [CI], 1.21–1.65) and 2.27 (95% CI, 1.90–2.73), respectively.⁷ Reports of medical resident suicides are regrettably easy to find, and in 2011, a pharmacy resident in South Carolina took her own life.⁸ Despite the obvious negative impact on the individual resident, patients are also potentially at risk. Le and Young evaluated the relationship between pharmacy residents' stress and medication errors.⁹ Residents were asked to respond to the PSS10 and self-report medication errors. Perceived stress scores were positively correlated with self-reported medication errors ($p < .001$) among all residents surveyed.

At West Virginia University (WVU) Medicine, a Pharmacy Residency Wellness Program was designed to educate residents about wellness, provide them with the tools to help combat burnout, and remove the stigma associated with mental illness. The program began as a small session hosted by two preceptors, in which the preceptors provided anecdotes about their own experiences as well as tools they used to cope with stress. The program was expanded after residents gave positive feedback.

The first formal session was an introduction to the wellness program that included the reasons for implementing the program (outlined above), along with important information about WVU Medicine's Employee Assistance Program, mental health resources in the community, and stories of preceptors' personal experiences, all of which helped to remove the stigma associated with mental illness.

The director of the SupportingYOU Second Victim program at WVU Medicine Children's Hospital spoke with the residents and preceptors about that program. WVU Health Sciences Building Wellness Center staff provided presentations by a neuroscientist, a clinical therapist, and a yoga instructor, who educated residents and preceptors on mindfulness and meditation, covering the scientific evidence for practicing meditation and instruction on yoga poses; a meditation session was also included. The clinical therapist discussed different types of mental health care, mental illness stereotyping, and the physiological responses to stress. Three preceptors collaborated to create an activity to help residents name their values and target their actions to match those values, both at work and at home. Members from the pediatric supportive care team discussed death and dying with the residents and preceptors. Future sessions will cover exercise, faith, sleep hygiene, financial health, and career transitions. We are incredibly lucky to have the support from our leadership and department to develop and maintain a wellness program.

(continued on p. 20)

NOT ALL FOLLICULAR LYMPHOMA IS THE SAME.

NEITHER ARE ALL FOLLICULAR LYMPHOMA TREATMENTS.

Indication

GAZYVA, in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, is indicated for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma (FL).

Important Safety Information

BOXED WARNINGS: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- **Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation**
- **Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA**

Contraindications

- GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g. anaphylaxis) to obinutuzumab or to any of the excipients, or serum sickness with prior obinutuzumab use

Additional Warnings and Precautions

- **Infusion Reactions:** Premedicate patients with glucocorticoid, acetaminophen, and anti-histamine. Monitor patients closely during infusions. Interrupt or discontinue infusion for reactions
- **Hypersensitivity Reactions Including Serum Sickness:** Discontinue GAZYVA permanently

Please see the following pages for additional Important Safety Information and the brief summary of the full Prescribing Information, including BOXED WARNINGS.



GAZYVA[®]

obinutuzumab
injection | 1,000mg/40mL

It's time to consider a GAZYVA regimen

For more information, visit GAZYVA.com

Important Safety Information (cont'd)

Additional Warnings and Precautions (cont'd)

- **Tumor Lysis Syndrome (TLS):** Anticipate tumor lysis syndrome; premedicate with anti-hyperuremics and adequate hydration especially for patients with high tumor burden, high circulating lymphocyte count or renal impairment. Correct electrolyte abnormalities, provide supportive care, and monitor renal function and fluid balance
- **Infections:** Monitor for infection during and after treatment
- **Neutropenia:** Monitor for infection and promptly treat
- **Thrombocytopenia:** Monitor platelet counts and for bleeding. Management of hemorrhage may require blood product support
- **Immunization:** Do not administer live virus vaccines prior to or during GAZYVA treatment

Additional Important Safety Information

- The most common adverse reactions (incidence $\geq 10\%$ and $\geq 2\%$ greater in the GAZYVA treated arm) in previously untreated NHL were infusion reactions (72%), neutropenia (53%), upper respiratory tract infection (50%), cough (35%), constipation (32%), diarrhea (30%), headache (18%), herpesvirus infection (18%), arthralgia (16%), insomnia (15%), pneumonia (14%), thrombocytopenia (14%), decreased appetite (14%), alopecia (13%) and pruritus (11%)

You are encouraged to report side effects to Genentech and the FDA. You may contact Genentech by calling 1-888-835-2555. You may contact the FDA by visiting www.fda.gov/medwatch, or calling 1-800-FDA-1088.

GAZYVA® (obinutuzumab) injection, for intravenous use

Initial U.S. Approval: 2013

This is a brief summary of information about GAZYVA. Before prescribing, please see full Prescribing Information.

WARNING: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including GAZYVA. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with GAZYVA. Discontinue GAZYVA and concomitant medications in the event of HBV reactivation [see Warnings and Precautions (5.1)].
- Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving GAZYVA [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

GAZYVA, in combination with chlorambucil, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia [see Clinical Studies (14.1)].

1.2 Follicular Lymphoma (FL)

GAZYVA, in combination with bendamustine followed by GAZYVA monotherapy, is indicated for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen [see Clinical Studies (14.2)].

GAZYVA, in combination with chemotherapy followed by GAZYVA monotherapy in patients achieving at least a partial remission, is indicated for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma [see Clinical Studies (14.2)].

4 CONTRAINDICATIONS

GAZYVA is contraindicated in patients with known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or to any of the excipients, or serum sickness with prior obinutuzumab use [see Warnings and Precautions Section (5.4)].

5 WARNINGS AND PRECAUTIONS

5.1 Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies such as GAZYVA. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with GAZYVA. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with GAZYVA. HBV reactivation has been reported for other CD20-directed cytolytic antibodies following completion of therapy.

In patients who develop reactivation of HBV while receiving GAZYVA, immediately discontinue GAZYVA and any concomitant chemotherapy and institute appropriate treatment. Resumption of GAZYVA in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming GAZYVA in patients who develop HBV reactivation.

5.2 Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, was observed in patients treated with GAZYVA. Consider the diagnosis of PML in any patient presenting with new onset or changes to preexisting neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue GAZYVA therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

5.3 Infusion Reactions

GAZYVA can cause severe and life-threatening infusion reactions. Sixty-five percent of patients with CLL experienced a reaction to the first 1000 mg of GAZYVA infused. Thirty-eight percent of patients with relapsed or refractory NHL and 60% of patients with previously untreated NHL experienced a reaction on Day 1 of GAZYVA infusion. Infusion reactions can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, laryngeal edema). The most frequently reported symptoms include nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills [see Adverse Reactions (6.1)].

Premedicate patients with acetaminophen, antihistamine, and a glucocorticoid. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for infusion reactions as needed. Closely monitor patients during the entire infusion. Infusion reactions within 24 hours of receiving GAZYVA have occurred [see Dosage and Administration (2)].

For patients with any Grade 4 infusion reactions, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction: Stop the GAZYVA infusion. Permanently discontinue GAZYVA therapy. For patients with Grade 1, 2, or 3 infusion reactions: Interrupt GAZYVA for Grade 3 reactions until resolution of symptoms. Interrupt or reduce the rate of the infusion for Grade 1 or 2 reactions and manage symptoms [see Dosage and Administration (2)].

For patients with preexisting cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period since they may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the GAZYVA infusion reaction. Consider withholding antihypertensive treatments for 12 hours prior to, during each GAZYVA infusion, and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their antihypertensive medication as is suggested here.

5.4 Hypersensitivity Reactions Including Serum Sickness

Hypersensitivity reactions have been reported in patients treated with GAZYVA. Signs of immediate-onset hypersensitivity included dyspnea, bronchospasm, hypotension, urticaria and tachycardia. Late-onset hypersensitivity diagnosed as serum sickness has also been reported, with symptoms that include chest pain, diffuse arthralgia and fever. Hypersensitivity reactions may be difficult to clinically distinguish from infusion related reactions. However, hypersensitivity very rarely occurs with the first infusion and, when observed, often occurs after previous exposure. If a hypersensitivity reaction is suspected during or after an infusion, the infusion must be stopped and treatment permanently discontinued. Patients with known hypersensitivity reactions to GAZYVA, including serum sickness, must not be retreated.

5.5 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), including fatal cases, has been reported in patients receiving GAZYVA. Patients with high tumor burden, high circulating lymphocyte count ($> 25 \times 10^9/L$) or renal impairment are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of GAZYVA [see Dosage and Administration (2.3)].

During the initial days of GAZYVA treatment, monitor the laboratory parameters of patients considered at risk for TLS. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

5.6 Infections

Fatal and serious bacterial, fungal, and new or reactivated viral infections can occur during and following GAZYVA therapy. When GAZYVA is administered with chemotherapy followed by

GAZYVA monotherapy, Grade 3 to 5 infections have been reported in up to 8% of patients during combination therapy, up to 13% of patients during monotherapy, and up to 8% of patients after treatment [see Adverse Reactions (6.1)]. Do not administer GAZYVA to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection.

In GALLIUM, more Grade 3 to 5 infections were reported in the recipients of GAZYVA and bendamustine (117/410 patients, 29%), as compared to GAZYVA plus CHOP or CVP (43/281 patients, 15%). More fatal infections were reported in patients treated with GAZYVA and bendamustine (3%), as compared to GAZYVA plus CHOP or CVP ($< 1\%$), including during the monotherapy phase and after completion of treatment.

5.7 Neutropenia

Severe and life threatening neutropenia, including febrile neutropenia, has been reported during treatment with GAZYVA. Monitor patients with Grade 3 to 4 neutropenia frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Consider administration of granulocyte colony-stimulating factors (G-CSF) in patients with Grade 3 or 4 neutropenia.

Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days).

Consider dose delays in the case of Grade 3 or 4 neutropenia. Patients with severe and long lasting (> 1 week) neutropenia are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Consider antiviral and antifungal prophylaxis.

5.8 Thrombocytopenia

Severe and life threatening thrombocytopenia has been reported during treatment with GAZYVA in combination with chemotherapy. Fatal hemorrhagic events have been reported in patients with NHL and CLL treated with GAZYVA in combination with chemotherapy, including during Cycle 1.

Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider subsequent dose delays of GAZYVA and chemotherapy or dose reductions of chemotherapy. Transfusion of blood products (i.e., platelet transfusion) may be necessary. Consider withholding concomitant medications, which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.

5.9 Immunization

The safety and efficacy of immunization with live or attenuated viral vaccines during or following GAZYVA therapy have not been studied. Immunization with live virus vaccines is not recommended during treatment and until B-cell recovery.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hepatitis B virus reactivation [see Warnings and Precautions (5.1)]
- Progressive multifocal leukoencephalopathy [see Warnings and Precautions (5.2)]
- Infusion reactions [see Warnings and Precautions (5.3)]
- Hypersensitivity reactions including serum sickness [see Warnings and Precautions (5.4)]
- Tumor lysis syndrome [see Warnings and Precautions (5.5)]
- Infections [see Warnings and Precautions (5.6)]
- Neutropenia [see Warnings and Precautions (5.7)]
- Thrombocytopenia [see Warnings and Precautions (5.8)]

6.1 Clinical Trial 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.

Summary of Clinical Trial Experience in Chronic Lymphocytic Leukemia

The data described in Tables 4-5 below are based on a safety population of 773 previously untreated patients with CLL in the CLL11 study. Patients were treated with chlorambucil alone, GAZYVA in combination with chlorambucil, or rituximab product in combination with chlorambucil. The Stage 1 analysis compared GAZYVA in combination with chlorambucil vs. chlorambucil alone, and Stage 2 compared GAZYVA in combination with chlorambucil vs. rituximab product in combination with chlorambucil. Adverse reaction rates and laboratory abnormalities from the Stage 2 phase are presented below and are consistent with the

rates in Stage 1. In addition to the adverse reactions observed in Stage 2, in Stage 1 back pain (5% vs. 2%), anemia (12% vs. 10%) and cough (10% vs. 7%) were observed at a higher incidence in the obinutuzumab treated patients. The incidence of Grade 3 to 4 back pain (< 1% vs. 0%), cough (0% vs. < 1%) and anemia (5% vs. 4%) was similar in both treatment arms. With regard to laboratory abnormalities, in Stage 1 hyperkalemia (33% vs. 18%), creatinine increased (30% vs. 20%) and alkaline phosphatase increased (18% vs. 11%) were observed at a higher incidence in patients treated with obinutuzumab with similar incidences of Grade 3 to 4 abnormalities between the two arms.

