# HOPA NEWS

*Pharmacists Optimizing Cancer Care®*

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# Vaccinations in Cancer: A Pharmacist's Survival Guide

**page 3**

IN THIS ISSUE: A Joint Position Statement from HOPA and the Oncology Nursing Society


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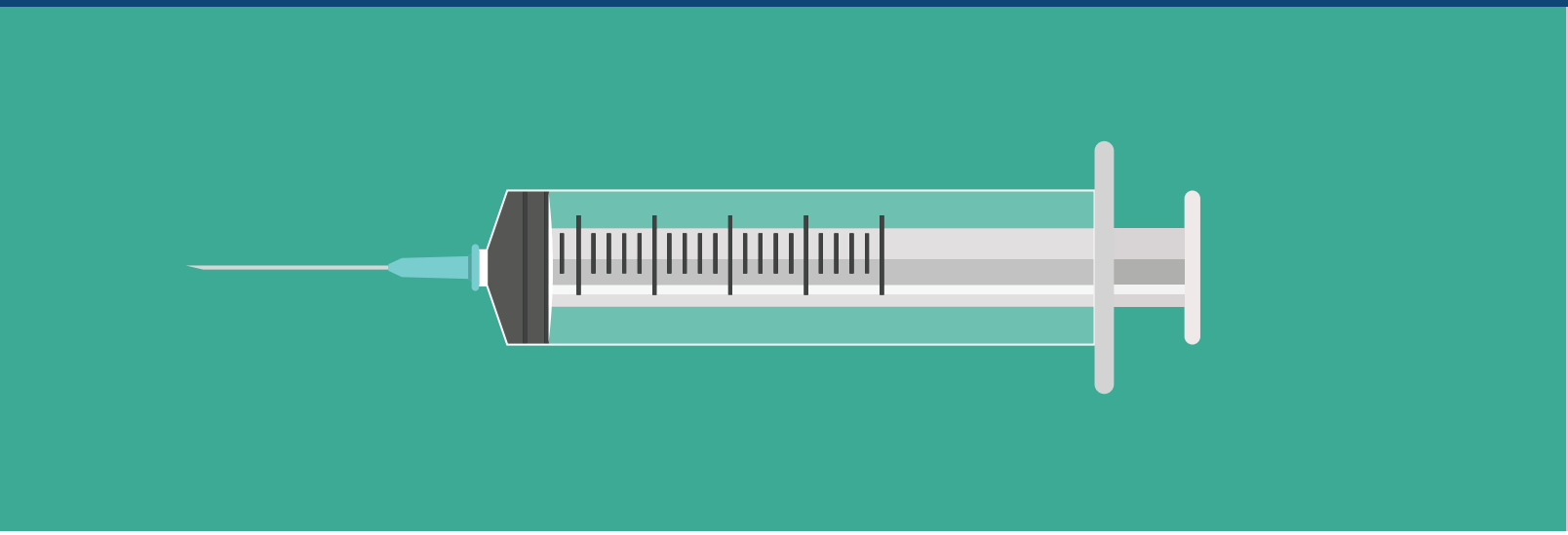
## CONTENTS

FEATURE



# Vaccinations in Cancer: A Pharmacist's Survival Guide

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Between January 1 and April 26, 2019, 704 cases of measles had already been reported in the United States. (This figure puts 2019 on track to have the highest number of U.S. cases reported in a single year since 1994, when 963 cases were reported.) Of the 704 cases, 71% occurred in unvaccinated persons, and 6 out of 13 reported outbreaks occurred in underimmunized settings.[1] This recent outbreak not only highlights the importance of increasing vaccination efforts in the general population but warrants increased attention to ensure that individuals with cancer are being adequately screened for appropriate vaccinations.

People with cancer are at an increased risk of vaccine-preventable disease compared to the general population. Oncologic and hematologic malignancy, immunosuppressive therapy (IST), and exposure to pathogens from healthcare personnel, the environment, and nonvaccinated individuals increase the risk for infection. Although it is known that the rate of infection-related morbidity is high,[2] barriers to having individuals with cancer receive vaccinations remain.[3]

## Influenza

Individuals with malignancy are at a particularly high risk for contracting influenza because of multiple risk factors, including co-infections, advanced age, comorbid conditions, and the underlying malignancy itself.[4] Influenza in individuals with cancer is associated with more severe disease, a greater number of complications and hospitalizations, and higher mortality; however, adherence to recommendations for routine influenza vaccination remains low.[4-6] The 2013 Infectious Diseases Society of America (IDSA) guidelines for vaccination in immunocompromised persons recommend that inactivated influenza vaccine (IIV) be given annually in cases of hematologic or solid tumor malignancy, except in those receiving anti-B-cell antibodies (e.g., rituximab) or intensive chemotherapy (defined as induction or consolidation chemotherapy in acute leukemia).[7] Live attenuated influenza vaccines are not recommended. Similar recommendations are proposed by the National Comprehensive Cancer Network (NCCN) and Advisory Committee on Immunization Practices (ACIP).[8,9] Guidelines recommend that IIVs be given at least 2 weeks prior to starting IST, because viral replication and development of immunologic response occur within 3 weeks of administration.[10] Although the guidelines make this distinction, studies have demonstrated that immunogenicity of IIV is similar pre- and peri-IST.[11,12] Considering the risk of complications from influenza in those with cancer, one can see that the benefit of annual IIV administration peri-IST in providing protection against seasonal influenza strains may outweigh potential risks.

## Herpes Zoster

Herpes zoster (shingles) is a disease caused by reactivation of latent varicella zoster virus (VZV) in the dorsal root and cranial nerve ganglia, most commonly caused by a decline in VZV-cellular immunity.[13] Because of immune dysfunction from therapy or underlying malignancy, individuals with cancer are at a 40% higher risk of developing shingles—with the greatest risk among those with hematologic malignancies and those receiving chemotherapy. Interestingly, the risk of shingles can be elevated for up to 2 years before the initial diagnosis, likely because of diminished T-cell-mediated immunity from the underlying hematologic malignancy itself.[14] The two shingles vaccines currently available are zoster vaccine live (ZVL) (Zostavax) and recombinant

zoster vaccine (RZV) (Shingrix).[15,16] RZV has gained widespread use since it was approved by the U.S. Food and Drug Administration in 2017. Its appeal is largely due to its better and longer-lasting efficacy and its recombinant formulation compared to ZVL.[15-17] ACIP now recommends RZV for persons on low-dose IST (<20 mg/day of prednisone or equivalent).[21]

RZV has shown sustained efficacy of >95% in adults 50 years and older and approximately 90% efficacy in adults 70 years and older; by contrast, ZVL efficacy declines with advanced age and has only 38% efficacy in adults 70 years and older.[17-20] Because of unexpected widespread use, however, RZV has been in shortage since 2018. This has led to challenges with using ZVL because current guidelines do not recommend administration of live vaccines to individuals receiving chemotherapy or radiation until they have been off therapy for at least 3 months and until evidence of substantial T-cell-mediated immunity has been seen.[7,9] If ZVL is given, it should not be administered within 4 weeks of starting highly immunosuppressive therapy because administration while the patient is immunocompromised increases the risk of disseminated disease.[7,15] Pharmacists should be aware of differences in efficacy, formulation, dosing schedules, route of administration, and appropriate timing of vaccinations when considering the use of either zoster vaccine product in individuals with cancer.

## Pneumococcal Disease

Underlying malignancy is also associated with a greater risk for invasive pneumococcal disease (IPD). The incidence of IPD is the highest in adults with hematologic malignancy (422.9 of 100,000 persons); the incidence in adults with solid tumor malignancies is 300.4 of 100,000 persons.[22] This risk is 23- to 48-fold higher than that for healthy adults. The two pneumococcal vaccinations approved in the United States are pneumococcal polysaccharide vaccine 23-valent (Pneumovax 23/PPSV23) and pneumococcal conjugate vaccine 13-valent (Prevnar 13/PCV13)[23-24]. The use of pneumococcal vaccines is reported to be 65%–84% effective against IPD; however, its protective effects in immunocompromised individuals are limited, with response rates reported to be <50% in those with hematologic malignancy.[22,25-27]

PCV13 was initially approved in 2010 for the prevention of IPD and otitis media in infants and children and received approval the following year for prevention of pneumonia and IPD in adults 50 years and older.[28] PCV13 is also recommended for adults newly diagnosed with hematologic or solid tumor malignancies.[7,9] PPSV23 is recommended for adults 60 years and older and for those ages 19–59 years who are at high risk (e.g., those with malignancy or functional or anatomic asplenia). The products differ in indication, dosing schedule, presence of serotypes, and formulation.[9] They also have distinct effects on the immune system. Protein-conjugated vaccines (PCVs) are associated with sustained memory cells and production of high-affinity antibodies by a T-cell-dependent response.[29] In contrast, pneumococcal polysaccharide vaccines (PPSVs) do not elicit a T-cell-dependent response; therefore, production of memory B cells is reduced, decreasing the duration of protection.[30] These differences in immune response are important considerations when one is determining timing, order of administration, and appropriateness of pneumococcal vaccination.

## Functional and Anatomic Asplenia

The spleen is a complex secondary lymphoid organ that serves to clear blood-borne antigens, microorganisms, and aging blood cells.[31] The spleen has two primary anatomic regions: the red pulp and the white pulp. The red pulp primarily contains macrophages that serve to filter blood and recycle iron. The white pulp is similar to a lymph node and contains T cells and marginal zone (MZ) B cells. In the presence of microorganisms and antigens, the white pulp regulates antigen-specific immune responses that are recruited in response to the presence of foreign antigens, produced or amplified within the spleen, and mobilized from the spleen to other tissues.[32] It's important to note that MZ B cells are uniquely capable of producing antibodies, generating memory B cells arising from the spleen, and initiating T-cell-dependent immune responses to encapsulated antigens. In addition, specific subsets of macrophages in the spleen express pathogen receptors to encapsulated bacteria, allowing for recognition and destruction of these bacteria through the complement system for adequate elimination.[33] Therefore, in persons with functional or anatomic asplenia (i.e., tumor involvement in spleen, immune thrombocytopenic purpura, autoimmune hemolytic anemia, sickle cell anemia, and malignant hematologic disease), the risk of infection from encapsulated organisms (*Streptococcus pneumoniae, Haemophilus influenzae* type b [Hib], and *Neisseria meningitidis*) is high because of decreased phagocytic activity, decreased immunoglobulin production, and depressed T-cell function. In a cohort of veterans with splenectomies, patients were at a twofold to threefold increased risk of pneumococcal pneumonia, meningitis, and septicemia, which highlights the importance of appropriate vaccinations in this population.[34]

No vaccine is contraindicated for this population, except for live attenuated influenza vaccines. All vaccines recommended for asplenic individuals should be administered 2 weeks before an elective splenectomy (preferred) or 2 weeks after surgery. PCV13 is recommended for asplenic patients 2 years of age and older. Subsequent doses of PPSV should follow ACIP recommendations for number of doses and timing of administration.[9] One dose of Hib is recommended if it has not previously been given. Those with functional or anatomic asplenia should also be vaccinated against meningococcal groups A, B, C, Y, and W-135. Four meningococcal vaccinations are currently on the market: meningococcal (groups A/C/Y and W-135) diphtheria conjugate vaccine (Menveo and Menactra) and the meningococcal group-B vaccine (Bexsero and Trumenba). Both Menveo and Menactra contain *N. meningitidis* oligosaccharides conjugated to a diphtheria protein derived from *C. diphtheriae* to produce a robust immune response to the polysaccharide component of the vaccine.[35,36] Either product is given as a two-dose series at least 8 weeks apart with revaccination every 5 years.[9,35,36] Bexsero and Trumenba are composed of recombinant proteins from *N. meningitidis* and given as either a two-dose series

(Bexsero) or a three-dose series (Trumenba). It is recommended that the same vaccine be used to complete the series because these products are not interchangeable.[9,37,38]

## Current Challenges and Future Directions

### Measles Outbreaks

In 2000, measles was declared eradicated from the United States. Since then, antivaccination efforts triggered by a fabricated link between autism and the measles, mumps, and rubella (MMR) vaccination have resulted in exponential year-over-year increases in measles cases.[1] Cancer patients are a high-risk population for infection with measles, particularly if they have never been vaccinated with MMR. Because the MMR vaccine is a live attenuated vaccine, it is contraindicated for individuals with a severe immunodeficiency, such as those with hematologic or solid tumors or those receiving chemotherapy or IST. This presents a dilemma for cancer patients, particularly for those who have not previously received the MMR vaccine. Thus, the Centers for Disease Control and Prevention recommends that eligible family members and close contacts of those with cancer receive the two-dose MMR vaccination series in order to gain some level of protection in the patient's environment. Caution is warranted in areas with recent outbreaks of measles cases, especially for patients undergoing treatment and those without a history of MMR vaccination.