Patients received three 1000 mg doses of GAZYVA on the first cycle and a single dose of 1000 mg once every 28 days for 5 additional cycles in combination with chlorambucil (6 cycles of 28 days each in total). In the last 140 patients enrolled, the first dose of GAZYVA was split between day 1 (100 mg) and day 2 (900 mg) [see *Dosage and Administration (2.1)*]. In total, 81% of patients received all 6 cycles (of 28 days each) of GAZYVA-based therapy.

The most common adverse reactions (incidence ≥ 10% observed in patients with CLL in the GAZYVA containing arm were infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, nausea, and diarrhea.

The most common Grade 3 to 4 adverse reactions (incidence ≥ 10% observed in patients with CLL in the GAZYVA containing arm were neutropenia, infusion reactions, and thrombocytopenia.

Table 4 Summary of Adverse Reactions Reported in ≥ 5% of Patients with CLL and at Least 2% Greater in the GAZYVA Treated Arm (Stage 2)

Body System Adverse Reactions	GAZYVA + Chlorambucil n = 336		Rituximab product + Chlorambucil n = 321	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
Injury, Poisoning and Procedural Complications				
Infusion Related Reaction	66	20	38	4
Blood and Lymphatic System Disorders^a				
Neutropenia	38	33	32	28
Thrombocytopenia	14	10	7	3
Leukopenia	6	4	2	< 1
General Disorders and Administration Site Conditions				
Pyrexia	9	< 1	7	< 1
Gastrointestinal Disorders				
Diarrhea	10	2	8	< 1
Constipation	8	0	5	0
Infections and Infestations				
Nasopharyngitis	6	< 1	3	0
Urinary Tract Infection	5	1	2	< 1

^a Adverse reactions reported under "Blood and lymphatic system disorders" reflect those reported by investigator as clinically significant.

Table 5 Post-Baseline Laboratory Abnormalities by CTCAE Grade in ≥ 5% of Patients with CLL and at Least 2% Greater in the GAZYVA Treated Arm (Stage 2)

Laboratory Abnormalities	GAZYVA + Chlorambucil n = 336		Rituximab product + Chlorambucil n = 321	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
Hematology				
Neutropenia	76	46	69	41
Lymphopenia	80	39	50	16
Leukopenia	84	35	62	16
Thrombocytopenia	48	13	40	8
Anemia	39	10	37	10
Chemistry				
Hypocalcemia	37	3	32	< 1
Hypokalemia	14	1	10	< 1
Hyponatremia	26	7	18	2
AST/SGOT increased	27	2	21	< 1
ALT/SGPT increased	28	2	21	1
Hypoalbuminemia	23	< 1	16	< 1

Summary of Clinical Trial Experience in Non-Hodgkin Lymphoma
GADOLIN

The GADOLIN study evaluated safety in 392 patients with relapsed or refractory NHL, including FL (81%),

small lymphocytic lymphoma and marginal zone lymphoma (a disease for which GAZYVA is not indicated), who did not respond to or progressed within 6 months of treatment with rituximab product or a rituximab product-containing regimen. In the population of patients with FL, the profile of adverse reactions was consistent with the overall NHL population. Patients were treated with either GAZYVA in combination with bendamustine, followed by GAZYVA monotherapy in patients that have not progressed, or with bendamustine alone.

Patients randomized to the GAZYVA + bendamustine arm received three weekly 1000 mg doses of GAZYVA in the first cycle and a single dose of 1000 mg once every 28 days for 5 additional cycles in combination with bendamustine 90 mg/m² on Days 1 and 2 in all 6 cycles. Patient randomized to the bendamustine alone arm received 120 mg/m² on Days 1 and 2. This regimen continued for 6 cycles of 28 days in duration. For patients who did not progress on GAZYVA in combination with bendamustine, a single dose of 1000 mg GAZYVA monotherapy was given every two months until progression or for a maximum of two years. During combination therapy with GAZYVA and bendamustine, 79% of patients received all 6 treatment cycles of GAZYVA and 76% received all 6 treatment cycles of bendamustine compared to 67% of patients in the bendamustine alone arm.

The most common adverse reactions (incidence ≥ 10% observed in GADOLIN in the GAZYVA containing arm were infusion reactions, neutropenia, nausea, fatigue, cough, diarrhea, constipation, pyrexia, thrombocytopenia, vomiting, upper respiratory tract infection, decreased appetite, arthralgia, sinusitis, anemia, asthenia and urinary tract infection.

The most common Grade 3 to 4 adverse reactions (incidence ≥ 10% observed in GADOLIN in the GAZYVA containing arm were neutropenia, thrombocytopenia and infusion reactions.

Table 6 Summary of Adverse Reactions Reported in ≥ 5% of Patients with Relapsed or Refractory NHL and at Least 2% Greater in the GAZYVA plus Bendamustine Followed by GAZYVA Monotherapy Treated Arm (GADOLIN)

Body System Adverse Reactions	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 194		Bendamustine n = 198	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
Injury, Poisoning and Procedural Complications				
Infusion Related Reaction ^a	69	11	63	6
Blood and Lymphatic System Disorders				
Neutropenia	35	33	28	26
Gastrointestinal Disorders				
Constipation	19	0	16	0
Dyspepsia	5	0	3	0
General Disorders and Administration Site Conditions				
Pyrexia	18	1	14	0
Asthenia	11	1	8	0
Infections and Infestations				
Upper Respiratory Tract Infection	13	2	8	1
Sinusitis	12	1	5	0
Urinary Tract Infection	10	3	6	0
Nasopharyngitis	9	0	4	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	12	0	5	0
Pain in Extremity	9	1	4	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	26	0	17	0
Nasal Congestion	7	0	2	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	9	0	6	0

^a Defined as any related adverse reaction that occurred during or within 24 hours of infusion.

During the monotherapy period with GAZYVA, the most common adverse reactions (incidence ≥ 5% in GADOLIN) were cough (15%), upper respiratory tract infections (12%), neutropenia (11%), sinusitis (10%), diarrhea (8%), infusion related reactions (8%), nausea (8%), fatigue (8%), bronchitis (7%), arthralgia (7%), pyrexia (6%), nasopharyngitis (6%), and urinary tract infection (6%). Grade 3 to 4 adverse reactions during the monotherapy period included neutropenia (10%) and, at 1% each, anemia, febrile neutropenia, thrombocytopenia,

sepsis, upper respiratory tract infection, and urinary tract infection.

Table 7 Post-Baseline Laboratory Abnormalities by CTCAE Grade in ≥ 5% of Patients with Relapsed or Refractory NHL and at Least 2% Greater in the GAZYVA plus Bendamustine Followed by GAZYVA Monotherapy Treated Arm^a (GADOLIN)

Laboratory Abnormalities	GAZYVA + Bendamustine followed by GAZYVA monotherapy n = 194		Bendamustine n = 198	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
Hematology				
Neutropenia	75	52	77	42
Leukopenia	86	47	88	34
Lymphopenia	99	93	99	85
Chemistry				
Hypocalcemia	38	2	26	2
Hypophosphatemia	41	7	38	7
ALT/SGPT increased	35	1	31	4
Elevated creatinine	87	4	92	2
Creatinine clearance decreased	58	6	61	4

^a Two percent different in either the All Grades or Grade 3 to 4 Lab Abnormalities.

In the monotherapy phase of treatment with GAZYVA, the most frequently reported hematological laboratory abnormalities (incidence ≥ 20%) were lymphopenia (80%), leukopenia (63%), low hemoglobin (50%), neutropenia (46%) and thrombocytopenia (35%). The most frequently reported hematological Grade 3 to 4 laboratory abnormalities (incidence ≥ 1%) during the monotherapy period were lymphopenia (52%), neutropenia (27%), leukopenia (20%) and thrombocytopenia (4%).

In the monotherapy phase of treatment with GAZYVA, the most frequently reported chemistry laboratory abnormalities (incidence ≥ 20%) were elevated creatinine (69%), decreased creatinine clearance (CrCl; 43%), hypophosphatemia (25%), AST/SGOT increased (24%) and ALT/SGPT increased (21%). The most frequently reported chemistry Grade 3 to 4 laboratory abnormalities (incidence ≥ 1%) during the monotherapy period were hypophosphatemia (5%), hyponatremia (3%) and decreased CrCl (1%).

GALLIUM

A randomized, open-label multicenter trial (GALLIUM) evaluated the safety of GAZYVA as compared to rituximab product in 1385 patients with previously untreated follicular lymphoma (86%) or marginal zone lymphoma (14%). Patients received chemotherapy (bendamustine, CHOP, or CVP) combined with either GAZYVA (691 patients) or rituximab product (694 patients), followed in responding patients by GAZYVA or rituximab product monotherapy every two months until disease progression or for a maximum of two years. The study excluded patients having an absolute neutrophil count (ANC) < 1500 / μL, platelets < 75,000 / μL, CrCl < 40 mL/min and, unless attributable to lymphoma, hepatic transaminases > 2.5 x upper limit of normal.

The median age was 60 (range: 23-88), 47% were male, 82% were white, and 97% had an ECOG performance status of 0 or 1. The chemotherapy was bendamustine in 59%, CHOP in 31% and CVP in 10% of patients. Following combination therapy, 624 patients (90%) in the GAZYVA arm and 612 patients (88%) in the rituximab product arm received monotherapy.

Serious adverse reactions occurred in 50% of patients on the GAZYVA arm and 43% of patients on the rituximab product arm. Fatal adverse reactions were reported during treatment in 3% in the GAZYVA arm and 2% in the rituximab product arm, most often from infections in the GAZYVA arm. During treatment and follow-up combined, fatal adverse reactions were reported in 5% of the GAZYVA arm and 4% of the rituximab product arm, with infections and second malignancies being leading causes. In the GAZYVA arm, fatal infections occurred in 2% of patients compared to < 1% in the rituximab product arm.

During combination therapy, 93% of patients received all treatment cycles in the GAZYVA arm, and 92% received all treatment cycles in the rituximab product arm. Of the responding patients who began monotherapy with GAZYVA or rituximab

product, 76% and 73%, respectively, completed the full course. Dose modification due to adverse reactions occurred in 74% of the GAZYVA arm and 63% of the rituximab product arm throughout study treatment, and discontinuation of any study drug due to adverse reactions occurred in 18% and 15%, respectively.

Throughout treatment and follow-up, the most common adverse reactions (incidence $\geq 20\%$) observed at least 2% more in the GAZYVA arm included infusion related reactions, neutropenia, upper respiratory tract infection, cough, constipation and diarrhea (Table 8). Neutropenia, infusion related reactions, febrile neutropenia and thrombocytopenia were the most common Grade 3 to 5 adverse reactions (incidence $\geq 5\%$) observed more frequently in the GAZYVA arm.

Table 8 Common Adverse Reactions ($\geq 10\%$ Incidence and $\geq 2\%$ Greater in the GAZYVA Arm) in Patients with Previously Untreated NHL (GALLIUM)

Body System Adverse Reactions ^{a, b}	GAZYVA + chemotherapy followed by GAZYVA monotherapy n = 691		Rituximab product + chemotherapy followed by rituximab product monotherapy n = 694	
	All Grades %	Grades 3 to 5 %	All Grades %	Grades 3 to 5 %
Injury, Poisoning and Procedural Complications				
Infusion Related Reaction ^c	72	12	60	8
Blood and Lymphatic System Disorders				
Neutropenia ^d	53	49	47	41
Thrombocytopenia ^d	14	7	8	3
Infections and Infestations				
Upper Respiratory Tract Infection	50	3	43	1
Herpesvirus Infection	18	3	14	1
Pneumonia	14	7	12	6
Respiratory, Thoracic and Mediastinal Disorders				
Cough	35	< 1	28	< 1
Gastrointestinal Disorders				
Constipation	32	< 1	29	< 1
Diarrhea	30	3	26	2
Nervous System Disorders				
Headache	18	< 1	15	< 1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	16	0	14	< 1
Psychiatric Disorders				
Insomnia	15	< 1	12	< 1
Metabolism and Nutrition Disorders				
Decreased Appetite	14	< 1	12	< 1
Skin and Subcutaneous Tissue Disorders				
Alopecia	13	0	10	< 1
Pruritus	11	< 1	9	0

^a Includes adverse reactions reported throughout study treatment and follow-up.

^b Includes grouped preferred terms.

^c Except where noted, individual events that meet the definition of "infusion related reaction" are excluded from Table 8 above, as they are already included in the group term "Infusion Related Reaction". The most common individual terms within the group term "Infusion Related Reaction" in decreasing order of frequency are nausea, chills, pyrexia and vomiting.

^d Includes adverse reactions reported as infusion related reactions.

Infusion related reactions are defined as any related adverse reaction that occurred during or within 24 hours of infusion.

Neutropenia includes neutropenia, agranulocytosis, febrile neutropenia, granulocytopenia and neutrophil count decreased; **febrile neutropenia** includes febrile neutropenia, neutropenic infection, neutropenic sepsis, and febrile bone marrow aplasia.

Thrombocytopenia includes thrombocytopenia and platelet count decreased.

Upper respiratory tract infection includes upper respiratory tract congestion, upper respiratory tract inflammation, sinusitis bacterial, upper respiratory tract infection bacterial, pharyngitis streptococcal, sinusitis fungal, upper respiratory fungal infection, acute sinusitis, chronic sinusitis, laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, rhinovirus infection, viral pharyngitis, viral rhinitis, viral upper respiratory tract infection.

Herpesvirus infection includes genital herpes, genital herpes zoster, herpes dermatitis, herpes ophthalmic, herpes simplex, herpes simplex pharyngitis, herpes virus infection, herpes zoster, herpes zoster disseminated, herpes zoster infection neurological, herpes zoster oticus, nasal herpes,

ophthalmic herpes simplex, ophthalmic herpes zoster, oral herpes, varicella, varicella zoster virus infection.

Pneumonia includes pneumonia bacterial, pneumonia haemophilus, pneumonia pneumococcal, pneumonia fungal, pneumocystis jirovecii infection, pneumocystis jirovecii pneumonia, atypical pneumonia, lung infection, pneumonia, pneumonia aspiration, lung infiltration.

Cough includes cough, productive cough, upper-airway cough syndrome.

Diarrhea includes diarrhea, defecation urgency, frequent bowel movement, gastroenteritis, gastroenteritis viral.

Headache includes cluster headache, headache, sinus headache, tension headache, migraine.

Insomnia includes initial insomnia, insomnia, sleep disorder.

Pruritus includes pruritus and pruritus generalized. During the monotherapy period, the common adverse reactions (incidence $\geq 10\%$) observed at least 2% more with GAZYVA were upper respiratory tract infection (40%), cough (23%), musculoskeletal pain (20%), neutropenia (19%) and herpesvirus infection (13%).

Table 9 summarizes treatment-emergent laboratory abnormalities during treatment and follow-up. The Grade 3 to 4 abnormalities reported at least 2% more in the GAZYVA arm were lymphopenia, leukopenia, neutropenia, thrombocytopenia and hyperuricemia. Patients in the GAZYVA arm, as compared to the rituximab product arm, had higher incidences of Grade 4 neutropenia (38% vs. 30%, respectively), Grade 4 lymphopenia (33% vs. 22%), and Grade 4 leukopenia (17% vs. 12%).

Table 9 Common New or Worsening Laboratory Abnormalities ($\geq 10\%$ Incidence and $\geq 2\%$ Greater in the GAZYVA Arm) in Patients with Previously Untreated NHL (GALLIUM)

Laboratory Abnormalities ^a	GAZYVA + chemotherapy followed by GAZYVA monotherapy n = 691		Rituximab product + chemotherapy followed by rituximab product monotherapy n = 694	
	All Grades %	Grades 3 to 4 %	All Grades %	Grades 3 to 4 %
Hematology				
Lymphopenia	97	83	95	67
Leukopenia	92	49	89	39
Neutropenia	84	59	76	50
Thrombocytopenia	68	11	50	4
Chemistry				
ALT/SGPT increased	50	3	43	2
AST/SGOT increased	44	1	41	1
Hypophosphatemia	36	5	33	5
Hypoalbuminemia	33	1	25	1
Hypoproteinemia	32	0	30	0
Hypocalcemia	32	1	26	1
Hyperuricemia	28	28	22	22
Hyponatremia	26	4	20	3
Hyperkalemia	23	1	17	1
Hypernatremia	16	< 1	13	0

^a Includes lab abnormalities, reported throughout treatment and follow-up, that were new or worsening, or worsening from baseline unknown.

In the monotherapy phase, new-onset Grade 3 or 4 neutropenia was reported in 21% of patients in the GAZYVA arm (Grade 4, 10%) and 17% of patients in the rituximab product arm (Grade 4, 9%).

Infusion Reactions:

Chronic Lymphocytic Leukemia
The incidence of infusion reactions in the CLL11 study was 65% with the first infusion of GAZYVA. The incidence of Grade 3 or 4 infusion reactions was 20% with 7% of patients discontinuing therapy. The incidence of reactions with subsequent infusions was 3% with the second 1000 mg and < 1% thereafter. No Grade 3 or 4 infusion reactions were reported beyond the first 1000 mg infused.

Of the first 53 patients receiving GAZYVA in CLL11, 47 (89%) experienced an infusion reaction. After this experience, study protocol modifications were made to require pre-medication with a corticosteroid, antihistamine, and acetaminophen. The first dose was also divided into two infusions (100 mg on day 1 and 900 mg on day 2). For the 140 patients for whom these mitigation measures were implemented, 74 patients (53%) experienced a reaction with the first 1000 mg (64 patients on day 1, 3 patients on day 2, and 7 patients on both days) and < 3% thereafter [see *Dosage and Administration* (2)].

Non-Hodgkin Lymphoma

Overall, 69% of patients in the GADOLIN study experienced an infusion reaction (all grades) during treatment with GAZYVA in combination with bendamustine. The incidence of Grade 3 to 4 infusion reactions in GADOLIN was 11%. In Cycle 1, the incidence of infusion reactions (all grades) was 55% in patients receiving GAZYVA in combination with bendamustine with Grade 3 to 4 infusion reactions reported in 9%. In patients receiving GAZYVA in combination with bendamustine, the incidence of infusion reactions was highest on Day 1 (38%), and gradually decreased on Days 2, 8 and 15 (25%, 7% and 4%, respectively).

During Cycle 2, the incidence of infusion reactions was 24% in patients receiving GAZYVA in combination with bendamustine and decreased with subsequent cycles.

During GAZYVA monotherapy in GADOLIN, infusion reactions (all grades) were observed in 8% of patients. No Grade 3 to 4 infusion reactions were reported during GAZYVA monotherapy.

Overall, 2% of patients in GADOLIN experienced an infusion reaction leading to discontinuation of GAZYVA.

In GALLIUM, 72% of patients in the GAZYVA treated arm experienced an infusion reaction (all grades). The incidence of Grade 3 to 4 infusion reactions for these patients was 12%. In Cycle 1, the incidence of infusion reactions (all grades) was 62% in the GAZYVA treated arm with Grade 3 to 4 infusion reactions reported in 10%. The incidence of infusion reactions (all grades) was highest on Day 1 (60%), and decreased on Days 8 and 15 (9% and 6%, respectively).

During Cycle 2, the incidence of infusion reactions (all grades) in the GAZYVA treated arm was 13% and decreased with subsequent cycles.

During GAZYVA monotherapy treatment in GALLIUM, infusion reactions (all grades) were observed in 9% of patients.

Overall, 1% of patients in GALLIUM experienced an infusion reaction leading to discontinuation of GAZYVA.

Neutropenia:
Chronic Lymphocytic Leukemia

The incidence of neutropenia reported as an adverse reaction in CLL11 was 38% in the GAZYVA treated arm and 32% in the rituximab product treated arm, with the incidence of serious adverse reactions being 1% and < 1%, respectively (Table 4). Cases of late-onset neutropenia (occurring 28 days after completion of treatment or later) were 16% in the GAZYVA treated arm and 12% in the rituximab product treated arm.

Non-Hodgkin Lymphoma

The incidence of neutropenia in GADOLIN was higher in the GAZYVA plus bendamustine arm (38%) compared to the arm treated with bendamustine alone (32%). Cases of prolonged neutropenia (3%) and late onset neutropenia (7%) were also reported in the GAZYVA plus bendamustine arm. The incidence of neutropenia was higher during treatment with GAZYVA in combination with bendamustine (31%) compared to the GAZYVA monotherapy treatment phase (12%).

The incidence of neutropenia in GALLIUM was higher in the GAZYVA treated arm (53%) compared to the rituximab product treated arm (47%).

Cases of prolonged neutropenia (1%) and late onset neutropenia (4%) were also reported in the GAZYVA treated arm. The incidence of neutropenia was higher during treatment with GAZYVA in combination with chemotherapy (45%) compared to the GAZYVA monotherapy treatment phase (20%).

Infection:

Chronic Lymphocytic Leukemia

The incidence of infections was similar between GAZYVA and rituximab product treated arms. Thirty-eight percent of patients in the GAZYVA treated arm and 37% in the rituximab product treated arm experienced an infection, with Grade 3 to 4 rates being 11% and 13%, respectively. Fatal events were reported in 1% of patients in both arms.

Non-Hodgkin Lymphoma

The incidence of infection in GADOLIN was 66% in the GAZYVA plus bendamustine arm and 56% in the bendamustine arm, with Grade 3 to 4 events reported in 16% and 14%, respectively. Fatal events were reported in 3% of patients in the GAZYVA plus bendamustine arm and 4% in the bendamustine arm.

The incidence of infections in GALLIUM was 82% in the GAZYVA treated arm and 73% in the rituximab product treated arm, with Grade 3 to 4 events reported in 21% and 17%, respectively. In the GAZYVA arm, fatal infections occurred in 2% of patients compared to < 1% in the rituximab product arm.

The incidence of Grade 3 to 4 infections in the GAZYVA and rituximab product treated arms was lower in patients receiving GCSF prophylaxis (14%; 16%) compared with patients not receiving GCSF prophylaxis (24%; 18%). The incidence of fatal infections in patients receiving GCSF prophylaxis in the GAZYVA and rituximab product treated arms was 2% and 0%, respectively, and was 2% and < 1% in patients not receiving GCSF prophylaxis.

Thrombocytopenia:

Chronic Lymphocytic Leukemia

The overall incidence of thrombocytopenia reported as an adverse reaction was higher in the GAZYVA treated arm (14%) compared to the rituximab product treated arm (7%), with the incidence of Grade 3 to 4 events being 10% and 3%, respectively (Table 4). The difference in incidences between the treatment arms is driven by events occurring during the first cycle. The incidence of thrombocytopenia (all grades) in the first cycle was 11% in the GAZYVA and 3% in the rituximab product treated arms, with Grade 3 to 4 rates being 8% and 2%, respectively. Four percent of patients in the GAZYVA treated arm experienced acute thrombocytopenia (occurring within 24 hours after the GAZYVA infusion).

The overall incidence of hemorrhagic events and the number of fatal hemorrhagic events were similar between the treatment arms, with 3 in the rituximab product and 4 in the GAZYVA treated arms.

However, all fatal hemorrhagic events in patients treated with GAZYVA occurred in Cycle 1.

Non-Hodgkin Lymphoma

The incidence of thrombocytopenia in GADOLIN was lower in the GAZYVA plus bendamustine arm (15%) compared to the arm treated with bendamustine alone (24%). The incidence of hemorrhagic events in GAZYVA plus bendamustine treated patients compared to bendamustine alone was 11% and 10%, respectively. Grade 3 to 4 hemorrhagic events were similar in both treatment arms (5% in the GAZYVA plus bendamustine arm and 3% in the bendamustine arm).

In GALLIUM, thrombocytopenia was reported as an adverse reaction in 14% of the GAZYVA treated arm and 8% of the rituximab product treated arm, with the incidence of Grade 3 to 4 events being 7% and 3% respectively. The difference in incidences between the treatment arms is driven by events occurring during the first cycle. The incidence of thrombocytopenia (all grades) in the first cycle were 9% in the GAZYVA and 3% in the rituximab product treated arms, with Grade 3 to 4 rates being 5% and 1%, respectively. In GALLIUM, both treatment arms had a 12% overall incidence of hemorrhagic events and a < 1% incidence of fatal hemorrhagic events.

Tumor Lysis Syndrome: The incidence of Grade 3 or 4 tumor lysis syndrome in GAZYVA treated patients was 2% in CLL11, 0.5% in GADOLIN and 0.9% in GALLIUM.

Musculoskeletal Disorders:

Chronic Lymphocytic Leukemia

Adverse reactions related to musculoskeletal disorders (all events from the body system), including pain, have been reported in the GAZYVA treated arm with higher incidence than in the rituximab product treated arm (18% vs. 15%).

Non-Hodgkin Lymphoma

In GADOLIN, adverse reactions related to musculoskeletal disorders (all events from the body system), including pain, have been reported in the GAZYVA plus bendamustine treated arm with higher incidence than in the bendamustine alone arm (41% vs. 29%).

In GALLIUM, musculoskeletal disorders were reported in 54% of patients in the GAZYVA treated arm and 49% of patients in the rituximab product treated arm.