### Determining Protective Immunity for Pneumococcal and VZV Vaccines

The ability to determine protective immunity is heavily dependent on the type of assay used and the ability to correlate the results with clinical interpretation. Ideally, full protective effects from vaccinations should induce both humoral and cell-mediated immunity.[39] Determining what constitutes an effective antibody response to particular vaccinations remains controversial. For example, response to the pneumococcal vaccines (PCV13 and PPSV23) is determined by the percentage of serotypes that show a twofold to fourfold increase in antibody response from baseline. Measuring antipneumococcal antibodies (PnAb) at baseline and after vaccination is the current practice for determining protective immunity. The accepted PnAb level that constitutes protective immunity for the polysaccharide vaccine is 1–1.5 μg/mL 1-month postvaccination and theoretically provides protection for 5 years. People can be classified as having deficient production of antibodies if they respond to less than 50%–70% of the serotypes analyzed in the assay.[40]

Because of differences in analytical methods used to define thresholds (particularly in people with cancer or immunocompromised individuals), as well as changes in the PnAb based on age, clinicians should use clinical judgment when considering patients for revaccination and should consider obtaining a PnAb level if deficient production of antibodies is suspected. Protection against VZV is highly dependent on T-cell-mediated immunity (CMI) to maintain VZV latency and minimize the severity of infection if it occurs. Unfortunately, VZV-CMI and age are negatively correlated, and no standard marker of CMI confers protection. However, the new shingles vaccine (RZV) is uniquely formulated to include a VZV glycoprotein E (gE) conjugate that is a target for the VZV-specific antibody and CD4-positive T cells.

In addition, the AS01B adjuvant system that contains gE has the ability to stimulate both humoral immunity (including VZV-specific memory immunity) and cell-mediated immunity.[41] Although a measure of immune response that confers protection against herpes zoster is unknown, the immunologic response of RZV has been evaluated and is based on anti-gE antibody levels. RZV given at 0 and 2 months or 0 and 6 months showed similar immunologic response based on anti-gE levels 1 month after the second dose was given.[16] For those with cancer and those who are immunocompromised, RZV is predicted to provide reactogenicity similar to that for those who are immunocompetent. Phase 1/2 trials to date in autologous transplant recipients and in people with Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, or acute leukemia showed sustained immunogenicity for up to 12–18 months.[41-43]

To summarize, what constitutes an effective response to a particular vaccination for those with cancer remains controversial. Although newer vaccination formulations (e.g., RZV) have demonstrated immunogenicity in this population, similar research is needed for other vaccinations in order to define protective immunity.

### Intravenous Immune Globulin

Intravenous immune globulin (IVIG) is a polyclonal immunoglobulin derived from pooled plasma from blood donors. It is hypothesized that polyclonal antibodies in the IVIG product can interfere with immunity against active immunizations, particularly the MMR vaccine and varicella vaccine. Passively acquired immunity from IVIG can inhibit an immune response to the MMR vaccine for 3 months or longer; however, the duration is based on the dose of IVIG given. MMR and varicella vaccines should be given at least 2 weeks before IVIG because vaccine viral replication and immune response can take 2–3 weeks to develop. If IVIG is given within 2 weeks of MMR or varicella vaccine, clinicians should consider doing serologic testing for protective immunity following completion of IVIG or readministering the vaccines per ACIP recommendations. If either vaccine cannot be given prior to IVIG, vaccination should be delayed until 3–11 months after IVIG to provide ample time for elimination of the passively acquired immune effects from IVIG.[44-47] Per ACIP recommendations, typhoid, yellow fever, live influenza vaccine, zoster, and rotavirus can be given any time before, during, or after administration of IVIG.[45]

### Immunotherapy

Immunotherapy has revolutionized the treatment of cancer. Immune checkpoint inhibitor (ICI) augmentation of T-cell immunity and blockade of programmed cell death-1 (PD-1) signaling increases virus-specific immunity.[48] It is unknown whether vaccination during treatment with ICIs alters the frequency of immune-related adverse events (irAEs). Clinical trials for ICIs have varied in their guidance regarding administration of vaccinations. Data on the safety and efficacy of vaccination in patients receiving ICIs are lacking. One cohort study of 23 patients with solid tumors

treated with PD-1/programmed death-ligand 1 blockade who received the seasonal influenza vaccine showed seroprotective levels similar to those of healthy age-matched controls and a higher rate of seroconversion, indicating a more robust immune response. However, the rate of irAEs was higher (52.2%) than anticipated, with 26.1% of patients experiencing a severe complication, which indicates a possible hyper-response due to cross-presentation of shared antigens.[49] This finding raises the question of optimal timing of vaccination administration and safety in combination with immunotherapy. Although it is hypothesized that seroprotection against influenza is robust, larger prospective studies are needed to determine the safety and efficacy of vaccination with immunotherapy. Until more is known, caution should be taken with vaccination for patients who are receiving immunotherapy.

## Conclusion

Identifying vaccination needs in patients with cancer has become increasingly complex in light of new vaccination formulations and a continuously changing therapeutic landscape. Hematology/oncology pharmacists should have a working knowledge of how anticancer therapies may augment the immune response to vaccination and guide optimal decision making on their use in those with cancer. ●●

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*(continued on p. 9)*

# A Circuitous Route to Oncology Pharmacy—Does It Matter How We Get There?

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If asked to write about an "atypical" path to oncology pharmacy, I might reply, "Is there a *normal* one?" Prior to the advent of the PGY2 oncology residency, I am not sure that there was. Today, to move into a dedicated oncology position in a timely fashion, you would start a PGY1 residency after pharmacy school graduation, enroll next in a PGY2 oncology residency, and then come out looking for a job.

Briefly, my path was, and continues to be, a little different. I skipped the graduation ceremony for my bachelor's degree in pharmacy and got married that day instead (best decision of my life), and I went to work as an assistant manager for Hook's Drugs in Indianapolis. Six years later (by then I was manager of the Hook's in Edinburgh, IN), I decided that I wanted to explore different clinical opportunities and left retail work for hospital pharmacy. On my last day in Indianapolis, we loaded up the Ryder truck, my wife went to her medical school graduation, I went to my graduation from the MBA program I had been attending in the evenings, we returned our gowns, and we drove to Oregon. My wife, Frances, started her medical residency, and I, after several months of looking and 14 interviews, was hired into a relief position at Oregon Health and Science University Hospital. Volunteering for any position needing coverage, I was trained in inpatient psychiatry, sterile products, medicine, surgery, and pediatrics, and I eventually procured a position as an ICU pharmacist.

About 6 months into my ICU pharmacy career, the oncology pharmacist needed vacation coverage, and with some trepidation, I agreed to do it. I had not been attracted to oncology during pharmacy school—having to deal with nausea and vomiting, alopecia, and worse did not hold great appeal—but I was surprised to find that rounding with the team, managing patient symptoms, and overseeing chemotherapy orders were both mentally stimulating and rewarding. The patient contact was among the things I had missed most from my retail days. From then on, I volunteered to do relief coverage for oncology, and in 1992, when the regular position opened up, I successfully bid for it. My practice has developed from that starting point, with time spent in many clinical endeavors, research in clinical and practical aspects of oncology, teaching and precepting, and a stint in management followed by a return to clinical practice and research. With additional study I received a postbaccalaureate PharmD degree as well as BCPS and BCOP certifications, among other things.

## Perspectives on Taking an Indirect Route

**No experience is wasted.** Numerous aspects of my retail career and other work experiences have benefited me in my hospital-based practice. Experience working with people, skills in self-management and management of others, public speaking experience, work in sales and budgeting, and many other experieces continue to serve me well as a steward of oncology practice.

**Put yourself outside of your comfort zone.** Progress rarely occurs if you do not seek out new methods, look at new areas, and apply yourself in new ways. Though I often grumble about technology, when something really useful comes along, I try to be an early adopter. Use past experiences to gauge where your talents lie, and try not to repeat old mistakes in new ways as you take opportunities to develop your practice.

**Be a team player.** I learn continually from my coworkers and would never have had some of my practice opportunities without them. I encourage you to view the "team" as including those beyond your fellow pharmacists, though they are likely your closest team members and the ones you engage with most frequently. I have learned valuable life lessons, practices, and skills from nurses, physicians, nurse practitioners and physician assistants, sales representatives, medical science liaisons, and students—and frequently from patients. The peers whom I have watched and emulated during my work experience include those who follow the current template for oncology pharmacy practice and those who do not. Although I don't enjoy every aspect of my daily practice, I try to participate fully in all of them and have found that this effort results in better patient care.

**Change is the one constant.** Whether driven by technology, new therapeutics, institutional growth, social or family pressures, or other forces, you should expect to remake yourself and possibly your practice about every 5 years. This path is challenging to predict, and the rate of change may be speeding up, but I can say that change has been my constant companion in my nearly 34 years of pharmacy practice.

**Enjoy being outside of work.** My spouse, my children, and my family have a tremendous influence on my life. I could not be where I am today without my spouse, and I look forward to seeing her every day. Together we have found a love of hiking and camping,

*(continued on p. 9)*

# Evaluation of Pain Management in Sickle Cell Patients Through the Use of Pain-Control Algorithms and Provider Education

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Sickle cell disease is a group of inherited red blood cell disorders in which hemoglobin forms into an unusually sickled shape, causing the natural red blood cell to shorten its life span and lose its flexibility.[1] Sickle cell patients often have frequent hospital readmissions throughout their lives, with one of the precipitating factors being vaso-occlusive crisis (VOC). VOC occurs when the sickled cells occlude the vasculature, leading to hypoxia in the tissue following the occlusion.[1] Tissue hypoxia is known to cause an intense amount of pain and is the main cause of sickle cell patients' admission to the hospital. Optimal treatment for VOC is rapid administration of intravenous (IV) opioids followed by physician-driven pain management.[2] Inconsistencies in the maintenance of patients experiencing VOC have been observed at Jackson Memorial Hospital, inconsistencies likely due to the subjective nature of a patient's pain level and provider preference. The variability in the treatment of this condition has led to an increase in hospital length of stay, variable prescribing of pain regimens, and a decline in patient satisfaction at Jackson Memorial Hospital.