Liver Enzyme Elevations: Hepatic enzyme elevations have occurred in CLL patients who received GAZYVA in clinical trials and had normal baseline hepatic enzyme levels (AST, ALT and ALP). The events occurred most frequently within 24–48 hours of the first infusion. In some patients, elevations in liver enzymes were observed concurrently with infusion reactions or tumor lysis syndrome. In the CLL11 study, there was no clinically meaningful difference in overall hepatotoxicity adverse reactions between all arms (4% of patients in the GAZYVA treated arm). Medications commonly used to prevent infusion reactions (e.g., acetaminophen) may also be implicated in these events. Monitor liver function tests during treatment, especially during the first cycle. Consider treatment interruption or discontinuation for hepatotoxicity.

Gastrointestinal Perforation: Cases of gastrointestinal perforation have been reported in patients receiving GAZYVA, mainly in NHL.

Worsening of Pre-existing Cardiac Conditions:

Fatal cardiac events have been reported in patients treated with GAZYVA.

6.2 Immunogenicity

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

Seven percent (18/271) of patients with CLL tested positive for anti-GAZYVA antibodies at one or more time points in CLL11. No patients developed anti-GAZYVA antibodies during or following GAZYVA treatment in GADOLIN, while 1 patient (1/564, 0.2%) developed anti-GAZYVA antibodies in GALLIUM. Neutralizing activity of anti-GAZYVA antibodies has not been assessed.

6.3 Postmarketing Safety Information

The following adverse reactions have been identified during post-approval use of GAZYVA.

- Immune/Autoimmune Events: Serum sickness

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

GAZYVA is likely to cause fetal B-cell depletion based on findings from animal studies and the drug's mechanism of action [see *Clinical Pharmacology* (12.1)]. There are no data with GAZYVA use in pregnant women to inform a drug-associated risk. Monoclonal antibodies are transferred across the placenta. In animal reproduction studies, weekly intravenous administration of obinutuzumab to pregnant cynomolgus monkeys from day 20 of pregnancy until parturition which includes the period of organogenesis at doses with exposures up to 2.4 times the exposure at the clinical dose of 1000 mg monthly produced opportunistic infections and immune complex mediated hypersensitivity reactions. No embryo-toxic or teratogenic effects were observed in the monkeys [see *Data*]. Consider the potential risk to the fetus when prescribing GAZYVA to a pregnant woman.

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

GAZYVA is likely to cause fetal B-cell depletion [see *Data*]. Avoid administering live vaccines to neonates and infants exposed to GAZYVA in utero until B-cell recovery occurs [see *Warnings and Precautions* (5.8) and *Clinical Pharmacology* (12.2)].

Data

Animal Data

In a pre- and post-natal development study, pregnant cynomolgus monkeys received weekly intravenous doses of 25 or 50 mg/kg obinutuzumab from day 20 of pregnancy until parturition, which includes the period of organogenesis. The high dose results in an exposure (AUC) that is 2.4 times the exposure in patients with CLL at the recommended label dose. There were no embryo-toxic or teratogenic effects in animals. Secondary opportunistic infections, immune complex mediated hypersensitivity reactions, or a combination of both were observed in exposed dams. When first measured on day 28 postpartum, obinutuzumab was detected in offspring at levels in the range of maternal serum levels on the same day, and B-cells were completely depleted. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months after birth.

Obinutuzumab was measured in the milk of lactating cynomolgus monkeys on day 28 postpartum after weekly intravenous administration from day 20 of pregnancy until parturition. Concentrations in milk were approximately 0.04% and 0.13% of concentrations in maternal serum in the 25 and 50 mg/kg groups, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of GAZYVA in human milk, the effects on the breastfed child, or the effects on milk production. However, low levels of obinutuzumab were present in the milk of lactating cynomolgus monkeys [see *Use in Specific Populations* (8.1)]. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and child circulations in substantial amounts. The developmental and health benefits of

breastfeeding should be considered along with the mother's clinical need for GAZYVA and any potential adverse effects on the breastfed child from GAZYVA or from the underlying maternal condition.

8.4 Pediatric Use

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

8.5 Geriatric Use

Chronic Lymphocytic Leukemia

Of 336 patients with previously untreated CLL who received GAZYVA in combination with chlorambucil, 81% were 65 years and older, while 46% were 75 and older. Of the patients 75 years and older, 46% experienced serious adverse reactions and 7% experienced adverse reactions leading to death. Of the patients younger than 75, 33% experienced a serious adverse reaction and 2% an adverse reaction leading to death. No significant differences in efficacy were observed between younger and older patients [see *Clinical Studies* (14.1)].

Non-Hodgkin Lymphoma

Of 194 patients in GADOLIN with relapsed or refractory NHL treated with GAZYVA plus bendamustine, 44% were 65 and over, while 14% were 75 and over. In patients 65 and over, 52% of patients experienced serious adverse reactions and 26% experienced adverse reactions leading to treatment withdrawal while in patients under 65, 28% and 12% experienced serious adverse reactions and adverse reactions leading to treatment withdrawal, respectively. No clinically meaningful differences in efficacy were observed between these patients and younger patients in GADOLIN.

Of the 691 patients in GALLIUM treated with GAZYVA plus chemotherapy as first-line therapy, 33% were 65 and over, while 7% were 75 and over. Of patients 65 and over, 63% experienced serious adverse reactions and 26% experienced adverse reactions leading to treatment withdrawal, while in patients under 65, 43% experienced serious adverse reactions and 13% had an adverse reaction leading to treatment withdrawal. No clinically meaningful differences in efficacy were observed between these patients and younger patients in GALLIUM.

10 OVERDOSAGE

There has been no experience with overdose in human clinical trials. For patients who experience overdose, treatment should consist of immediate interruption or reduction of GAZYVA and supportive therapy.

17 PATIENT COUNSELING INFORMATION

Advise patients to seek immediate medical attention for any of the following:

- Signs and symptoms of infusion reactions including dizziness, nausea, chills, fever, vomiting, diarrhea, breathing problems, or chest pain [see *Warnings and Precautions* (5.3) and *Adverse Reactions* (6.1)].
- Symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy [see *Warnings and Precautions* (5.5) and *Adverse Reactions* (6.1)].
- Signs of infections including fever and cough [see *Warnings and Precautions* (5.6) and *Adverse Reactions* (6.1)].
- Symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes [see *Warnings and Precautions* (5.1)].
- New or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems [see *Warnings and Precautions* (5.2)].

Advise patients of the need for:

- Periodic monitoring of blood counts [see *Warnings and Precautions* (5.7 and 5.8) and *Adverse Reactions* (6.1)].
- Avoid vaccinations with live viral vaccines [see *Warnings and Precautions* (5.9)].
- Patients with a history of hepatitis B infection (based on the blood test) should be monitored and sometimes treated for their hepatitis [see *Warnings and Precautions* (5.1)].

Advise pregnant women of potential fetal B-cell depletion [see *Use in Specific Populations* (8.1)].

Genentech

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GAZYVA® (obinutuzumab)

Manufactured by:

Genentech, Inc.

A Member of the Roche Group
South San Francisco, CA 94080-4990

U.S. License No. 1048

Initial US Approval: 2013

Code Revision Date: November 2017

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Pharmacy Residents' Mental Wellness: Why and How to Prioritize Resilience in Residency *(continued from p. 13)*

Wellness Tips from the Pharmacy Residency Mentorship and Wellness Coordinator

- *Know what tools are available and reach out.* Seek out employee assistance programs or local mental health offices. Do not be afraid to set up a baseline appointment with a therapist; an advantage is that after you become an established patient, it will be easier for you to schedule future appointments. The National Suicide Prevention Lifeline number is 1.800.273.8255, and the Crisis Text Line can be contacted by texting CONNECT to 741741.⁵
- *Develop coping skills.* Maintain work-life balance, and do not be afraid to set boundaries where necessary. Maintain social connections by reaching out to friends and family members or by building new relationships. Learn positive coping skills from mentors.
- *Manage your time well.* Managing your time can help reduce stress. Knowing first what your weaknesses are and then addressing what may hold you back can help propel you forward. Make a priority list instead of a to-do list. Break those priorities into bite-size pieces. For example: "Review 5 patient charts" does not seem as daunting as "Conduct research."¹⁰ Avoid social media: not only does it derail productivity, but in 2014, Vogel and colleagues found a negative correlation between time spent on Facebook and self-esteem, especially when one is viewing people whose lives seem better than that of the study subject.¹¹
- *Advocate for mental health care.* Be an advocate for mental health care within your health system.

Wellness Tips from Oncology Residents

The idea that high stress levels are expected and should be tolerated throughout residency exists throughout the healthcare community. The implementation of the wellness program at our

institution has helped correct that erroneous idea. Our key take-aways are these:

- *Don't wait for mental health concerns to arise before seeking help.* Feeling stressed and inadequate are common experiences for residents and are no less important than the residency program itself. Early recognition of these concerns is important and can help residents obtain early assistance to learn strategies for addressing them.
- *Set reasonable expectations.* Residents may struggle with how they are perceived by their preceptors. The associated stress may accumulate throughout the year, resulting in lack of confidence, feelings of unease, and burnout. The wellness program at our institution gave residents and preceptors the opportunity to unite and address these topics upfront, set the standard for expectations and progression throughout the residency year, and alleviate the burden of troublesome worries and concerns.
- *Find meaningful downtime.* Finding meaningful downtime activities between rotations and work shifts should be a goal for all residents. Meaningful downtime may differ from resident to resident, but that time should be spent doing an activity that appeals to and provides benefit to the resident. Though free time during residency is limited, the time available should be used wisely. Our Pharmacy Resident Wellness Program offers suggestions for activity sessions and actively encourages residents to acknowledge and act upon their need for meaningful downtime.
- *Be proud of and grateful for your own achievements.* It is very easy for residents to focus on the negative aspects of life, but doing so creates a poor psychological environment. Our Pharmacy Resident Wellness Program provides us with tools to help us see ourselves positively and recognize the effort we display daily.

REFERENCES

1. Bridgeman PJ, Bridgeman MB, Barone J. Burnout syndrome among healthcare professionals. *Am J Health Syst Pharm.* 2018;75:147-152.
2. Freudenberger HJ. Staff burn-out. *J Soc Issues.* 1974;50(1):159-165.
3. Chatterjee R, Wroth C. WHO redefines burnout as a 'syndrome' linked to chronic stress at work. National Public Radio, Morning Edition, May 28, 2019. Accessed October 17, 2019. Available at <https://www.npr.org/sections/health-shots/2019/05/28/727637944/who-redefines-burnout-as-a-syndrome-linked-to-chronic-stress-at-work>.
4. Le HM, Young SD. Evaluation of stress experienced by pharmacy residents. *Am J Health Syst Pharm.* 2017;74:599-604.
5. Mayberry KM, Miller LN. Incidence of self-reported depression among pharmacy residents in Tennessee. *Am J Pharm Educ.* 2017;81(8):5960.
6. Williams E, Martin SL, Fabrikant A, Wang A, Pojasek M. Rates of depressive symptoms among pharmacy residents. *Am J Health Syst Pharm.* 2018;75(5):292-297.
7. Schernhammer ES, Colditz GA. Suicide rates among physicians: a quantitative and gender assessment (meta-analysis). *Am J Psychiatry.* 2004;161(12):2295-2302.
8. Bowers P. Bridge jumper identified as Tosin Oyelowo. *Charleston City Paper.* December 19, 2011. Accessed October 17, 2019. Available at <https://www.charlestoncitypaper.com/charleston/bridge-jumper-identified-as-tosin-oyelowo/Content?oid=3662179>.
9. Le HM, Young SD. Exploring the relationship between environmental stressors, pharmacy residents' stress and medication errors. *J Psychol Cognition.* 2017;2(3):192-197.
10. Flaxington BD. Developing time management skills: how to become more organized and find more time in a day. *Psychology Today.* July 27, 2015. Accessed October 17, 2019. Available at <https://www.psychologytoday.com/us/blog/understand-other-people/201507/developing-time-management-skills>.
11. Vogel EA, Rose JP, Roberts L, Eckles K. Social comparison, social media, and self-esteem. *Am Psych Assoc.* 2014;3(4):206-222.

Deprescribing in Palliative Care: An Overview



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Deprescribing is the practice of discontinuing potentially inappropriate prescription and nonprescription medications, including complementary and alternative medicine (CAM), in patients when the possible risks outweigh the benefits. Potentially inappropriate medications (PIMs) are largely referred to as medications lacking evidence-based indications, medications with treatment risks that may outweigh their benefits, medications associated with significant adverse reactions, and those that may potentially interact with other medications or diseases.¹ This practice was initially developed for use in geriatric patients who had significant polypharmacy and limited life expectancy, but it has slowly been adopted in palliative care and oncology. Deprescribing has many benefits, including reducing medication costs, minimizing adverse drug effects, improving patients' quality of life, improving adherence to beneficial medications, and decreasing the burden of polypharmacy in the last months of life.