**"The success of the implemented algorithm and order set was found to be dependent on prescriber participation and education on the mechanics of using the power plan and algorithm."**

Because of the concerns addressed above, an inpatient sickle cell pain management algorithm was formulated and implemented at Jackson. This pharmacy-driven protocol involved a multidisciplinary team of physicians, nurses, nurse practitioners, and a pharmacy resident. The inpatient sickle cell pain management algorithm outlines preferred opioid regimens, options for nonopioid adjunctive therapies, guidance to transition from IV to oral opioids, and suggested opioid regimens upon discharge. This algorithm was created by a team of pharmacists using the current literature on VOC and guidelines for treating it. In conjunction with the algorithm implementation, a power plan was released in the Cerner electronic medical record database at the same time. A *power plan* is an order set that aids physicians when they are ordering several medications for a patient subset. The sickle cell power plan provides an easy way to order medications that a sickle cell patient may need and follows the algorithm for initial pain management. The power plan was implemented as a tool for physicians, though its use was not mandatory. The purpose of this project was to standardize the approach to pain management for admitted sickle cell patients who were experiencing a VOC.

The pharmacy resident completed a retrospective two-phase study that evaluated VOC pain management before and after implementation of the sickle cell pain management algorithm. Phase 1 was conducted retrospectively to evaluate data from July 2018 to September 2018. Data were collected in order to establish a baseline for prescribing patterns, morphine equivalence trends, and the effect of prescribing trends on length of stay. Phase 2 was conducted from January 2019 to March 2019 following implementation of the algorithm. Patients admitted for VOC were identified via an International Classification of Diseases-10 code. As part of the implemented protocol, each patient's medication profile was evaluated daily by a pharmacy resident to consider appropriateness of the pain regimen and identify potential areas of deescalation of therapy. The goal of the medication review was to aid the providers in adhering to the sickle cell pain management algorithm. If the resident found room for improvement, the patient's primary medical team was contacted in order to optimize therapy.

The primary outcome measured was hospital length of stay. Secondary outcomes were time to transition from IV to oral opioids, use of concomitant central nervous system (CNS) depressant medications, the appropriateness of hydroxyurea use, overall power plan use, and 30-day readmission rates related to VOC.

After implementing the sickle cell inpatient power plan and sickle cell pain management algorithm, data from 114 patients (phase 1, $n = 57$; phase 2, $n = 57$) showed a trend toward a decreased length of stay, with an overall reduction of 0.7 days ($p = .25$), though the results were not statistically significant. VOC-related hospital readmission rates at 30 days did decrease significantly from 41% pre-algorithm to 26% post-algorithm ($p = .02$). The sickle cell power plan was used in 63% of cases. The most significant change seen with the implementation of the sickle cell algorithm was a decrease in the concomitant use of IV diphenhydramine. Preimplementation of the algorithm, 84% of patients received at least one dose of IV diphenhydramine versus 68% of patients postimplementation ($p = .08$). Additionally, 63% of patients were receiving more than five doses of IV diphenhydramine preimplementation, whereas only 16% received that many in the postimplementation group ($p = .002$). The reduction of IV diphenhydramine use was targeted in order to mitigate potentially harmful adverse CNS effects that may arise because of concomitant CNS depressant usage.

After implementation of the sickle cell pain management algorithm, a nonstatistically significant decrease in length of stay and statistically significant 30-day readmission rate for sickle cell

patients admitted for VOC were found. The success of the implemented algorithm and order set was found to be dependent on prescriber participation and education on the mechanics of using the power plan and algorithm. Deescalating therapy was most successful when an interdisciplinary approach was used. On the basis of these results, a sickle cell task force that meets weekly to optimize the care of these patients has been established at Jackson Memorial Hospital.

One limitation of this study was that use of the sickle cell power plan was optional. As more providers choose to use the power plan, a more standardized approach to treating VOC will develop. Another limitation was the number of patients who were frequently readmitted to the hospital. These patients were inpatients several times throughout the course of the study and had comorbidities outside of sickle cell disease that could have contributed to their longer length of stay and therefore confounded the study results.

It is expected that with further education of providers and greater use of the sickle cell power plan and algorithm over time, a more significant decrease in hospital length of stay will be seen. The newly implemented sickle cell task force continues to aid in the optimization of care for these patients at Jackson Memorial Hospital. ●●

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# Vaccinations in Cancer: A Pharmacist's Survival Guide *(continued from p. 6)*

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# A Circuitous Route to Oncology Pharmacy—Does It Matter How We Get There? *(continued from p. 7)*

board games, quirky movies, and a variety of other things that enrich our lives. I am admittedly a workaholic at times, but I try to give as much time to others and hope that I succeed. I also try to bring outside interests into work—ask me about growing tomatoes!

Whatever your path to oncology pharmacy, I cannot think of a career that provides more opportunities, professionally and in life. I would be happy to take comments at bubaloj@ohsu.edu. Best of luck to you all. ●●

# Update on Biosimilars

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## HOPA's Issue Brief on Biosimilars: Improving Access and Decreasing Costs for Cancer Patients

In May 2019, the HOPA Board of Directors approved an updated issue brief on biosimilars. HOPA uses issue briefs (two-page documents that summarize a topic or problem) during visits with Congressional leaders and staffers as a way to update them on a topic of importance to HOPA. The biosimilars work group—members Kim Campbell, Chris Campen, Sarah Cimino, and Bhavesh Shah, led by chair Ali McBride—began the task of updating the issue brief in late December 2018.

The first issue brief on biosimilars was developed in 2014 and then revised in 2015. The world of biosimilars has changed since 2014, and the 2019 issue brief reflects the new reality, making the following recommendations—all with the goal of ensuring appropriate and affordable access to, and safe use of, biosimilars:

- Support the elimination of manufacturers' rebate incentives for payers and pharmacy benefit managers that restrict access to biosimilars. This restricted access inhibits providers' decision making regarding patients' access to lower-cost treatments and increases financial toxicity for patients.
- Support parity access to all biosimilars with third-party payers, which would eliminate preference for a particular biosimilar product within a class. This change would eliminate undue administrative, financial, and legal liabilities that arise with increased complexity in inventory management.
- Promote education on the scientific, regulatory, pharmacovigilance, and practice implications of using biosimilars. This information should be provided to all healthcare stakeholders, but especially to providers, payers, and patients.
- Infrastructure should be improved to facilitate provider reporting and monitoring of any unique toxicities that are observed after the biological drugs have been approved.
- Future legislation on biosimilar substitution should be developed with input from state boards of pharmacy, local pharmacy organizations, and healthcare providers. Key parameters in current law regarding generic substitution should be a basis for the legislative discussion.

To learn more, read the issue brief on HOPA's website at hoparx.org/images/hopa/advocacy/Issue-Briefs.

## S. 1681: Advancing Education on Biosimilars Act of 2019

On May 23, 2019, Senators Michael Enzi (R-WY) and Margaret Hassan (D-NH) introduced a bill that would create a website to house educational materials on biosimilars. This bill is important because it acknowledges the need to educate providers, patients, and families on the use of biosimilars. The bill provides direction on the format and type of content for the website in light of the recognition that different audiences will have different educational needs and that the educational material should be tailored to meet those needs. If the bill passes, it is possible that HOPA would have the opportunity to provide expertise and content for the website. In addition, a Merit-Based Incentive Payment System (MIPS)–eligible clinician may be able to earn points toward a MIPS score by completing continuing medical education programs created under this act. HOPA will continue to monitor this bill and provide updates.

## Biosimilar Interchangeability

In May 2019, the U.S. Food and Drug Administration (FDA) finalized its guidance on biosimilar interchangeability in "Considerations in Demonstrating Interchangeability with a Reference Product: Guidance for Industry."[1] The guidance document presents the FDA's perspective on how the pharmaceuticals industry can demonstrate interchangeability between a biological product and a reference product. The document defines a biological product as a product that "can be expected to produce the same clinical result as the reference product in any given patient."[2] Although the guidance is nonbinding, it gives a glimpse into the possible direction of future industry plans. Interchangeability offers an opportunity for patients' out-of-pocket costs for needed medications to be reduced.

As Congress continues to address out-of-pocket medication costs for consumers, we may see additional efforts that target biosimilar availability and interchangeability. Until then, HOPA remains dedicated to ensuring that patients have access to the right medication at the right time. ●●

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# Evaluation of AHCC Supplementation to Clear High-Risk Human Papillomavirus Infections: A Bench-to-Bedside Approach

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Cervical cancer remains a prevalent disease, accounting for almost 10% of all cancer diagnoses worldwide. Cervical cancer is known to be associated with the human papillomavirus (HPV), particularly with high-risk (HR) strains such as HPV 16 and 18. HPV infection is ubiquitous in the population. However, most HR-HPV infections are cleared without intervention in about 6–18 months. Although the use of the HPV 9-valent vaccine can decrease HR-HPV infections, about 10% of women will have persistent HR-HPV infections. Persistent HR-HPV infections put these patients at high risk for cervical cancer because the vaccine is ineffective in patients already infected with the HR strains. The only interventions available for treating persistent HR-HPV infections are local surgical procedures, but lesions that are removed often recur.

Recently, interest in modulating the host immune system to try to eradicate HR-HPV infection has increased. Judith A. Smith and colleagues evaluated the effect of AHCC, proprietary extract of shiitake mushroom (Lentinula edodes mycelia).[1] In animal studies, AHCC has shown immune-modulating effects such as enhancing antigen activation of CD4 and CD8 T cells as well as increasing natural killer cells and production of other antigen-specific T cells. In clinical studies, AHCC has shown the ability to decrease risk of infections and improve symptoms associated with infections. The hypothesis of this study was that AHCC supplementation would modulate the host immune system to effectively clear chronic HR-HPV infection. The current study is unique in that it evaluated this hypothesis from bench to bedside, looking at *in vitro* studies, *in vivo* mouse studies, and human studies, demonstrating an effective translational medicine approach.

Smith and colleagues first looked to demonstrate the efficacy of AHCC supplementation *in vitro*. Four human cervical cancer cell lines, including SiHa (HPV 16/18 positive) and C-33A (HPV negative), were treated with a one-time dose of AHCC at a concentration of 0.42 mg/mL (estimate of the clinically relevant plasma concentration after a 3-gram oral dose, as recommended by the manufacturer). AHCC suppressed HR-HPV expression in the first 24 hours, but the expression was recovered by 48 hours. However, when AHCC supplementation was given at this concentration every 24 hours for 7 consecutive days, HR-HPV expression was cleared.

**"This bench-to-bedside approach allowed Smith and the study team to identify efficacy in the lab that could be translated directly to patient care in the clinic setting."**

In the *in vivo* mouse studies, AHCC was given at a dose of 50 mg/kg once daily for 60 days and was associated with clearance of HR-HPV expression sustained after 30 days off supplementation. Smith and colleagues then completed two pilot studies in patients with confirmed chronic HR-HPV infections, defined as infections persisting for more than 2 years. The primary objective of these studies was to determine the success rate of AHCC supplementation, defined as the proportion of women free of HR-HPV infection at 6 months following initiation of supplementation. In the first pilot study, patients were given supplementation with AHCC 3 grams by mouth once daily on an empty stomach. Based on immune-response data, the dosing time was extended to 3–6 months of continuous AHCC supplementation and required 1 month of AHCC supplementation beyond the first negative HR-HPV result. Six patients completed this dosing strategy, and of those, four patients were able to achieve durable clearance of HR-HPV infection (no HR-HPV DNA for more than 30 days off supplementation). No side effects were reported with this dosing strategy. An additional pilot study was completed with AHCC supplementation of 1 gram by mouth once daily on an empty stomach for 6–8 months to see whether lower doses would also be effective. Nine patients completed this pilot study, and of those, four patients achieved durable clearance of HR-HPV. As in the other pilot study, no side effects were reported with this dosing strategy.

In both human pilot studies, interferon beta suppression was measured, and a level of <25 pg/mL was found to be a marker for successful clearance of HR-HPV infection, which has been seen in clearance of other chronic viral infections. As such, this ability to suppress interferon beta and upregulate interferon gamma is the defined mechanism of AHCC immune modulation that leads to clearance of chronic HR-HPV infections. In the human pilot studies, the AHCC 3-gram dosing regimen achieved response slightly more quickly and more consistently than the lower AHCC dose, with good tolerability. Confirmatory phase 2 randomized double-blinded placebo-controlled studies are ongoing to further determine the efficacy of AHCC in HR-HPV clearance in a larger patient population.

This bench-to-bedside approach allowed Smith and the study team to identify efficacy in the lab that could be translated directly to patient care in the clinic setting. No medications are currently available to eradicate chronic HR-HPV infections, and these patients represent women with a high risk of progression to cervical cancer. In this study, Smith and colleagues were able to show

*(continued on p. 30)*


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# Blastic Plasmacytoid Dendritic Cell Neoplasm

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematologic malignancy.[1] The exact incidence is unknown, but BPDCN is believed to account for 0.5% of all hematologic malignancies, with approximately 1,000 new cases diagnosed per year in the United States. Although it has been described in children, it is more commonly reported in adults; the median age at diagnosis is 65 years. The incidence is three times more common in men.[2] The majority of patients present with skin manifestations; however, bone marrow, lymph node, and splenic involvement are also commonly reported.[1]

Because of the rarity of BPDCN, no prospective clinical trials have been conducted for its treatment, and no standard of care has been established.[3] Commonly, lymphoma- or leukemia-based chemotherapy regimens have been used to treat BPDCN, with 50%–90% of patients achieving complete remission after initial treatment. However, virtually all patients relapse, and survival outcomes are poor, with a median survival of 12–14 months after diagnosis.[1] Tagraxofusp is the first medication that has been prospectively studied and approved for treating BPDCN.[4]

## Tagraxofusp

Tagraxofusp is the only approved CD123-directed cytotoxin that is composed of recombinant human interleukin-3 (IL-3) fused to truncated diphtheria toxin. Tagraxofusp binds to IL-3 receptors, which are overexpressed in almost all cases of BPDCN, allowing it to be internalized and the diphtheria toxin to be released. This results in the ADP-ribosylation of elongation factor 2, inhibition of protein synthesis, and apoptosis.[4-6]

Tagraxofusp is the first therapy to be approved by the U.S. Food and Drug Administration (FDA) for treating BPDCN in adults and pediatric patients 2 years and older.[4] After receiving orphan-drug status for treating both acute myeloid leukemia (AML) and BPDCN in 2011 and 2013, respectively, tagraxofusp was granted breakthrough-therapy designation for BPDCN in August 2016 and approved by the FDA in December 2018.[7]

## Clinical Trials

The first prospective study for BPDCN was a phase 1/2 study of SL-401 (tagraxofusp) in 11 patients who had either recurrent or refractory BPDCN or were ineligible for standard chemotherapy treatments.[6] Participants received 12.5 mcg/kg intravenously (IV) once daily for five doses. Treatment could be delayed if a patient experienced toxicities, but all doses had to be administered within 10 days. Nine patients were evaluated for response, with 5 having a complete response and 2 having a partial response. The median duration of response was 5 months (range, 1–20 months). The majority of adverse events reported were grade 1 or 2, with the most common being chills, fever, hypoalbuminemia, transaminitis, and myelosuppression. Grade 3 or 4 adverse events included thrombocytopenia (5 patients), elevated liver transaminases (5 patients), neutropenia (1 patient) and hyponatremia (1 patient).[6]

The approval for tagraxofusp was based on a nonrandomized open-label trial that consisted of three stages.[3] Stage 1 was a dose-escalation design that determined 12 mcg/kg on days 1 through 5 every 21 days to be the recommended dosage. Stage 2 evaluated efficacy and safety. Stage 3 further confirmed efficacy. Forty-seven patients with BPDCN were treated: 32 were treatment naive, and 15 had received previous treatment. Of the 29 treatment-naive patients who were evaluated, 72% had a complete response, and the overall response rate was 90%. The response rate was 67% in the 15 patients who had received previous therapy. The most common adverse events reported were elevated hepatic transaminases (60%), hypoalbuminemia (55%), peripheral edema (51%), and thrombocytopenia (49%).[3]

## Preparation and Administration

Preparation of tagraxofusp consists of several complex steps.[4] Step 1 includes diluting 1 mL of tagraxofusp in 9 mL of 0.9% sodium chloride to obtain a final concentration of 100 mcg/mL of tagraxofusp. Step 2 involves preparing the infusion set for tagraxofusp. The required dose of tagraxofusp should be drawn up into a syringe. A separate syringe should also be drawn up to flush the infusion set. The manufacturer recommends a *minimum* volume of 3 mL of 0.9% sodium chloride in the flush syringe to ensure that all the tagraxofusp has been flushed out of the tubing set. Each syringe should be attached to one arm of the mini-bifuse Y-connector, and the Y-connector should be attached to microbore tubing. The entire infusion set, including the filter, should be primed with tagraxofusp. After the infusion set is ready for administration, the entire dose should be administered via syringe pump over 15 minutes.[4]

## Safety

Although the drug is generally well tolerated, capillary leak syndrome (CLS) has been reported in 55% (9% ≥ grade 3) of patients.[3,4] All but one of the CLS events occurred during the first cycle of treatment.[3] Although the mechanism of action has not been fully elucidated, the authors hypothesized that the CLS is due to the uptake of diphtheroid toxin by vascular endothelium, resulting in endothelial cell apoptosis and vessel wall leakage.[6] Symptoms include hypoalbuminemia, edema, hypotension, elevated creatinine, fatigue, and weight gain. The most reliable predictor of CLS was hypoalbuminemia during the earliest days of the first cycle.[3] To mitigate this effect, it is recommended that the first cycle of tagraxofusp be administered while the patient is hospitalized and that the first dose of tagraxofusp be withheld until the patient's serum albumin level is 3.2 g/dL or higher.[4] The median time to onset of CLS was 5 days (range, 4–51 days), and the median duration was 4 days (range, 3–19 days).[3] Management of

CLS is described in the package insert and includes administering albumin as frequently as necessary, administering corticosteroids, and giving additional supportive care management (see **Table 1**). Administration of tagraxofusp can be resumed after symptoms resolve. Permanent discontinuation is recommended if patients show signs of hemodynamic instability that require intervention.[4]

Hypersensitivity reactions have occurred with tagraxofusp (46%, any grade; 10%, grade ≥3).[3,4] The mechanism is unknown, but the reactions are hypothesized to be caused by the release of cytokines from damaged BPDCN blasts.[6] The majority of the reactions were reported within the first few hours, although several infusion reactions occurred 4–8 hours after administration. Premedication with an H1 antagonist, a corticosteroid, and acetaminophen is recommended 60 minutes prior to tagraxofusp to mitigate hypersensitivity reactions.[4]

Other side effects reported in clinical trials included elevated liver enzymes (88%, any grade; 40%, grade ≥3) that resolved several weeks after therapy, thrombocytopenia (49%), nausea (45%), hyperglycemia (36%), and anemia (23%).[3,4]

## Future Directions

Tagraxofusp use is being studied in a variety of other diseases, including AML, chronic myelomonocytic leukemia, myelofibrosis, and multiple myeloma.[7-9] In addition, trials evaluating tagraxofusp in combination with other therapeutic agents, such as hypomethylators, are in active development.[10]

## Conclusion

Tagraxofusp is the first CD123-directed cytotoxin approved by the FDA and the first agent approved for the treatment of BPDCN in both adults and children 2 years of age or older.[4] Although the drug is generally well tolerated, hepatotoxicity, infusion reactions, and CLS have been reported. CLS commonly occurs within 5 days of cycle 1 and requires close inpatient monitoring for the first cycle. The patient's serum albumin levels should be checked frequently, and therapy should be withheld if signs of hypoalbuminemia are present.[3,4] Despite these careful monitoring requirements, tagraxofusp represents one of the first therapeutic advances for BPDCN, and further studies are required to determine its place in therapy for other malignancies.●●

**Table 1. Capillary Leak Syndrome Management[4]**

| CLS Symptoms | Management |
|---|---|
| Serum albumin <3.5 g/dL or decreased by ≥0.5 g/dL from baseline albumin level prior to dose initiation | • 25 g albumin IV every 12 hours (or as frequently as practical) until symptoms resolve |
| Weight increase by ≥1.5 kg in 1 day | • 25 g albumin IV every 12 hours (or as frequently as practical) until symptoms resolve<br>• Supportive care as indicated (fluids, vasopressors, diuretics) |
| Edema, fluid overloaded, or hypotension | • 25 g albumin IV every 12 hours (or as frequently as practical) until serum albumin ≥ 3.5 g/dL<br>• Methylprednisolone 1 mg/kg IV daily until symptoms resolve<br>• Supportive care as indicated (fluids, vasopressors, diuretics) |

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# Preparing for a Professional Interview

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## *What factors should residents consider when they are looking at potential job prospects?*

**Clemmons:** First, a resident should determine what type of practice setting holds the most interest—do you enjoy inpatient or outpatient work and a specific area of hematology/oncology, or do you prefer a rotating position? Consider how each position is structured, how much time is spent in various activities, and how this distribution relates to your preferences. Second, consider the institution type and expected variety of responsibilities. For example, if you enjoy (or dislike) teaching, research, or management roles, then ensure that the duties of a prospective position align with your desires. Last, consider whether there is opportunity for growth and innovation in the position and institution if that is important in light of your career goals.

**Maldonado:** The first factor would be location. Can you see yourself being happy living there? Even if a job is great, it won't make up for the fact that it's in Seattle and you suffer from seasonal depression. Also, look at the relationship between pharmacists and other healthcare personnel. For example, were physicians and nurses included as part of the interview day? And finally, pay close attention to employee turnaround, specifically in the pharmacy department.

**Kennerly-Shah:** First is the type of institution: Is this a place where you will be challenged, have mentors, and be able to grow? Will you be the only hematology/oncology clinical pharmacist, or will you be part of a large team? What type of practice model does the institution have—is the pharmacist's role that of a specialist or generalist? Subspecialized or rotating? Second is geographical location: Is this a place you would be happy living? Last, try to think beyond wanting to work in a specific disease state. It is extremely common for residents to tell me they are interested only in inpatient hematology or bone marrow transplant. I have convinced many residents to come to the James Hospital for an outpatient solid tumor position, with the promise of a future transition to hematology. No pharmacist has actually taken the offer to transition to hematology after starting their position working with solid tumors. Most people grow to love their teams and the disease state they first work in!

## *When would you recommend that candidates start searching for employment?*

**Clemmons:** Each year the recruitment timetable and availability of open positions are slightly different. In most years, the residents begin their job search around early November if they are pursuing interviews at the Personnel Placement Services (PPS) recruitment event at the American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting. However, some institutions may not have new positions approved until mid-spring. Therefore, residents are advised to keep their search for employment open through the winter and spring months until they find the best fit.