Polypharmacy, frequently defined as taking five or more prescriptions concurrently for the treatment of one or more coexisting diseases, is common in older cancer patients.² Polypharmacy in this setting can be appropriate if the additional medications are indicated and are benefiting the patient, but each added medication should be thoroughly assessed for benefits and risks. Trends in prescription drug use was evaluated by Kantor and colleagues with the National Health and Nutrition Examination Survey from 1992 to 2012.³ A significant increase in polypharmacy was seen over the years in all adult age and ethnic groups.³ During the 2011–2012 period, 39% of adults aged 65 years and older reported polypharmacy.

Cancer, often diagnosed in older patients, is difficult to treat, and the management of cancer symptoms and the adverse effects of treatment further complicate that treatment. The prevalence of polypharmacy at time of diagnosis in older acute myelogenous leukemia (AML) patients has been reported as 38%, with a median of four prescription medications prescribed.⁴ Several other clinical trials report an average of four to nine prescription medications per patient with 50%–69% of patients reporting use of CAM.^{4–6} Milic and colleagues reported that 37% of metastatic breast cancer patients were taking 10 or more tablets per day.⁷

The impact of polypharmacy in oncology patients has been evaluated in several studies. Woopen and colleagues analyzed prospective ovarian cancer trials to evaluate the influence of polypharmacy on grade 3/4 toxicity, prior discontinuation of chemotherapy, and survival.⁸ Increased medication use was associated with overall grade 3/4 toxicity ($p < .001$) and hematological ($p < .001$) and non-hematological ($p < .001$) toxicities. However, increased medication use was not associated with early discontinuation of chemotherapy

($p = .196$) or with overall survival ($p = .068$). In addition, Elliot and colleagues conducted a retrospective analysis of newly diagnosed AML patients ($N = 150$) and demonstrated that the total number of prescription medications at baseline was associated with increased 30-day mortality.⁴ The authors suggest that the increase in mortality could be caused by comorbidities and poorer health rather than resulting from an effect of polypharmacy. However, although an increased number of medications has been associated with chemotoxicity in some studies, overall results have been inconsistent, and many of the trials have not shown any adverse effects of PIMs. It is possible that some of the supportive care medications that could be classified as PIMs still have benefit to mitigate adverse effects from treatment in older patients.¹

Several studies have described the common medications taken by patients near the end of life. Woopen and colleagues conducted a meta-analysis of three ovarian cancer trials ($N = 1,213$) and reported that the most frequent medications taken by the patients, besides those prescribed for symptomatic relief, were beta blockers (17.4%), diuretics (13.4%), and angiotensin-converting enzyme inhibitors (11%).⁸ Medications appropriate for deprescribing may seem evident in some cases, but others may have some positive attributes despite the negative ones. In addition, some prescribers may be reluctant to discontinue certain medications (e.g., proton pump inhibitors [PPIs] and statins) because of fear of adverse effects or other complications. PPIs are a mainstay in treating many acid-related disorders. Strong data support the short-term use of PPIs to control dyspepsia and gastroesophageal reflux disease (GERD). Because dyspepsia and other acid-related disorders can decrease a patient's quality of life, the use of PPIs could be viewed as appropriate. However, long-term use of PPIs has been associated with hypergastrinemia, hypochlorhydria, idiosyncratic reactions, and pharmacokinetic interactions. Each of these can lead to health problems such as malabsorption of nutrients and tissue dysplasia.

Deprescribing of PPIs has been recommended for adults who are symptom-free after completion of a minimum 4-week PPI treatment for GERD.⁹ Kutner and colleagues conducted a randomized unblinded clinical trial that included 381 patients with limited life expectancy to evaluate the effects of statin deprescribing.¹⁰ Forty-eight percent of the patients had cancer. The primary outcome of death within 60 days was not different between the two groups ($p = .36$). Very few cardiovascular events occurred during the trial, with no difference between groups. Quality of life was statistically better in the group that discontinued statin use. Deprescribing was associated with cost savings of \$3.37 per day and \$716 per patient.

Deprescribing Process

The geriatric literature describes several models for deprescribing, and a few models appear in oncology and palliative care literature. Scott and colleagues described a five-step process for

deprescribing (**Table 1**).¹¹ The first step in deprescribing is to perform medication reconciliation, including over-the-counter medications and medications used in CAM. The patient should be interviewed to determine the indication for the use of each medication; contacting the patient’s other providers to help determine the indication may also be necessary. After a determination has been made about which medications are to be discontinued, a decision can be made about which medications to stop first. When prioritizing drugs for discontinuation, the provider should choose to stop medications that have the greatest risk of harm and the least benefit, followed by those easiest to discontinue and then those that the patient is most willing to discontinue. Medications should be discontinued one at a time. The provider and patient should develop a written plan for discontinuation, including tapering instructions and a plan for follow-up and monitoring for any adverse effects of discontinuation. The provider should fully document the reasons for, and outcome of, discontinuation. Shared decision making is important in this process because deprescribing can have a psychological impact on both patients and caregivers. Deprescribing medication could be interpreted as having “given up on the patient” or believing that “the patient will soon die.” Other patients and caregivers may embrace having fewer medications and decreased medication costs.

Tools for Deprescribing Medications

Several tools can help determine which medications should be discontinued; a list of available resources is given in **Table 3**. The Beers Criteria, an explicit list of PIMs that are usually best avoided in older adults, is published by the American Geriatrics Society on a 3-year update cycle, with the most recent update published in 2019.¹² In addition, the Medication Appropriateness Index (MAI) was developed in 1992 to identify PIMs by asking 10 questions that incorporate a 1–3 rating option depending on the appropriateness. The higher the score, the more likely it is that the medication is inappropriate for the patient. MAI is one of the few tools that also considers drug-drug interactions.¹³ The National Comprehensive Cancer Network (NCCN) Guidelines for Older Adult Oncology provides a list of medications that are commonly used for supportive care and that are a concern in older cancer patients. The guideline provides recommendations and alternative options for commonly prescribed supportive care medications.¹⁴ The Screening Tool of Older Persons’ Prescriptions (STOPP) criteria note the medications that increase the risk of falls and those with a high chance of adverse events (drug-drug and drug-disease interactions are included).¹⁵ These are explicit criteria for determining optimal prescribing and can be applied to most patients. The Drug Burden Index was developed to measure the cumulative exposure to medications with anticholinergic and sedative effects in older adults and its impact on physical and cognitive function.¹⁶

Table 1. Steps for Deprescribing¹¹

1. Perform medication reconciliation and determine indications.
2. Evaluate risks and benefits of medication considering the patient’s prognosis and potential health complications of deprescribing.
3. Assess each drug for discontinuation.
4. Prioritize drugs for discontinuation.
5. Implement and monitor drug discontinuation.

Table 2 lists common medication classes that are recommended to be tapered when they are being discontinued. A general rule of thumb when tapering is to decrease the dose by 50% for a prespecified amount of time and then decrease by 50% again or permanently discontinue the medication if a subsequent decrease is not feasible with the available dosage options. Tapering may take a week or up to several months depending on the medication and patient response. However, only one medication should be tapered or discontinued at a time.¹¹

Table 2. Medications That May Need to Be Tapered When Deprescribed

- Antidepressants
- Antiepileptics (e.g., topiramate)
- Antihypertensives (e.g., beta-blockers, central acting alpha agonists)
- Barbiturates
- Benzodiazepines
- Opioids
- Steroids
- Stimulants

Table 3. Tools for Deprescribing¹²⁻¹⁸

- American Geriatrics Society Beers Criteria
- Deprescribing.org
- Disease Burden Index
- Medications Appropriateness Index
- MedStopper.com
- NCCN Guidelines for Older Adult Oncology
- STOPP criteria

Note. NCCN = National Comprehensive Cancer Network; STOPP = Screening Tool of Older Persons’ Prescriptions

The MedStopper online tool (MedStopper.com) incorporates data from the Beers Criteria, STOPP, and the Drug Burden Index.¹⁷ The tool allows multiple medications to be entered along with the associated indication. Of note, not all common indications are currently listed. For example, when warfarin, an anticoagulant, is entered, no deep vein thrombosis treatment or prevention indication is given. Also, no nausea or vomiting indication option is provided for prochlorperazine, a common antiemetic. However, an “unknown” indication option is available in these situations. Smiley and frowny faces indicate the extent to which the medicine may improve symptoms, may reduce risk for future illness, or may cause harm. The recommendations can be modified for frail or fit patients. The tool is very user-friendly and provides analysis of the medications, including suggestions for deprescribing and tapering. The analysis can be printed to aid the provider when discussing deprescribing with patient and caregivers. The smiley and frowny

faces and colors can be easily understood by most patients, and reports are available in both English and French.

Additional information and decision aid tools on deprescribing can be found at www.deprescribing.org.¹⁸ The website was developed and is supported by a pharmacist and physician who work with older patients and are concerned about the risks associated with medications at the Bruyère Research Institute (Ottawa) and Université de Montréal. The available information includes webinars and other educational tools about deprescribing for healthcare professionals.

Barriers to Deprescribing

Although deprescribing has many benefits for patients, some barriers for the process exist, including a reluctance to cease medications prescribed by specialists, the perception of inability to change patients' attitudes, and the belief that a strong indication for a medication existed. Djatche and colleagues surveyed 160 Italian physicians concerning their attitudes about deprescribing in elderly patients who were not primarily cancer patients.¹⁹ The majority of physicians surveyed were primary care physicians, and only 5% were hematology specialists. Seventy-eight percent of the physicians were comfortable deprescribing preventive medications in elderly patients, and 40% of physicians reported hesitance in discontinuing medications prescribed by other prescribers. One in four physicians reported lack of time and difficulty engaging the patient or caregiver as barriers to deprescribing.

In 2013, Reeve and colleagues published a study evaluating attitudes about deprescribing for patients with multiple comorbidities.²⁰ Of the 100 Australian participants, 92% reported

being willing to stop one or more medications if possible. In a separate study, Reeve and colleagues evaluated 1,981 United States Medicare beneficiaries using the Patients' Attitudes Towards Deprescribing Questionnaire.²¹ Ninety-two percent of participants reported being willing to stop taking one or more of their medications if their physician agreed. Overall, more than two-thirds of participants wanted to reduce the number of medications they were taking.

Overall, research does not support the hypothesis that barriers toward deprescribing are prevalent among patients. Physicians are open to deprescribing, but they are reluctant to deprescribe medications initiated by another prescriber. The research pertaining to deprescribing statin medications and PPIs initiated by a specialist or during hospitalization provides helpful guidance for some cases,^{9,10} but further research and education may be needed to increase comfort with deprescribing, especially in cancer patients, in other situations.

Deprescribing medications is an important part of the care of all patients, including cancer patients, near the end of life. Medications once taken to ensure long-term health are often no longer a beneficial choice and may have more health risks than benefits. Oncology and palliative care pharmacists are in an ideal position to help in the deprescribing process because they are aware of the patient's prognosis and medications. Deprescribing can decrease the burden of polypharmacy, decrease medication costs, and reduce possible adverse drug reactions and interactions. For these reasons, deprescribing is an appropriate step for patients near the end of life. ●●

REFERENCES

- Sharma M, Loh KP, Nightingale G, Mohile SG, Homes HM. Polypharmacy and potentially inappropriate medication use in geriatric oncology. *J Geriatr Oncol*. 2016;7:346-353.
- Lees J, Chan A. Polypharmacy in elderly patients with cancer: clinical implications and management. *Lancet Oncol*. 2011;12:1249-1257.
- Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA*. 2015;314:1818-1831.
- Elliot K, Tooze JA, Geller R, et al. The prognostic importance of polypharmacy in older adults treated for acute myelogenous leukemia (AML). *Leuk Res*. 2014;38:1184-1190.
- Cashman J, Wright J, Ring A. The treatment of co-morbidities in older patients with metastatic cancer. *Support Care Cancer*. 2010;18:651-655.
- Sokol KC, Knudsen JF, Li MM. Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management. *J Clin Pharm Ther*. 2007;32:169-175.
- Milic M, Foster A, Rihawi K, Anthony A, Twelves C. 'Tablet burden' in patients with metastatic breast cancer. *Eur J Cancer*. 2016;55:1-6.
- Woopen H, Richter R, Ismaeel F, et al. The influence of polypharmacy on grade III/IV toxicity, prior discontinuation of chemotherapy and overall survival in ovarian cancer. *Gynecol Oncol*. 2016;140:554-558.
- Helgadottir H, Bjornsson ES. Problems associated with deprescribing of proton pump inhibitors. *Int J Mol Sci*. 2019;20:E5469.
- Kutner JS, Blatchford PJ, Taylor DH Jr, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med*. 2015;175:691-700.
- Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med*. 2015;175:827-834.
- 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67:674-694.
- Hanlon JT, Schumacher KE. The medication appropriateness index at 20: where it started, where it has been, and where it may be going. *Drugs Aging*. 2013;30:893-900.
- National Comprehensive Cancer Network. Older Adult Oncology (Version 1.2019). http://www.nccn.org/professionals/physician_gls/pdf/senior.pdf. Accessed: December 29, 2019.
- O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing*. 2015;44:213-218.
- Hilmer SN. Calculating and using the drug burden index score in research and practice. *Expert Rev Clin Pharmacol*. 2018;11:1053-1055.
- MedStopper. MedStopper deprescribing resource. Available at <http://medstopper.com/>. Accessed December 29, 2019.
- Bruyere. Optimizing medication use. Available at <http://deprescribing.org/>. Accessed: December 29, 2019.
- Djatche L, Lee S, Singer D, Hegarty SE, Lombardi M, Maio V. How confident are physicians in deprescribing for the elderly and what barriers prevent deprescribing? *J Clin Pharm Ther*. 2018;43:550-555.
- Reeve E, Wiese MD, Hendrix I, Roberts MS, Shakib S. People's attitudes, beliefs, and experiences regarding polypharmacy and willingness to deprescribe. *J Am Geriatr Soc*. 2013;61:1508-1514.
- Reeve E, Wolff JL, Skehan M, Bayliss EA, Hilmer SN, Boyd CM. Assessment of attitudes toward deprescribing in older Medicare beneficiaries in the United States. *JAMA Intern Med*. 2018;178:1673-1680.