**Maldonado:** I recommend beginning in October–November, especially if you are thinking of using PPS, because interview slots can fill pretty quickly. If you wait until days before the Midyear Clinical Meeting, you may not get to meet with every institution you had in mind.

**Kennerly-Shah:** I recommend that residents start searching in October–November in preparation for attending PPS at the ASHP Midyear Clinical Meeting. If you are geographically limited, it is a good idea to reach out to the institutions in those areas to ask if they expect to have any job openings and let them know you are interested.

## *Would you recommend that PGY2 residents participate in PPS at the ASHP Midyear Clinical Meeting? Why or why not?*

**Clemmons:** Yes, I encourage residents to participate. This event offers residents the ability to meet in person with current practitioners and managers who work for a variety of potential employers. Residents can learn about the position and institution in a brief individual interview. The ability to discuss numerous job options in one location can save time and money by allowing future onsite interviews to be selected for only the positions deemed to be the best fit after the initial PPS discussions. Even if a resident pursues a career option outside of those contacted during PPS, the PPS interviews themselves provide opportunities to network and to enhance knowledge of various job structures.

**Maldonado:** Yes, I feel that this event is important for data gathering. It may not tell you where you definitely want to go, but it may help you identify places to be crossed off your list.

**Kennerly-Shah:** Absolutely, this is a great way to quickly rule institutions in or out of your list of job prospects.

## *What qualities are employers looking for in a candidate?*

**Clemmons:** Each employer may prioritize certain qualities over others. In general, most are looking for a candidate who demonstrates excellent time and project management and communication

skills as well as a positive, eager attitude. I also look for those who act calm under pressure, can multitask throughout the work day, and are open to constructive feedback.

**Maldonado:** They are seeking an adaptable, personable, and proactive team player.

**Kennerly-Shah:** The top two qualities I look for are flexibility and positivity!

### *What should candidates avoid doing or discussing during the interview?*

**Clemmons:** Candidates who focus on salary, benefits, or non-primary requirements (e.g., staffing, on-call responsibilities) can give the wrong impression. Let the employer provide that type of information, or wait until a job offer is extended before inquiring about those details. Avoid the use of personal electronic devices (e.g., a smartwatch), even during the informal portions of an interview. Leaving devices in your car is a great method for avoiding the distraction! Although this is common sense, never "bad talk" former colleagues or employers. If you need to answer a question that involves constructive criticism of persons or institutions encountered in former jobs, ensure that your answer is stated professionally.

**Maldonado:** Do not discuss pay. You should definitely discuss funding for conferences and BCOP testing, but I would stay away from asking about other benefits. This is something you can inquire more about after you get an offer.

**Kennerly-Shah:** I would focus on the culture of the organization and the practice model. I wouldn't spend time on the salary, benefits, schedule, and so on. You can ask all those questions after you receive an offer for a position.

### *Do you have any other advice for residents preparing for their first job interview following their residency?*

**Clemmons:** Apply only to positions you are truly excited about working in for at least a few years. Be authentic and honest.

**Maldonado:** Do not ignore your gut feeling when you visit a place. More often than not, it can tell you a lot. Pay attention to who participates in your interviews—this tells you a lot about who you will be working with more closely. Maybe stay an extra day or come a day early to get a better feel for the city in which you may be living for a significant amount of time. And remember that they are trying to recruit you as much as you want to be hired, so don't feel intimidated. Your training and hard work got you to the interview, so try to enjoy the day and learn as much as you can.

**Kennerly-Shah:** Practice! Being a great interviewee takes practice. Review behavior-based interviewing questions and be prepared to give thorough but concise answers to questions. ●●

FEATURE

# Updates on the Treatment of Renal Cell Carcinoma

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Renal cell carcinoma (RCC) accounts for approximately 85% of all primary renal malignancies, and up to 88% of RCC diagnoses are clear cell subtype.[1,2] Less frequently encountered are the papillary, sarcomatoid, and chromophobe subtypes. RCC is the eighth most common cancer diagnosis in the United States, and it is predicted to account for 4.2% of all new cancer diagnoses and 2.4% of all cancer-related deaths in 2019.[3]

The Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Score and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria are models that have been developed to assess prognosis and survival in patients with metastatic RCC (mRCC). The MSKCC Prognostic Score was developed and validated on the basis of clinical trials that studied the use of interferon for treatment of mRCC; the IMDC Criteria was developed and validated on the basis of clinical trials that studied the use of tyrosine kinase inhibitors for treatment of mRCC.[4,5] The MSKCC Prognostic Score takes into account the following clinical features: interval from diagnosis to treatment of less than 1 year, Karnofsky Performance Status score less than 80%, serum lactose dehydrogenase greater than 1.5 times the upper limit of normal (ULN), corrected serum calcium greater than ULN, and serum hemoglobin less than the lower limit of normal (LLN).[4] The IMDC Criteria is similar and takes into account the following clinical features: interval from diagnosis to treatment of less than 1 year, Karnofsky Performance Status score less than 80%, corrected serum calcium greater than ULN, serum hemoglobin less than LLN, neutrophil count greater than ULN, and platelet count greater than ULN.[5] For both prognostic models, patients with zero clinical features are considered favorable risk, patients with 1–2 clinical features are considered intermediate risk, and patients with 3 or more clinical features are considered poor risk.[4,5] The IMDC Criteria estimates 2-year overall survival (OS) to be 75% for favorable-risk patients, 53% for intermediate-risk patients, and 7% for poor-risk patients.[5] The IMDC Criteria has become the standard risk stratification tool; however, some ongoing studies are still using the MSKCC Prognostic Score because they were initiated before the validation of the IMDC Criteria.

Several new drug approvals and RCC treatment guideline updates have occurred in the past 3 years, making RCC one of the most rapidly changing areas in oncology. Historically, management of non-mRCC consisted primarily of surgical or locally directed therapies.[1,2] First-line management of mRCC historically consisted of vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI)–directed therapies (such as pazopanib or sunitinib), which inhibit tumor growth primarily via inhibition of angiogenesis. However, on the basis of emerging data, the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for treating kidney cancer were recently updated to include the option of adjuvant therapy for certain patients with non-mRCC and several new regimens for treatment of mRCC.[6]

## Treatment Updates in the Adjuvant Setting

Several clinical trials investigating the use of adjuvant therapy for patients with high-risk stage III RCC have had results published, are awaiting final results, or are ongoing. Four studies have been published thus far: two (S-TRAC and the first arm of ASSURE) examined the use of sunitinib; one (the second arm of ASSURE), the use of sorafenib; one, the use of pazopanib (PROTECT); and one, the use of axitinib (ATLAS).[7-10] Only one of these studies, S-TRAC, met its primary endpoint of disease-free survival (DFS).[7]

S-TRAC was a double-blind phase 3 trial that randomized 615 patients with locoregional, high-risk, clear cell RCC 1:1 to receive either sunitinib 50 mg orally daily or placebo for 4 weeks on the medication followed by 2 weeks off for 1 year.[7] Patients were required to initiate treatment within 3–12 weeks of nephrectomy. The primary endpoint of DFS was 6.8 years in the sunitinib group versus 5.6 years in the placebo group ($p$ = .03). Many patients in the sunitinib group required dose reductions (34.3%), dose interruptions (46.4%), and drug discontinuation (28.1%). Adverse events reported were similar to those in prior sunitinib studies, with the most common all-grade adverse events being diarrhea (56.9%), palmar-plantar erythrodysesthesia (50.3%), hypertension (36.9%), fatigue (36.6%), nausea (34.3%), and dysgeusia (33.7%). Overall survival (OS) data were not mature at the time of original publication, and updated results showed that median OS had not yet been reached in either group after an additional 10 months of follow-up.[11] As previously mentioned, the ASSURE trial did not find an improvement in DFS with 1 year of adjuvant sunitinib; however, it is worth noting that differences in the patient population (inclusion of non-clear cell histology and inclusion of higher-risk patients) may have had an impact on the results.[8] On the basis of the results of the S-TRAC trial, the U.S. Food and Drug Administration (FDA) approved sunitinib for adjuvant treatment of RCC on November 16, 2017.[12]

The only study of an oral agent that remains unpublished is EVEREST, a phase 3 double-blind trial that randomized 1,545 high-risk patients to everolimus versus placebo for 1 year.[13] Patients were required to initiate treatment within 84 days of nephrectomy. This study is closed to accrual, and results are expected in October 2021. Several studies are ongoing; all are investigating the use of immune checkpoint inhibitors in the neoadjuvant or adjuvant setting. These clinical trials are studying the use of neoadjuvant pembrolizumab, neoadjuvant durvalumab plus tremelimumab, perioperative nivolumab, adjuvant atezolizumab, and adjuvant ipilimumab plus nivolumab.[14]

The NCCN clinical practice guidelines for kidney cancer recommend adjuvant sunitinib (category 2B) for patients with clear cell RCC and high-risk features (tumor Stage 3 or higher, regional lymph-node metastasis, or both).[6] This category-2B recommendation is based on the lack of OS benefit, the discordance between the ASSURE and S-TRAC trials, and the concern for patients having to undergo 1 year of potential sunitinib toxicity during treatment in exchange for a 1-year improvement in DFS. No other systemic therapies are recommended in the adjuvant setting at this time.

Practical considerations for a pharmacist managing a patient on sunitinib therapy include counseling on appropriate administration (4 weeks on and 2 weeks off), monitoring for drug interactions (sunitinib is a major CYP3A4 substrate), and managing common VEGF receptor (VEGFR) inhibitor adverse effects such as diarrhea, hypertension, and palmar-plantar erythrodysesthesia.[15] Although sunitinib was studied at the standard dose in the S-TRAC and ASSURE trials (as well as in the various studies discussed in the next section), it is common for patients to require dose reductions of sunitinib.

## Treatment Updates in the Metastatic Setting

As previously mentioned, the treatment landscape of mRCC has changed dramatically over the past several years: four new therapies have been approved by the FDA in the first-line setting alone. Given the rapidly emerging data, the NCCN clinical practice guidelines for kidney cancer have undergone several recent updates and are likely to be updated again as additional therapies gain FDA approval.

### Cabozantinib

Cabozantinib is an oral VEGF receptor (VEGFR) 1/2/3 inhibitor that was initially approved by the FDA in the second-line setting for mRCC on the basis of the results of the METEOR trial.[16] Cabozantinib subsequently received FDA approval in December 2017 in the first-line setting for patients with mRCC on the basis of the results of the CABOSUN trial.[17]

CABOSUN was an open-label phase 2 trial that randomized 157 treatment-naive patients with intermediate or poor risk (per the IMDC Criteria) clear cell mRCC 1:1 to receive cabozantinib 60 mg orally daily continuously or sunitinib 50 mg orally daily for 4 weeks on followed by 2 weeks off.[18] The primary endpoint of progression-free survival (PFS) was significantly longer in the cabozantinib group compared to the sunitinib group, at 8.2 months versus 5.6 months, respectively, which was associated with a 34% reduction in the rate of disease progression or death ($p$ = .012). A subgroup analysis showed that 36% of patients included in this study had bone metastases, and these patients in particular had improved outcomes with cabozantinib over sunitinib. The most common all-grade adverse events seen in both groups were fatigue, hypertension, diarrhea, elevations in liver function tests, and palmar-plantar erythrodysesthesia, which is consistent with prior studies of both cabozantinib and sunitinib. The rates of grade 3-4 adverse events were similar in both the cabozantinib group (67%) and sunitinib group (68%).