Financial Toxicity in Cancer Care



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If you spend a day in an oncology clinic, in only a few minutes you will hear discussion about the prevention or treatment of common toxicities. Myelosuppression, neuropathy, diarrhea, and nausea and vomiting are routinely discussed toxicities in the management of cancer care. Financial toxicity, however, may not be the first toxicity that comes to mind, or it may not even be considered at all.

Financial toxicity in cancer care can be viewed through many lenses. In our work on this article, we took the opportunity to interview four individuals who have distinct roles in cancer care: an oncology nurse practitioner, an oncology pharmacist, an oncology clinical social worker, and a pharmacy technician who works as an outpatient medication assistance coordinator. We asked them several questions about financial toxicity. It is our hope that the answers below (which contain our own thoughts and those of the four professionals) will highlight areas for improvement in clinical practice.

How do you define financial toxicity of cancer care?

As pharmacists, we often think of financial toxicity as the cost of cancer treatments. We know that these costs continue to increase, especially for newer treatment options like immunotherapy and oral chemotherapies.¹ Medication assistance coordinator Samantha Shaver states that “patients who are newly diagnosed not only worry about life-changing news but also have to worry about the affordability of treatment while maintaining the normal costs of living.” When considering the cost of medication therapy alone, “clinic staff members should be cognizant of how their patients are tolerating the treatment financially,” according to pharmacist Ashish Suthar. “Patients may be just as likely to dose-reduce or stop treatment on their own because of cost, just as we would for a lab abnormality.”

But financial toxicity may extend beyond the cost of medications. Oncology nurse practitioner Anne Courtney defines *financial toxicity* as “any cost of cancer treatment that alters the way people may make treatment decisions or that impacts their ability to live their baseline life.” This extends beyond medication therapy,

because cancer treatment can include surgery, radiation, frequent office visits, and lab tests. The cost of medication therapy alone can be high, but it does not exist in a vacuum and should be viewed in combination with all potential causes of financial toxicity for cancer patients and their loved ones. Oncology clinical social worker Angela Luna adds, “Financial toxicity is what happens when healthcare costs eat up so much of a family’s disposable income that they can’t afford daily necessities, much less save for the future.” Her perspective introduces financial toxicity as not just a concern for the present but something that may extend far beyond the time of the initial diagnosis and treatment.

In your opinion, what are the biggest financial issues for cancer patients right now?

Each of our four respondents (nurse practitioner, clinical social worker, pharmacist, and medication assistance coordinator) identified a different area as the biggest financial concern for cancer patients. They spoke about the cost of medication therapy and the frequency of treatments, the cost of copayments for diagnostic imaging, the cost of hospital and emergency department admissions, worries about being underinsured (having insurance but with either costly copayments for every aspect of care or else high deductibles), and the need for patients and healthcare providers to have better access to information on assistance programs. This list highlights the need for awareness of financial toxicity from all disciplines and perspectives, because the overall costs of cancer care can quickly accumulate.

Clinicians may be aware of costs related to their own areas of practice but fail to view the overall financial situation, which identifies an additional area of need. Luna points out that “financial toxicity is a tricky area because you really need an expert who knows the ins and outs of all the resources and strategies. The irony is that many institutions don’t prioritize that in their funding of positions. This situation means that dealing with these issues is left to people who are trying their best but may not be operating in their area of expertise.” Suthar adds, speaking specifically about medication-related costs, “Depending on the size of the practice, it could take one (or more) full-time staff members to help patients find and enroll in assistance programs.”

The other difficulty in navigating through concerns about financial toxicity is the fact that cancer care costs are not always known upfront, and our responses are often reactive rather than proactive. Healthcare organization and insurance disclosures about upfront costs for procedures, imaging, medications, and office visits could shift this paradigm. In addition, Luna suggests that more detailed education on the selection of insurance plans could offset the problem of patients’ being underinsured.

(continued on p. 28)

Highlights of 2019 HOPA Practice Management



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 Indianapolis, IN

The 2019 Hematology/Oncology Pharmacy Association Practice Management program¹ was held in Charlotte, NC, on Friday, September 13, and Saturday, September 14. This meeting offered both live and virtual participation, and attendees included 250 hematology and oncology pharmacists and administrators from across the country.

Three preconference sessions were offered on September 13: “Investigational Drug Services” (covering safety, standards, and regulatory issues), “The Growing Role of Specialty Pharmacy as an Extension of the Cancer Care Team,” and “Best Practices for Cancer Care at Integrated Delivery Networks.” In addition, a Quality Improvement (QI) Workshop was held on September 12. This workshop was organized by the HOPA Quality Oversight Committee as an introduction to the American Society of Clinical Oncology (ASCO) Quality Training Program (QTP). Thirty-one HOPA members attended this workshop to learn about the components of QI in health care from ASCO QTP leaders Michael Keng, MD; Vedner Guerrier, MBA LSSBB; and Amy Morris, PharmD. (See *HOPA News*, Vol. 16, no. 4, for additional coverage of this workshop.)

The general sessions kicked off at noon on Friday with a presentation on the practical implementation of biosimilars. This session included comments from three pharmacists (two working with Kaiser Permanente and one working with BlueCross BlueShield of North Carolina) about considerations for payers and providers related to biosimilar use. Next, Russell Greenfield, MD, gave the presentation “Integrative Oncology: Separating Wheat from Chaff.” Dr. Greenfield discussed the expanding role of the pharmacist and included a number of patient scenarios to highlight the need for healthcare providers to communicate with patients regarding integrative or alternative medications. One study noted that 38% of the American population is interested in complementary or alternative medicine, and interest is even higher in the cancer population (up to 68%).² Above all else, Dr. Greenfield emphasized the need for pharmacists to take the lead in supporting the well-being of each patient through safely managing patients’ use of vitamins, supplements, and herbs in addition to their traditional cancer treatment.

Along with the continuing education programming offered at the meeting, a number of presentations and networking events allowed attendees the opportunity to get to know one another. On Friday evening an update on HOPA’s Pilot Mentorship Program was led by Becky Fahrenbruch, PharmD BCOP. This program was developed by the Leadership Development Subcommittee to gauge interest in a mentorship program for HOPA and determine the best steps for implementing such a program. This year, five pairs of mentees and mentors met in monthly calls to discuss various leadership topics. In conjunction with the monthly calls, the group

participated in a meet-and-greet event at HOPA’s 2019 Annual Conference in Fort Worth, TX. To conclude the pilot program, the group met for breakfast during HOPA’s 2019 Practice Management program to discuss the book *Conscious: The Power of Awareness in Business and Life*, by Bob Rosen and Emma-Kate Swann. The book-club breakfast was a great occasion for the participants to get to know one another and learn from the mentors’ involvement in HOPA over the years.

Friday night concluded with a presentation by Heidi Finnes, PharmD BCOP, titled “You Can Move Mountains.” Dr. Finnes discussed her nontraditional path to becoming a pharmacy leader and the ways that her melanoma diagnosis helped her gain perspective both personally and professionally. This session was informative and inspirational: Dr. Finnes gracefully discussed her experience as both a patient and a provider and helped the audience understand how these experiences shaped her leadership skills and management style. Her humble but impactful presentation left the audience feeling motivated and eager for day 2.

Saturday opened with a general session by Jason Bonner, PhD, on healthcare provider burnout and key strategies for developing resilience. Alarming, pharmacy ranks among the top professions with the highest rates of suicide. Dr. Bonner reviewed an article by Durham and colleagues revealing that pharmacists who had less than 15 years of experience were at higher risk of burnout.³ As a new practitioner, I was struck by this statistic, which really shifted my perspective on burnout. In his discussion of ways to develop resilience, Dr. Bonner highlighted the need for social support, optimism and confidence, effective communication, and the ability to manage powerful emotions and impulses.

Saturday’s later sessions included “Value-Based Care and the Role of Medication Optimization,” “Regulatory Updates,” “Strategies to Overcome Site-of-Care Restrictions,” and “Generational Differences.” Steven Gilmore, PharmD BCOP, Rowena Schwartz, PharmD BCOP FHOPA, and Damary Torres, PharmD, led the panel discussion of generational differences. The panelists described evidence-based differences between generations (Millennials, Generation X, Baby Boomers, and Generation Z) and ways to optimize collaboration between members of different generations. They reviewed positive and negative qualities attributed to each generation and discussed with the audience how to use each generation’s strengths to enhance teamwork.

The conference concluded Saturday afternoon with the keynote address “CPR for the Oncologist’s Soul” by Steven Eisenberg, DO. Dr. Eisenberg opened by expressing his appreciation for oncology pharmacists and the teamwork that is such an integral part of oncology care. He highlighted the ways that stress and anxiety have an impact on healthcare providers. In his heartfelt presentation, Dr. Eisenberg demonstrated how one of his patients changed his perspective on burnout through “the Flavie Effect.” Flavie, one of his patients, taught him that

“illness starts with ‘I,’ and wellness starts with ‘we.’” Throughout his address, Dr. Eisenberg emphasized the need for everyone to have Connection, be Present, and develop Resilience—CPR.

HOPA's 2020 Annual Conference will be held March 11–14, 2020, in Tampa, FL, and the 2020 Practice Management program will be held September 11–12, 2020, in Houston, TX. ●●

REFERENCES

1. Hematology/Oncology Pharmacy Association. 2019 Practice Management (course schedule and session descriptions).
2. Johnson SB, Park HS, Gross CP, Yu JB. Use of alternative medicine for cancer and its impact on survival. *J Natl Cancer Inst*. 2018 January 1;110(1):121-124. Available at <https://doi.org/10.1093/jnci/djx145>
3. Durham ME, Bush PW, Ball AM. Evidence of burnout in health-system pharmacists. *Am J Health Syst Pharm*. 2018 December 1;75(23 Supplement 4):S93-S100. Available at <https://doi.org/10.2146/ajhp170818>. Epub 2018 October 17.

Going Above and Beyond in Your Career Following Residency Training *(continued from p. 6)*

proficient in the oncology area; I presented monthly education sessions with formal lectures, gave updates on recent publications, and created annual competency assessments. At one time I was also responsible for developing annual competencies in compounding hazardous medications and tracking completion of this competency by staff pharmacists and technicians. After practicing for 4 years, I was able to show the value of having a PGY-2-trained oncology pharmacist on staff and completed a research project that demonstrated the need for a second pharmacy position in the Cancer Center to focus on patients receiving oral chemotherapy agents. On the basis of the project data, positions were created for a full-time PGY-2 trained oncology pharmacist and an oral chemotherapy financial navigator. After successfully hiring a financial navigator for patients receiving oral chemotherapy, the team and I were able to facilitate the creation of another new position for a financial navigator focusing on patients receiving intravenous medications.

In April 2019, I had the honor and privilege of accepting the HOPA New Practitioner Award at HOPA Ahead. The HOPA New Practitioner Award is given to an early-career practitioner who has made a significant contribution to developing or supporting clinical hematology/oncology pharmacy services. It is wonderful to know that I was nominated for this award by my current partner at work, a mentor of mine, and one of my past students, and I am humbled to have been chosen by the committee. Residency training set me up to be able to better serve my patients and community, even as a new practitioner. Residency also provided a framework that continues to be valuable as I seek to be an educator to other pharmacists and learners.

Oncology pharmacists are expanding their roles in both the clinic and inpatient settings. As more providers realize the benefits

of having a pharmacist working directly with them, they are requesting that a pharmacist join their team. I am still a newer practitioner, but in the 6 years I have been in practice, I have noticed that both nurses and providers rely on me to provide education to staff and patients and provide consultation on difficult patient cases. In some states, pharmacists can provide collaborative services to help reduce the medical practitioner's time and add value to the care of the cancer patient. Pharmacists are starting their own provider clinics to deliver supportive care management, patient instruction on oral chemotherapy (especially adherence), and education on many other aspects of cancer care. Our responsibilities and privileges will only increase as we promote our abilities and as our potential is realized by the providers we work with.

I believe that pharmacist-run clinics will continue to increase in number and expand in scope. Pharmacists provide a unique perspective for the patient and often incorporate specialized education, specialized knowledge about medicine, and information about cost into their treatment decisions. Looking back, I see that one of the biggest strengths of completing a PGY-2 oncology residency was the initial establishment of a professional network that continues to grow. It allows me to learn about the different roles oncology pharmacists are playing in clinics and infusion centers and bring suggestions back to my hospital for improvements in practice integration. Residency training advanced my skills and continues to give me opportunities for future advancement by teaching me how to navigate this complex healthcare system. As the American historian Daniel J. Boorstin said, “Education is learning what you didn't even know you didn't know.” ●●

REFERENCE

1. American Society of Health-System Pharmacists. Accreditation standards for PGY1 pharmacy residencies. Available at <https://www.ashp.org/Professional-Development/Residency-Information/Residency-Program-Directors/Residency-Accreditation/Accreditation-Standards-for-PGY1-Pharmacy-Residencies>. Accessed December 26, 2019.

Peripheral Neuropathy in Non-Hodgkin Lymphoma Patients Receiving Vincristine With and Without Aprepitant/Fosaprepitant



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Vincristine is a widely used agent in hematologic malignancies. Its efficacy and lack of myelosuppression make it an ideal antimicrotubule agent to include in combination chemotherapy regimens. Despite the widespread use of vincristine, dose-limiting peripheral neuropathy can occur. Risk factors for peripheral neuropathy include hepatic dysfunction (e.g., elevated total bilirubin) and concomitant use of CYP3A4 inhibitors (e.g., azole antifungals).

The antiemetic agent aprepitant and its IV formulation prodrug, fosaprepitant, are moderate CYP3A4 inhibitors. Aprepitant/fosaprepitant's CYP3A4 inhibition is illustrated by the dosing of dexamethasone, a CYP3A4 substrate, with and without concomitant aprepitant (12 mg vs. 20 mg, respectively).¹ It has been widely assumed that no significant drug-drug interaction between vincristine and aprepitant/fosaprepitant occurs. This assumption likely stems from a small pharmacokinetic study ($N = 12$) demonstrating similar plasma concentrations of vinorelbine when it is given with and without aprepitant.² Vinorelbine, also a vinca alkaloid, has minor differences in metabolism and elimination compared to vincristine, but both are primarily metabolized via CYP3A4.

However, Okada and colleagues identified aprepitant use as a risk factor for early-onset (after the first cycle) vincristine-induced peripheral neuropathy in Japanese patients receiving cyclophosphamide doxorubicin vincristine prednisone (CHOP)-like chemotherapy regimens.³ Given the biological plausibility of an aprepitant/fosaprepitant-vincristine interaction via CYP3A4 inhibition and these recent clinical data from Okada and colleagues, we decided to investigate the possibility of such an interaction in our patient population. Anecdotally, the ratio of local oncologists who routinely prescribe neurokinin-1 (NK-1) antagonists (aprepitant and fosaprepitant are the only NK-1 agents on formulary) with CHOP-like regimens is approximately 50:50. Therefore, we believed that a retrospective cohort study of CHOP-like chemotherapy patients who did or did not receive aprepitant/fosaprepitant would be feasible.

We retrospectively reviewed electronic medical records from July 1, 2010, to June 30, 2018, of all adults who received standard-dose vincristine-based chemotherapy regimens for non-Hodgkin lymphoma (NHL).⁴ The primary objective of our study was the incidence of early-onset peripheral neuropathy, with a secondary endpoint of cumulative rate of peripheral neuropathy. The incidence of peripheral neuropathy was determined by reviewing medical records for documented neuropathy symptoms or initiation of treatment for peripheral neuropathy (e.g., gabapentin). We determined that 186 patients would be needed to have 80% power to detect a 20% difference in early-onset peripheral neuropathy between the aprepitant/fosaprepitant group and the

group that did not receive an NK-1 antagonist. Fisher's exact test was used to analyze primary and secondary endpoints with a one-sided alpha of 0.05.

Ultimately, 115 patients were eligible for evaluation. The most common reason for exclusion was a cancer other than NHL ($n = 23$), multiple doses of vincristine/cycle ($n = 12$), lost to follow-up ($n = 9$), death ($n = 9$), and prior vincristine use ($n = 8$). More patients received aprepitant/fosaprepitant ($n = 71$) than did not ($n = 44$). However, baseline demographics were similar between the two groups regarding concomitant use of other 3A4 inhibitors such as fluconazole, vincristine dose, and age. There were fewer patients with diabetes in the aprepitant/fosaprepitant group (21.2% vs. 38.6%; $p = .04$). CHOP, rituximab-CHOP (R-CHOP), and rituximab cyclophosphamide vincristine prednisone (R-CVP) were the most common chemotherapy regimens in both groups (80.2% and 72.7%, respectively). There was no difference in the rate of early-onset peripheral neuropathy between groups (26.7% vs. 22.7%; $p = .627$). However, more overall peripheral neuropathy was seen in the aprepitant/fosaprepitant group (56% vs. 36%; $p = .036$). All cases of peripheral neuropathy were mild (grade 1).

The results suggest that CYP3A4-inhibiting NK-1 antagonists (aprepitant, fosaprepitant, netupitant) increase the risk of vincristine-induced peripheral neuropathy. However, one must consider the quality of evidence and balance that with the efficacy of NK-1 antagonists in preventing acute and delayed chemotherapy-induced nausea and vomiting (CINV). Certainly, our study suffers from several notable limitations. First and foremost, retrospective studies are subject to confounding variables, and any such results should be interpreted as hypothesis-generating rather than practice-changing. In addition, we included patients who were receiving treatment with common 3A4 inhibitors (such as fluconazole and diltiazem) to better represent real-world practice. Although the use of such drugs was well balanced between the groups, this inclusion may still confound results. Finally, our study was small and underpowered for our primary endpoint.

Given the quality of the evidence and the fact that all cases of peripheral neuropathy were mild, clinicians should feel comfortable using aprepitant or fosaprepitant with vincristine-containing regimens in patients at high risk of CINV. Given the frequency that CHOP-like regimens are administered with and without NK-1 antagonists at cancer centers around the country, similar studies should be conducted to better delineate the risk of vincristine-induced peripheral neuropathy with CYP3A4-inhibiting NK-1 antagonists. If you are reading this, please consider conducting such a study! Future considerations should include the possibility that longer 3A4 inhibition with aprepitant (given orally for 3 days) or netupitant (with a longer half-life) is a greater risk than fosaprepitant (given IV for 1 day), as well as the possible risk with vincristine-intensive regimens (e.g., EPOCH). One might also consider making a comparison of rolapitant use versus

aprepitant/fosaprepitant, because rolapitant is not a 3A4 inhibitor. Of course, a prospective study with similar cohorts would be ideal and would provide clinicians with higher-quality evidence. ●●

REFERENCES

1. McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther.* 2003;74:17-24.
2. Loos WJ, de Wit R, Freedman SJ, et al. Aprepitant when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone does not affect vinorelbine pharmacokinetics in cancer patients. *Cancer Chemother Pharmacol.* 2007;59:407-412.
3. Okada N, Hanafusa T, Sakurada T, et al. Risk factors for early-onset peripheral neuropathy caused by vincristine in patients with a first administration of R-CHOP or R-CHOP-like chemotherapy. *J Clin Med Res.* 2014;6:252-260.
4. Edwards JK, Bossaer JB, Lewis PO, Sant A. Peripheral neuropathy in non-Hodgkin's lymphoma patients receiving vincristine with and without aprepitant/fosaprepitant. *J Oncol Pharm Pract.* 2019. Published online ahead of publication on August 25, 2019.

Financial Toxicity in Cancer Care *(continued from p. 24)*

What strategies do you employ to help patients overcome the financial toxicity of cancer care?

Current strategies to combat financial toxicity include the use of drug manufacturers' copay cards, patient assistance programs, and disease-based grant funding for medication copay assistance. However, Shaver notes that some of the biggest difficulties she deals with are finding grants and funding related to rare diagnoses and off-label medication uses, in addition to accessing assistance with deductible payments for commercially insured patients. Suthar suggests keeping a list of resources and documents (phone numbers, points of contact, and eligibility and documentation requirements for various assistance programs) and connecting with field reimbursement representatives in drug companies who can help break down barriers to getting patients access to medications. He also recommends using online portals for real-time feedback. Courtney's strategy is proactive: she ensures that she "provides the best patient education to decrease toxicities and risks that may lead to the patient missing work or being admitted to the hospital." She highlighted the need to tackle financial toxicity from all angles. Luna points out that sometimes the only course of action is to help patients shift costs based on available resources. For example, you may find resources to assist with transportation so that patients can then apply the money saved toward another cost.

Discussion

We have many opportunities to improve how we manage the financial toxicity of cancer care. Institutions must make this improvement a priority because patients' inability to receive all aspects of care because of concerns about cost can have a negative impact on overall outcomes and survival. With rising healthcare and medication costs, this problem will only become more serious. Just as we assess for treatment-related toxicity during each visit, we should also assess a patient's risk for financial toxicity, particularly at high-risk points such as treatment initiations, dose changes, or changes in a patient's insurance. Although the perspectives shared here do not address all the problems, they show the variety of contributing factors and management strategies and highlight the importance of teamwork and inter-professional collaboration to help reduce the financial burden for cancer patients and their loved ones. ●●

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Request for Contributions of Best Practices

If you or your institution has a best practice related to financial toxicity, please contact Laura Cannon, member of HOPA's Patient Outreach Committee, at laura.cannon@austin.utexas.edu.

REFERENCE

1. Prasad V, De Jesus K, Mailankody S. The high price of anticancer drugs: origins, implications, barriers, solutions. *Nat Rev Clin Oncol.* 2017;14:381-390.

Larotrectinib and Entrectinib: A Golden Ticket for Adult and Pediatric Patients with NTRK Gene Fusion?



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A new class of anticancer agents has joined pembrolizumab as tissue-agnostic treatment options for solid tumor cancers. Pembrolizumab, an immune checkpoint inhibitor that targets the programmed cell death-1 (PD-1) pathway, was the first U.S. Food and Drug Administration (FDA)-approved tissue-agnostic agent targeting tumors with high microsatellite instability or DNA mismatch repair deficiency (dMMR) as a surrogate marker for high-somatic mutations.^{1,2} Pembrolizumab's tissue-agnostic approval added to the solid-tumor armamentarium based only on a tumor marker. Larotrectinib and entrectinib, which are tropomyosin receptor kinase (TRK) small-molecule inhibitors, are the second class of tissue-agnostic anticancer agents approved by the FDA, specifically for adult and pediatric patients with NTRK gene fusion.^{3,4} The NTRK genes NTRK1, NTRK2, and NTRK3 encode TRK proteins TRKA, TRKB, and TRKC, respectively. TRK expression is primarily limited to embryogenesis and regulation of the central nervous system (CNS).⁵ Somatic gene fusions involving the NTRK family of genes and subsequently downstream TRK fusion protein overexpression are implicated in driving proliferation in multiple solid tumors.

In common cancers, NTRK gene fusions are extremely rare, occurring in 0.1%–2% of patients as determined by highly sensitive next-generation sequencing (NGS).⁶ However, there is widespread variability in this incidence and bias, depending on the type of test used for NTRK gene fusions, with colorectal, appendiceal, and lung cancers and cancers such as sarcomas, melanomas, cholangiocarcinomas, and gliomas reportedly having an incidence of <5%. In certain exceedingly rare tumors, such as pediatric infantile fibrosarcomas, adult salivary gland tumors, and secretory breast cancers, the incidence of NTRK gene fusion is much higher, greater than 75%.⁶ Other rare tumors, such as thyroid carcinomas, congenital mesoblastic nephromas, and spitzoid melanomas, have reported incidences of 5%–75%, illustrating testing bias and variability in clinical laboratory technique.⁶ Detecting a NTRK gene fusion signal can currently be challenging, but its identification can give patients a long-term benefit.