On the basis of the results of the CABOSUN trial, the NCCN clinical practice guidelines for kidney cancer recommend cabozantinib as a category-2A recommendation for first-line treatment of patients with intermediate- or poor-risk clear cell mRCC, because the evidence is from a phase 2 trial. Although the CABOSUN trial did not include patients with favorable-risk clear cell mRCC, the guidelines also recommend cabozantinib (category 2B) as a first-line treatment for patients in this group.[6]

Practical considerations for a pharmacist managing a patient on cabozantinib therapy include counseling on appropriate administration (1 hour before or 2 hours after eating); monitoring for drug interactions (cabozantinib is a major CYP3A4 substrate); and managing common VEGFR inhibitor adverse effects such as diarrhea, hypertension, and palmar-plantar erythrodysesthesia.[19]

### Ipilimumab and Nivolumab

Nivolumab, a programmed cell death-1 (PD-1) inhibitor, and ipilimumab, a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor, are immune checkpoint inhibitors that work to upregulate T-cell activation and restore antitumor immune response.[20] Nivolumab was initially approved as a single agent in the second-line setting for mRCC in November 2015.[21] The next approval for immunotherapy use in mRCC was not given until April 2018, when ipilimumab plus nivolumab was the first immunotherapy regimen approved by the FDA for first-line treatment of mRCC on the basis of the results of CheckMate 214.[22]

CheckMate 214 was an open-label phase 3 trial that randomized 1,096 treatment-naive patients with clear cell mRCC (all IMDC risk groups) 1:1 to receive either ipilimumab 1 mg/kg plus nivolumab 3 mg/kg intravenously (IV) every 3 weeks for four doses followed by nivolumab 3 mg/kg IV every 2 weeks, or sunitinib 50 mg orally daily for 4 weeks on followed by 2 weeks off.[23] The coprimary endpoints were OS, objective response rate (ORR), and PFS in the subgroup of patients with intermediate- or poor-risk disease ($n$ = 847). The median OS was not reached in the ipilimumab plus nivolumab (I+N) group, versus 26 months in the sunitinib group ($p$ < .001). The ORR was 42% in the I+N group versus 27% in the sunitinib group ($p$ < .001), which included 40 complete responses (CR) in the I+N group and 5 CR in the sunitinib group. The median PFS was 11.6 months in the I+N group and 8.4 months in the sunitinib group ($p$ = .03; not significant, because the alpha level was set at 0.009 for PFS). All-grade adverse events occurred in similar numbers in each group, but the I+N group had fewer grade 3–4 adverse events (46% in the I+N group vs. 63% in the sunitinib group). The most common grade 3–4 adverse events in the I+N group were elevated lipase level (10%), fatigue (4%), and diarrhea (4%). The most common grade 3–4 adverse events in the sunitinib group were hypertension (16%), palmar-plantar erythrodysesthesia (9%), fatigue (9%), thrombocytopenia (5%), and diarrhea (5%). In addition to these clinical outcomes, a health-related quality of life (HRQoL) study showed more favorable HRQoL with the combination of I+N compared to sunitinib for patients with intermediate or poor risk.[24] Despite the benefit noted with I+N for the intermediate- and poor-risk groups, the same clinical outcomes

were not seen in the exploratory subgroup of patients with favorable risk.[23] The OS, ORR, and PFS were significantly greater in the sunitinib group versus the I+N group, although more CR were seen in the I+N group versus the sunitinib group.

The NCCN clinical practice guidelines for kidney cancer recommend I+N as a first-line preferred recommendation (category 1) for patients with intermediate- or poor-risk clear cell mRCC and as a nonpreferred first-line recommendation (category 2A) for patients with favorable-risk clear cell mRCC.[6] This regimen is a category-2A recommendation for favorable-risk patients despite the negative results of the CheckMate 214 trial because of results of the phase 1 CheckMate 016 study. CheckMate 016 did not report outcomes based on risk stratification but did report favorable outcomes for all patients included (favorable, intermediate, and poor risk).[25] The guidelines also list I+N as a preferred regimen for subsequent therapy for clear cell mRCC because the CheckMate 016 study also included patients who had received one prior line of therapy.[6]

Practical considerations for a pharmacist managing a patient on I+N include monitoring for and counseling patients on signs and symptoms of immune-related adverse events such as colitis (new diarrhea), pneumonitis (new shortness of breath), dermatitis (new rash), hepatitis (elevations in liver enzymes), arthritis (new joint aches), and adrenal insufficiency or hypophysitis (new fatigue or headache that won't go away).[20] Patients may also be given immunotherapy information cards to keep in their wallet or purse in the event that an adverse event takes them to an emergency room or urgent care center.

**Pembrolizumab and Axitinib**

Axitinib, an oral VEGFR 1/2/3 inhibitor, was previously approved for second-line treatment of mRCC on the basis of the results of the AXIS trial.[26] Pembrolizumab is a PD-1 inhibitor that gained its first indication for mRCC as a first-line treatment in combination with axitinib.[27] The combination of a VEGFR inhibitor and immunotherapy is believed to have a synergistic effect. It is thought that anti-angiogenic agents such as axitinib can also stimulate the immune system and that immunotherapy agents such as pembrolizumab can also have anti-angiogenic properties.[28] Pembrolizumab plus axitinib was the first immunotherapy/VEGFR inhibitor combination to achieve FDA approval. The approval of the combination in April 2019 was based on the results of KEYNOTE-426.[27]

KEYNOTE-426 was an open-label phase 3 trial that randomized 861 treatment-naive, clear cell mRCC patients (all IMDC risk groups) 1:1 to receive pembrolizumab 200 mg IV every 3 weeks plus axitinib 5 mg orally twice daily or sunitinib 50 mg orally daily for 4 weeks on followed by 2 weeks off.[29] The first primary endpoint, median OS, was not reached in either group. However, the 12-month OS was 89.9% in the pembrolizumab plus axitinib (P+A) group versus 78.3% in the sunitinib group ($p < .0001$). The second primary endpoint, PFS, was longer in the P+A group, at 15.1 months versus 1.1 months in the sunitinib group ($p < .001$). The ORR rate was 59.3% in the P+A group versus 35.7% in the sunitinib group ($p < .001$), including 25 CR in the P+A group versus 8 CR in the sunitinib group. The benefit of P+A was observed in all risk groups. All-grade adverse events occurred in similar numbers in each group; however, grade 3–4 adverse events occurred more frequently in the P+A group (75.8%) versus the sunitinib group (70.6%). The most common grade 3–4 adverse events seen in the P+A group include hypertension (22.1%), elevated alanine aminotransferase (13.3%), diarrhea (9.1%), and elevated aspartate aminotransferase (7%). The most common grade 3–4 adverse events seen in the sunitinib group include hypertension (19.3%), decreased platelet count (7.3%), decreased neutrophil count (6.8%), and fatigue (6.6%).

The NCCN clinical practice guidelines for kidney cancer recommend P+A as a first-line preferred recommendation (category 2A) for favorable-risk patients with mRCC and as a first-line preferred recommendation (category 1) for intermediate- and poor-risk patients with mRCC.[6] Although the KEYNOTE-426 study did not include patients who had received prior therapy, the guidelines also list the combination as an option for subsequent therapy.

Practical considerations for a pharmacist managing patients on P+A include monitoring for and counseling patients on the signs and symptoms of immune-related adverse events as described above; counseling on appropriate administration of axitinib (twice daily with or without food); detailing the difference in diarrhea seen with immunotherapy versus axitinib (axitinib diarrhea will typically respond to antidiarrhea agents such as loperamide); and managing common VEGFR-inhibitor adverse effects such as diarrhea, hypertension, and palmar-plantar erythrodysesthesia.[30,31]

**Avelumab and Axitinib**

Avelumab is a programmed death-ligand 1 (PD-L1) inhibitor that functions in the local tumor environment to upregulate T-cell activation and restore antitumor immune response.[32] Avelumab gained its first indication for mRCC as a first-line treatment in combination with axitinib in May 2019 on the basis of the results of the JAVELIN Renal 101 trial.[33]

JAVELIN Renal 101 was an open-label phase 3 trial that randomized 886 treatment-naive, clear cell mRCC patients (all IMDC risk groups) 1:1 to receive avelumab 10 mg/kg IV every 2 weeks plus axitinib 5 mg orally twice daily or sunitinib 50 mg orally once daily for 4 weeks on followed by 2 weeks off.[34] The coprimary endpoints were PFS and OS in patients with PD-L1-positive disease ($n = 560$). The median PFS for patients with PD-L1-positive disease was 13.8 months in the avelumab plus axitinib (A+A) group versus 7.2 months in the sunitinib group ($p < .001$). PFS in the overall population was similar, at 13.8 months for the A+A group versus 8.4 months for the sunitinib group ($p < .001$). OS data were not mature at the time of publication. The ORR for patients with PD-L1-positive disease was 55.2% for the A+A group versus 25.5% for the sunitinib group, which includes 12 CR in the A+A group and 6 CR in the sunitinib group. Both all-grade and grade 3–4 adverse events occurred in similar numbers in each group. The most common grade 3–4 adverse events that occurred in the A+A group include hypertension (25.6%), diarrhea (6.7%), elevated alanine aminotransferase level (6%), and palmar-plantar erythrodysesthesia (5.8%). The most common grade 3–4 adverse events that occurred in the sunitinib group include hypertension (17.1%), anemia (8.2%), neutropenia (8.0%), and thrombocytopenia (6.2%).

The NCCN clinical practice guidelines for kidney cancer have recently been updated to reflect this newest FDA approval.[6] The combination of avelumab plus axitinib was added as a first-line nonpreferred recommendation (category 2A) for treatment of favorable-, intermediate-, and poor-risk clear cell mRCC. It is also included as a category-3 recommendation for subsequent therapy for patients with clear cell mRCC.

Practical considerations for a pharmacist managing patients on A+A are the same as those for P+A, listed above.[31,32]

**Atezolizumab and Bevacizumab**

Bevacizumab is a monoclonal antibody that binds to VEGF to inhibit the binding of VEGF to VEGF receptors. Bevacizumab was initially approved in combination with interferon-alfa for the treatment of mRCC on the basis of results of the AVOREN trial.[35,36] Atezolizumab is a PD-L1 inhibitor that does not yet have an indication for mRCC. This combination has not yet been approved by the FDA; however, the results of the IMmotion151 trial were recently published, which suggests that the combination may obtain FDA approval in the near future.

IMmotion151 was an open-label phase 3 trial that randomized 915 treatment-naive, clear cell or sarcomatoid mRCC (all MSKCC risk groups) 1:1 to atezolizumab 1,200 mg plus bevacizumab 15 mg/kg IV once every 3 weeks or sunitinib 50 mg orally daily for 4 weeks on followed by 2 weeks off.[37] The coprimary endpoints were investigator-assessed PFS for PD-L1-positive disease ($n$ = 362) and OS in the intention-to-treat (ITT) population. The primary endpoint of PFS in PD-L1-positive disease was improved in the atezolizumab plus bevacizumab (A+B) group at 11.2 months versus 7.7 months in the sunitinib group ($p$ = .0217). Median OS data in the ITT population were not fully mature at publication; however, 43% of patients in the A+B group and 42% of patients in the sunitinib group had died at the data cutoff for the second OS interim analysis (hazard ratio = 0.93). The ORR for the ITT population was 37% in the A+B group versus 33% in the sunitinib group, which includes 24 CR in the A+B group and 10 CR in the sunitinib group. All-grade adverse events occurred in 91% of patients in the A+B group and in 96% of patients in the sunitinib group. Grade 3–4 adverse events occurred in 40% of patients in the A+B group and in 54% of patients in the sunitinib group. The most common grade 3–4 adverse events in the A+B group were hypertension (14%) and proteinuria (3%). The most common grade 3–4 adverse events in the sunitinib group were hypertension (17%), fatigue (5%), diarrhea (4%), and anemia (4%).