Larotrectinib

Larotrectinib was approved on the basis of three phase 1 studies, the LOXO-TRK-14001, SCOUT, and NAVIGATE trials, involving 55 adults and children with TRK fusion-positive tumors.⁷ Eligible patients had locally advanced or metastatic disease and had exhausted standard-of-care treatments. Of the 55 patients, 17 unique cancer diagnoses were identified, with the majority of patients ($n = 30$) having salivary gland carcinomas, soft tissue sarcomas, or pediatric

fibrosarcomas. In addition, only one patient had evidence of CNS metastasis in the pooled data. At primary data cutoff, the overall response rate by independent radiologic review was 75% (95% confidence interval [CI], 61–85).⁶ A total of 13% of patients had a complete response (CR), 62% had a partial response (PR), 13% had stable disease (SD), and 9% had progressive disease (PD).⁷ The median duration of response (DOR) and progression-free survival (PFS) had not been reached after the median follow-up duration of 8.3 and 9.9 months, respectively.⁷ At 1 year, 71% of responses were ongoing, and 55% of responding patients remained progression free. At data cutoff, 86% of the patients with a response were continuing to receive treatment or had undergone curative surgery.⁷ Acquired resistance was detected in 19 patients receiving larotrectinib from kinase domain mutations, which may have important implications in the development of second-generation NTRK inhibitors.⁷

Updated data presented at the European Society for Medical Oncology Congress 2019 that now includes 153 patients continued to demonstrate a high overall response rate (ORR) of 79% (95% CI, 72–85), with 16% with a CR and 63% with a PR.⁸ Median DOR was 35.2 months (95% CI, 22.8 to not evaluable [NE]), median PFS was 28.3 months (95% CI, 22.1 to NE), and median overall survival (OS) was 44.4 months (95% CI, 36.5 to NE).⁸ Additional subgroup analysis showed a response rate of 75% in solid tumors with brain metastasis demonstrating CNS activity.⁹

An examination of adverse events from the LOXO-TRK-14001, SCOUT, and NAVIGATE trials showed that, overall, larotrectinib was well tolerated. The most common adverse reactions (all grades $\geq 20\%$) include fatigue, nausea, dizziness, vomiting, anemia, increased aspartate aminotransferase (AST)/alanine aminotransferase (ALT), cough, constipation, and diarrhea.¹⁰ Dose modifications were required in 37% of patients because of increased AST/ALT and dizziness.¹⁰

Entrectinib

Entrectinib was approved on the basis of early-phase pooled analysis of three studies, the STARTRK-1, STARTRK-2, and ALKA-372-001 trials, composed of 54 adult patients with NTRK fusion-positive metastatic or advanced tumors with or without brain metastasis. Results demonstrated a high ORR of 57.4% (95% CI, 43.2–70.8) with 7.4% of patients achieving a CR.⁴ Median DOR was 10.4 months (95% CI, 7.1 to not reached [NR]), PFS was 11.2 months (95% CI, 8–14.9), and median OS was 20.9 months (95% CI, 14.9 to NR).¹¹

In adult patients with brain metastasis ($n = 12$) across the three studies, ORR was consistent with patients without brain metastasis at 50%, with median PFS of 7.7 months (95% CI, 4.7 to NR).¹¹ In addition, intracranial ORR was 54.5% in patients with baseline CNS disease, demonstrating entrectinib's activity across the blood-brain barrier.¹¹

Approval of entrectinib for pediatric patients was based on early results from the phase 1/1b study STARTRK-NG that enrolled 29 patients with primary CNS tumors, neuroblastomas, and other solid tumors with NTRK fusions, ROS1 fusions, or ALK fusions. Of six patients with CNS tumors, one patient achieved a CR, three patients achieved a PR, and two patient responses were yet to be confirmed.¹² Of eight patients with extracranial solid tumors, six patients responded, including two ALK-fusion patients who obtained a CR and PR, three NTRK-fusion patients who obtained a PR, and one ROS1-fusion patient who obtained a PR. Median time to response was 57 days (30–58 days).¹² The median duration of therapy was 85 days (6–592 days) for all patients, 56 days (6–338 days) for nonresponders, and 281 days (56–592 days) for responders.¹²

Adverse events with entrectinib were seen in NTRK fusion, ROS1 mutation–positive, and ALK mutation–positive patients. Examining the safety profile from STARTRK-1, STARTRK-2, STARTRK-NG, and ALKA-372-001 trials showed that entrectinib was well tolerated.⁹ The most common toxicities (all grades \geq 20%) include fatigue, edema, pyrexia, constipation, diarrhea, nausea, vomiting, dizziness, dysgeusia, dysesthesia, and myalgias. Dose reductions were required in 29% of patients because of dizziness, fatigue, anemia, increased creatinine, and weight gain.¹³

NTRK Gene Fusion Testing

The major hurdle in treating patients with larotrectinib or entrectinib is appropriately detecting patients with NTRK gene fusions. Approaches that may be used to directly or indirectly detect the presence of gene fusion include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT-PCR), and RNA or DNA

NGS.¹⁴ IHC, FISH, and RT-PCR are low cost and readily available but are associated with a higher proportion of false-positive and false-negative results. IHC enables detection of TRK overexpression as a surrogate marker for NTRK fusion proteins, leading to possible detection of nonpathogenic fusions.¹⁴ FISH and RT-PCR require a known target sequence to detect NTRK 5' fusions, which may lead to missing novel NTRK fusions and subsequently result in false negatives.¹⁴ NGS provides a precise method of detecting known and novel NTRK gene fusions, but its availability varies by region.¹⁴ Testing algorithms are still in development; a staged strategy has been proposed. Tumors with a high frequency of NTRK gene fusions, such as pediatric infantile fibrosarcomas and secretory breast cancers, can be screened with IHC or FISH and reflex to NGS to account for false-negative results.^{14,15} The treatment of tumors with a low frequency of NTRK gene fusion, such as colon cancer or lung cancer, should proceed directly to NGS.¹⁴

Conclusions

Positive early-phase studies have demonstrated high response rates and durable responses with larotrectinib and entrectinib in adult and pediatric patients with NTRK gene fusions. Similar to the results of microsatellite instability–high or dMMR testing, a positive signal can provide an extra line of therapy for patients with solid tumors. In the future, long-term follow-up and further studies are needed to determine differences in safety and efficacy between larotrectinib and entrectinib. Adult and pediatric pharmacists in all solid-tumor subspecialties should assess for the opportunity to advocate for NTRK gene fusion testing to potentially find a golden ticket for patients on their last line of treatment. ●●

REFERENCES

1. U.S. Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. Available at www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm. Accessed November 17, 2019.
2. Le DT, Uram JN, Wang H, et al. PD-1 blockage in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372:2509–2520.
3. U.S. Food and Drug Administration. FDA approves larotrectinib for solid tumors with NTRK gene fusions. Available at <https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions-o>. Accessed November 17, 2019.
4. U.S. Food and Drug Administration. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC. Available at <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc>. Accessed November 17, 2019.
5. Chao MV. Neurotrophins and their receptors: a convergence point for many signaling pathways. *Nat Rev Neurosci*. 2003;4:299–309.
6. Hsiao SJ, Zehir A, Sireci AN, Aisner DL. Detection of tumor NTRK gene fusions to identify patients who may benefit from tyrosine kinase (TRK) inhibitor therapy. *J Mol Diagn*. 2019;21:553–571.
7. Drilon A, Laetsch TW, Kummar SG, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378:731–739.
8. Hyman DM, van Tilburg CM, Albert CM, et al. Durability of response with larotrectinib in adults and paediatric patients with TRK fusion cancer. Presented at ESMO Congress 2019; September 27–October 1, 2019; Barcelona, Spain. Poster 445PD.
9. Drilon AE, DuBois SG, Farago AF, et al. Activity of larotrectinib in TRK fusion cancer patients with brain metastases or primary central nervous system tumors. *J Clin Oncol*. 37;15 suppl. 2006.
10. Vitakvi (larotrectinib) [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; July 2019.
11. Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive (NTRK-fp) tumors: pooled analysis of STARTRK-2, STARTRK-1, ALKA-372-001. Presented at ESMO Congress, October 21, 2018, Munich, Germany. Poster LBA17.
12. Robinson GW, Gajjar AJ, Gauvain KM, et al. Phase 1/1b trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumors including central nervous system (CNS) tumors. *J Clin Oncol*. 2019;37;15-suppl:10009.
13. Rozlytrek (entrectinib) [package insert]. South San Francisco, CA: Genentech USA, Inc.; 2019.
14. Penault-Llorca F, Rudzinski ER, Sepulveda AR. Testing algorithm for identification of patients with TRK fusion cancer. *J Clin Pathol*. 2019;72:460–467.
15. Albert CM, Davis JL, Federman N, Casanova M, Laetsch TW. TRK fusion cancers in children: a clinical review and recommendations for screening. *J Clin Oncol*. 2019;37:513–524.

≡ Board Update ≡

Looking Back, Looking Ahead



Susanne Liewer, PharmD BCOP FHOPA
HOPA President (2019-2020)

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The members of HOPA's board of directors hope you had a restful and enjoyable holiday season full of good times with family and friends, as well as some time to relax after a busy year. At the start of each new year, it is common to reflect on our past endeavors, and 2019 was a busy and productive year for HOPA and our members!

HOPA had many significant accomplishments during the past year. In 2019 our membership increased to more than 3,200! That membership includes pharmacists and technicians who are involved in all phases of oncology pharmacy. It is made up of students; residents; inpatient, outpatient, infusion center, and specialty pharmacists; and those who work in the pharmaceutical industry. HOPA's diverse membership allows us to provide a variety of educational and professional opportunities, whether a person is just starting out in oncology pharmacy or is a seasoned practitioner.

HOPA's educational offerings in 2019 were superb! Our annual conference, held in Fort Worth, TX, provided outstanding education for the more than 1,000 members who attended the live conference and those who attended virtually. HOPA also collaborated with the Academy of Managed Care Pharmacy to host a Value in Cancer Care Forum, "Pharmacy's Call to Action," in Washington, DC, in June 2019. Experts representing all phases of health care came together to discuss the ever challenging task of defining value in the treatment of cancer. In September, HOPA's Practice Management program, held in Charlotte, NC, was well attended and provided real-world education for our members who work in the field of pharmacy administration. In addition to our live educational offerings, HOPA continues to provide members with webinars, on-demand education, and opportunities for Board Certified Oncology Pharmacist (BCOP) credit. In 2019 HOPA was proud to offer sessions totaling 38 BCOP credits for members seeking continuing education or advanced clinical education.

HOPA members were incredibly productive in 2019 in various aspects of oncology pharmacy. Whether they were asking

questions or sharing their experiences in HOPA's e-mail discussion groups, completing committee charges, or participating in collaborations with allied organizations, our members were promoting the role of the oncology pharmacist. HOPA, in collaboration with the Oncology Nursing Society (ONS), published the position statement "Ensuring Healthcare Worker Safety When Handling Hazardous Drugs." HOPA and ONS highlighted the changes in U.S. Pharmacopeia General Chapter 800 and the ways to best protect our members from exposure to hazardous agents. In addition, HOPA also published a Women in Leadership white paper highlighting the challenges that women may face in leadership roles and issuing a call to action to address inequities. We thank each HOPA member who worked on our committees and task forces or served as writers, reviewers, or educational speakers. Your work is inspiring, and your contributions are truly appreciated.

As grateful as we are for HOPA's remarkable accomplishments in 2019, we are looking ahead to the many things lined up for a wonderful 2020! Our 2020 annual conference will be held in Tampa, FL, and our Annual Conference Committee has an exceptional roster of clinical experts in their fields who are looking forward to sharing their experiences with attendees. In the John G. Kuhn Keynote Lecture, Leigh Boehmer, PharmD BCOP, will share his personal experiences as a survivor of metastatic testicular cancer. We look forward to learning from Dr. Boehmer and our clinical faculty at the conference. In 2020 HOPA will also offer a BCOP Preparatory and Recertification Course for those members wishing to prepare for the BCOP exam or take a review course for their continuing education. HOPA looks forward to continued collaborations with Medscape Oncology to provide oncology education to a broader pharmacy audience. Check out the shared webpage by registering for free at www.medscape.org/sites/advances/hopa. Finally, be on the lookout for our first podcast and the launch of our core competency certificate program. The year ahead promises to be fruitful indeed! ●●



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PREPARATORY AND RECERTIFICATION COURSE

HOPA's BCOP Preparatory Course

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helps BCOP-certified oncology pharmacists earn the **CE credits needed for recertification**. Those completing the course can earn up to 28 hours of BCOP credit and up to 33.5 ACPE credits.



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