The FDA has yet to approve the combination of atezolizumab plus bevacizumab for the treatment of mRCC; therefore, it is not listed as a treatment option in the NCCN clinical practice guidelines for kidney cancer.[6] However, if this regimen obtains FDA approval, it is expected that it will also be included as a first-line (and possibly subsequent-line) treatment option for clear cell mRCC.

Practical considerations for a pharmacist managing patients on atezolizumab plus bevacizumab are similar to those detailed above for other immunotherapy plus VEGF inhibitor combinations.[35,38] Patients should also be counseled on the signs and symptoms of bleeding and the potential for delayed wound healing with bevacizumab and should be monitored closely for development of proteinuria. Patients receiving bevacizumab should also be monitored closely for infusion reactions.

## Conclusion

The treatment landscape for renal cell carcinoma has changed greatly over the past several years. Per the NCCN clinical practice guidelines for kidney cancer, first-line treatment for favorable-risk patients now includes axitinib plus pembrolizumab (preferred, category 2A), ipilimumab plus nivolumab (category 2A), avelumab plus axitinib (category 2A), and cabozantinib (category 2B).[6] First-line treatment for intermediate- and poor-risk patients now includes ipilimumab plus nivolumab (preferred, category 1), axitinib plus pembrolizumab (preferred, category 1), cabozantinib (preferred, category 2A), and avelumab plus axitinib (category 2A). Pazopanib and sunitinib are still listed as first-line regimens for both favorable-risk (preferred, category 2A) and intermediate- and poor-risk (category 2A) patients. For subsequent therapy, additions include ipilimumab plus nivolumab (preferred, category 2A), pembrolizumab plus axitinib (category 2A), and axitinib plus avelumab (category 3). It is likely that the guidelines will be updated again if atezolizumab plus bevacizumab obtains FDA approval.

In clinical practice, first-line therapies are chosen on the basis of risk stratification, the perceived ability of a patient to tolerate each option (combination versus single-agent therapy), schedule of administration (avelumab is given every 2 weeks, atezolizumab and pembrolizumab are given every 3 weeks, and nivolumab can be given every 4 weeks after the initial ipilimumab/nivolumab combination), and other factors such as drug cost and the patient's ability to receive funding assistance.[6] Subsequent lines of therapy are chosen after similar factors, in addition to the prior lines of therapy a patient has already received, have been weighed. ●●

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FOR THE TREATMENT OF METASTATIC EGFRm NSCLC

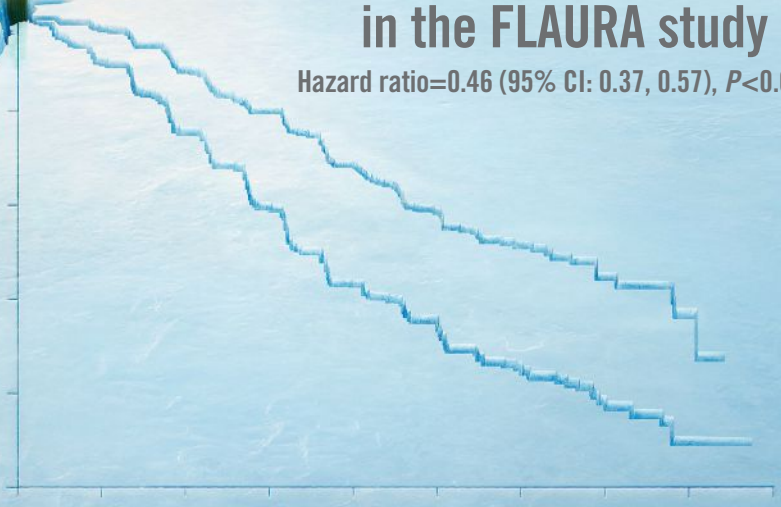
# GROUNDBREAKING EFFICACY

## AN UNPRECEDENTED

## 18.9 vs 10.2

### months median PFS vs erlotinib/gefitinib in the FLAURA study

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



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

## INDICATION

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

## SELECT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported.

AstraZeneca

# WITH FIRST-LINE TAGRISSO®

**OS** **Overall survival data were not mature at the time of the final PFS analysis[1]**

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

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

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

## SELECT SAFETY INFORMATION

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

- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

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

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

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

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TAGRISSO®
osimertinib

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

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

## INDICATIONS AND USAGE

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

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

## DOSAGE AND ADMINISTRATION

### Patient Selection

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

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

### Recommended Dosage Regimen

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

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

### Administration to Patients Who Have Difficulty Swallowing Solids

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

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

### Dosage Modifications

Adverse Reactions

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

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

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).
[b] ECGs = Electrocardiograms
† QTc = QT interval corrected for heart rate

Drug Interactions

*Strong CYP3A4 Inducers*

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when co-administering with a strong CYP3A inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer *[see Drug Interactions (7) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

### Interstitial Lung Disease/Pneumonitis

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

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

### QTc Interval Prolongation

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

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

### Cardiomyopathy

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

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

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

### Keratitis

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

### Embryo-Fetal Toxicity

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

## ADVERSE REACTIONS

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

Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

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

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

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

### Clinical Trials Experience

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

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

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

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

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

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

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

**Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA***

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

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

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

* NCI CTCAE v4.0

[a] One grade 5 (fatal) event was reported (diarrhea) for EGFR TKI comparator

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

[c] Includes dry skin, skin fissures, xerosis, eczema, xeroderma.

[d] Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

[e] Includes pruritus, pruritus generalized, eyelid pruritus.

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

[g] Includes fatigue, asthenia.

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

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

[a] NCI CTCAE v4.0

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

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

## DRUG INTERACTIONS

### Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

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

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

### Effect of Osimertinib on Other Drugs

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

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

### Drugs That Prolong the QTc Interval

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

## USE IN SPECIFIC POPULATIONS

### Pregnancy

*Risk Summary*

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

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

*Data*

Animal Data

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

### Lactation

Risk Summary

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

### Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

*Females*

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

*Males*

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

Infertility

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

### Pediatric Use

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

### Geriatric Use

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

### Renal Impairment

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

### Hepatic Impairment

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

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# Drug Pricing, Policy, and Innovation: An Interview with Richard Bagger

*In July 2019, HOPA's Public Policy Committee arranged a Q&A with Richard Bagger, chair of the board of directors of the National Pharmaceutical Council (NPC) and executive vice president, corporate affairs and market access, at Celgene Corporation. The NPC, founded in 1953 and supported by the nation's major research-based pharmaceutical companies, focuses on research development, information dissemination, and education on the critical issues of evidence, innovation, and the value of medicines for patients.*

### *Drug pricing is being discussed by both parties on Capitol Hill and is a complex and multifaceted issue. What are some of the ways the National Pharmaceutical Council (NPC) is addressing updated payment and reimbursement models to ensure that patients are able to access and afford the innovative care being developed?*

The issue of healthcare spending is complex and involves a number of factors. As new technologies like CAR T [chimeric antigen receptor T-cell] therapy change the care paradigm, payment and reimbursement models will need to keep pace. Today, these models are still largely designed to reimburse for acute or chronic treatments. That's why NPC's efforts to drive the discussion of innovative payment models and the policy reforms needed to enable value-based payment in public-sector healthcare programs are so important. For example, NPC's partnership with the Massachusetts Institute of Technology's FoCUS (Financing and Reimbursement of Cures in the U.S.) project helped facilitate an important conference held in February 2019 called "Paying for Cures," which discussed ways to ensure system sustainability and patients' access to new therapies.

Further, a narrow focus on the list price of medicines and the specific role of the biopharmaceutical sector can overlook the need for a broader conversation about where we're getting value in health care. If we focus only on biopharmaceuticals, which account for 10%–16% of overall spending within a massive healthcare economy, we will fail to achieve the larger goals of recognizing value and bending the healthcare cost curve—while also endangering continued medical innovation.

### *What are the most challenging barriers to the development of novel therapies in oncology? How can NPC help to foster an environment that drives innovation but still supports access for all patients?*

Innovation and access have a common denominator: value. If we miss the mark in defining and measuring value in health care, we risk creating an environment where the innovation that is transforming the lives of patients may be stifled, and patient access to the most innovative treatments may be affected.

In this area, two trends with potential implications for patient access are especially worth watching: value assessment frameworks and cost-sharing with patients.

To engage on the rapidly emerging field of value assessment, NPC published *Guiding Practices for Patient-Centered Value Assessment* in 2016 to advance the conversation about value assessment frameworks and to ensure that healthcare decision makers assess the right factors in defining and measuring value. As in any equation, if the right variables are not considered, problem solvers will come up with the wrong answer. Similarly, value assessment frameworks must consider value from the perspective of patients, not just from the perspective of payers or healthcare delivery systems. The value that innovative medicines bring to the overall economy and society, as well as to the future of innovation, is also important to include in the equation.

Another potential barrier to access is cost-sharing with patients. With a growing number of patients covered under high-deductible health plans, patient cost-sharing has continued to rise. But NPC-sponsored research has shown the unintended consequences of these mechanisms, including reduced patient compliance with necessary treatments or patients avoiding care altogether. This can translate into missed opportunities to improve patient outcomes and higher costs from health complications that could have been avoided. That's why it is important for all healthcare stakeholders to continue working with policymakers and payers to ensure that the value of innovative therapies is recognized and that patients have reasonable out-of-pocket costs for their medicines at the pharmacy counter.

### *What steps can health systems and providers take to prepare for, or implement, value-based programs in their clinical settings? How can they partner with manufacturers and payers to shift toward these newer reimbursement models?*

NPC's research with the Duke-Margolis Center for Health Policy, published in the February 2019 *American Journal of Managed Care*, provides important direction on this question. The research team evaluated the value-based agreements (VBAs) landscape and found that the shift is already well underway. VBAs are likely more common than previously thought and can take many forms. For example, at Celgene we've pursued innovative contracting with several commercial payers that eliminates patients' co-pay responsibility for enasidenib (Idhifa) through a negotiated arrangement.

On the basis of interviews, the research team also discerned the factors that contribute to the success of VBAs. Reasons for successful negotiations include an easy-to-identify target patient population, a reasonable administrative burden, and the availability

of measurable outcomes clearly related to product use. Some reasons for negotiation breakdowns include challenges related to data collection and evidence development, the availability of appropriate outcome measures, implementation costs, disagreement over incentive mechanisms, and financial terms.

These findings provide important learnings for manufacturers and payers seeking to negotiate successful value-based arrangements. As value-based programs continue to gain traction, it is critical to ensure that the performance measures are built to effectively capture the patient's experience. Though gaps exist in the current landscape, NPC's research on how to incorporate patients' input into oncology performance measures provides clear strategies for closing them.

### *What work is being done with payers to update payment models for innovative therapies (e.g., CAR T and gene therapy)?*

The imperative to investigate innovative new payment models couldn't be clearer. Experts expect an estimated 45–60 curative or durable therapies—those with short treatment regimens and lasting benefits—to reach the market by 2030. Most of these treatments are gene therapies, cellular therapies, and immunotherapies targeted to rare or ultrarare diseases for which no or very limited treatment options exist. We must be ready to bring those biopharmaceutical advances to patients with reimbursement models, including updated public reimbursement models, that are as innovative as the therapies themselves.

Because developing alternative payment models is a multifaceted endeavor, NPC's portfolio—including research and analysis on bundled payments, value-based contracts and risk-sharing agreements, accountable care organizations (ACOs), clinical care pathways, quality measurement, and value assessment—will play a critical role in helping stakeholders engage effectively in these efforts.

### *The emphasis on drug pricing has received bipartisan support in recent years. As we enter the 2020 election season, what should we be listening for regarding drug pricing policies and the stances of the candidates? What issues have an impact on drug innovation and pricing—for example, ensuring that markets allow for robust competition between brand-name products, developing solutions for the lack of competition for generic products that treat relatively uncommon diseases, and creating robust pathways for biosimilar products to compete with biologics? What resources do you recommend for educating ourselves on this issue?*

Some stakeholders seem to believe that most healthcare spending is excessive, and much of the debate on drug pricing is premised on this idea. However, we must challenge those notions through research and dig deeper, as the "Bang for the Buck" study by NPC and RTI Health Solutions did. This study, published in the January 2019 issue of *Health Affairs,* found that spending for six of the top seven causes of death and disease from 1995 to 2015 was cost-effective and also improved patient outcomes.

In order to effectively address healthcare access, quality, and costs, it is important to look beyond simple, surface-level answers. We must attempt to untangle the complexities within our healthcare system and seek to understand the value that medical innovation brings to patients, payers, healthcare systems, and society. Only then can we begin to tackle the root causes, through policy and market-based solutions.

What should stakeholders be looking for in proposed policy solutions? They should look for

- approaches that are grounded in value and recognize that value can vary from patient to patient
- disease-based solutions that reflect areas where health spending does not deliver sufficient value for patients
- protections for the innovations that create important advances in managing the most serious conditions patients face
- efforts to monitor the impact of policy approaches on patient access and health outcomes across different patient populations, to ensure that a high quality of care is being delivered.

As stakeholders navigate policy proposals, NPC's portfolio of research and analysis on evidence, value, access, and innovation provides important resources. For those engaged in health spending issues, NPC's multistakeholder "Going Below the Surface" initiative is another critically important asset. NPC plays a unique role in this effort, convening payers, providers, patient groups, and others around the same table to work toward common solutions. The initiative is driving research and analysis that goes beyond the headlines and simple talking points and provides a research-first approach to identifying solutions in the health spending debate.

# New Subcutaneous Monoclonal Antibodies

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Since their development more than 20 years ago, the targeted monoclonal antibodies (MABs) rituximab and trastuzumab have treated multitudes of patients. Newly developed subcutaneous (SC) formulations of these ubiquitous monoclonal antibodies may improve patient care while increasing the efficiency of infusion clinics. SC Herceptin Hylecta and Rituxan Hycela significantly reduce the treatment burden for patients because they eliminate the need for accessing central lines or placing peripheral intravenous lines before treatment, and administration requires only a few minutes.[1,2] Other monoclonal antibodies may soon be reformulated for SC administration, including an SC daratumumab product expected to become available in the near future.[3]

## Recombinant Human Hyaluronidase

The administration of such large volumes via the SC route is made possible by recombinant human hyaluronidase PH20 (rHuPH20).[4] SC rituximab, SC trastuzumab, and SC daratumumab are all coformulated with rHuPH20.[1-4] Hyaluron is a large glycosaminoglycan that is responsible for forming a gel-like substance with water in the skin, which creates resistance to bulk fluid flow. RHuPH20 temporarily degrades hyaluron, allowing large volumes to be administered into the SC space. The effect of rHuPH20 remains localized and temporary. Within 24 hours of administration, normal SC structure and function are restored.[4]

## Subcutaneous Trastuzumab

The U.S. Food and Drug Administration (FDA) approved Herceptin Hylecta in February 2019. This is a new SC formulation of trastuzumab 600 mg and hyaluronidase-oysk 10,000 units per 5 mL. This standard non-weight-based dose is for all patients and does not require a loading dose. Currently, Herceptin Hylecta is approved by the FDA for use in the adjuvant and metastatic breast cancer settings,[1] and it has been studied in the neoadjuvant setting as well. The National Comprehensive Cancer Network (NCCN) guidelines for treating breast cancer (Version 1.2019) indicate that Herceptin Hylecta is also appropriate for use in the preoperative setting.[5] Approval was based on the HannaH and SafeHER clinical trials.[1]

The SafeHER study was a prospective two-cohort nonrandomized trial that assessed the safety and tolerability of SC trastuzumab. Cohort A ($n$ = 1,864) received the Herceptin Hylecta formulation from a single-dose vial through a hand-held syringe. Cohort B ($n$ = 709) received a bioequivalent formulation of SC trastuzumab via a single-use injection device with an option for patient self-administration.[6] The FDA considered the safety outcomes of the patients in cohort A.[1] Within cohort A, 88.6% of participants experienced 1 or more adverse events (AEs) of any grade, and 7.8% of participants experienced AEs grade 3 or higher. In the study, 7.8% of patients experienced blood or lymphatic system disorders; 3.1% experienced infections and infestations; and 1.1% experienced respiratory, thoracic, or mediastinal AEs. Cardiac AEs were observed in 1.1% of participants, with 0.4% experiencing congestive heart failure.[6] Conversely, cardiac failure occurred in 2% of patients receiving 1 year of treatment with intravenous (IV) trastuzumab.[7]

The HannaH trial enrolled 596 women with HER2-positive early breast cancer in a prospective phase 3 non-inferiority trial. Participants were assigned 1:1 to receive either SC trastuzumab hyaluronidase-oysk 600 mg/10,000 units or IV trastuzumab (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) every 3 weeks. Trastuzumab was administered concurrently with 8 cycles of chemotherapy (4 cycles of docetaxel, followed by 4 cycles of fluorouracil, epirubicin, and cyclophosphamide [FEC]) in the neoadjuvant setting. Following surgery, the study groups continued treatment with either IV trastuzumab or SC trastuzumab every 3 weeks for an additional 10 cycles of single-agent anti-HER2 therapy. Both treatments showed similar efficacy at the clinical cutoff, with a median duration of follow-up of 5.9 years in the SC trastuzumab group and 6 years in the IV trastuzumab group. The 6-year event-free survival (EFS) rates were comparable: 65% in both study groups (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.74–1.29). Six-year overall survival (OS) rates were also similar, at 84% in both study groups (HR, 0.94; 95% CI, 0.61–1.45).[8]

## Subcutaneous Rituximab

Rituxan Hycela (SC rituximab and hyaluronidase) received FDA approval in June 2017.[2] Clinical trials showed its safety and efficacy when used for indications related to multiple malignancies. It is available in two strengths: 1,400 mg rituximab/23,400 units hyaluronidase per 11.7 mL single-use vial and 1,600 mg rituximab/26,800 units hyaluronidase in 13.4 mL. These are standard non-weight-based doses.[2] The NCCN clinical practice guidelines for B-cell lymphoma indicate that SC rituximab may be substituted for IV rituximab in all regimens with one exception: SC rituximab may not replace IV rituximab when used in combination with ibritumomab tiuxetan.[9] NCCN guidelines for chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL) also endorse substituting SC rituximab for IV rituximab.[10] Approval was based on the results of the SABRINA, MabEase, and SAWYER trials.[2]

The two-stage phase 3 randomized controlled SABRINA trial compared SC and IV rituximab in previously untreated CD-20-positive follicular lymphoma of grades 1, 2, and 3a. Participants ($N$ = 410) were randomized in a 1:1 ratio to receive either 1,400 mg SC rituximab or 375 mg/m$^2$ IV rituximab in combination with either 6–8 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or 8 cycles of cyclophosphamide, vincristine, and prednisone (CVP); the chemotherapy regimen was chosen at the discretion of the study center. Patients in both arms then received maintenance rituximab IV or SC every 8

weeks. In the IV group, 84.9% of patients achieved an unconfirmed (CRu) or confirmed complete response (CR) or a partial response (PR) during induction compared to 84.4% in the SC group. Overall response rate (ORR) at the end of maintenance was 78.1% (95% CI, 71.3–83.9) in the IV group and 77.9% (95% CI, 71–83.9) in the SC group. The safety profile of both formulations was considered similar, with patients experiencing one or more AEs or AEs grade 3 or higher in comparable frequencies in both the IV and SC treatment arms.[11]

The phase 3 MabEase trial randomized treatment-naive patients with diffuse large B-cell lymphoma in a 2:1 ratio to receive either SC rituximab 1,400 mg or IV rituximab 375 mg/m$^2$ in combination with either CHOP-14 or CHOP-21 regimens. This was a descriptive study designed to assess major differences in efficacy between treatment arms. In the intention-to-treat population, rates of CRu or CR were 50.6% (95% CI, 45.3%–55.9%) and 42.4% (95% CI, 35.1%–49.7%) in the SC and IV groups, respectively ($p$ = .076). PR and progressive disease rates were similar between treatment arms. CR/CRu rates for all randomized patients were 45.7% (40.7%–50.7%) for SC rituximab and 38.5% (31.6%–45.3%) for IV rituximab ($p$ = .099). At 24 months of follow-up, progression-free survival was 75% (69.9%–79.4%) in the SC group and 81.5% (74.7%– 86.6%) in the IV group ($p$ = .175), and EFS was 68.6% (63.3%–73.4%) and 73.4% (66%–79.4%), respectively ($p$ = .456). Safety profiles were similar between arms.[12]

The phase 1b randomized controlled SAWYER study compared SC rituximab 1,600 mg trough serum concentrations to those achieved with IV rituximab 500 mg/m$^2$ in 176 patients with CLL. Patients received SC rituximab or IV rituximab, plus fludarabine and cyclophosphamide (FC), every 4 weeks for up to 6 cycles. Geometric mean trough serum concentration at cycle 5 showed non-inferiority in the SC rituximab group, with 97.5 mcg/mL in the SC group and 61.5 mcg/mL in the IV group, yielding an adjusted geometric mean ratio of 1.53 (90% CI, 1.27–1.85).[13]

## Subcutaneous Daratumumab on the Horizon

Results of phase 1 studies have shown SC daratumumab 1,800 mg to be a tolerated dose in relapsed or refractory multiple myeloma.[14] The Danish company GenMab A/S announced in a press release in February 2019 limited results of the phase 3 COLUMBA trial. Both the reported ORR and the geometric mean of $C_{trough}$ for patients treated with SC daratumumab met the specified non-inferiority criteria.[11] ORR was 41.1% ($n$ = 263) for the SC daratumumab group compared to 37.1% in patients treated with IV daratumumab ($n$ = 259). The $C_{trough}$ for patients treated with SC daratumumab was 499 mg/mL ($n$ = 149) versus 463 mg/mL in patients treated with IV daratumumab ($n$ = 146). GenMab A/S plans to submit applications for drug approval with regulatory agencies in multiple countries.[3]

## Patient Perspective and Clinic Experience

SC formulations decrease the time it takes for patients to receive their treatments and may improve overall infusion clinic efficiency by decreasing the healthcare provider time required per patient because of reduced administration time. A few studies have evaluated patients' experience or clinic efficiency. MabEase assessed patient satisfaction using the Rituximab Administration Satisfaction Questionnaire (RASQ). Mean RASQ scores were higher across all areas for SC rituximab versus IV rituximab. Impact on activities of daily living mean scores were 83.8 (standard deviation = 16.1) and 57.4 (19.2) for the SC and IV groups, respectively. A majority (90.8%) of patients in the SC group specified a preference for SC over IV. The median administration time (cycles 2–8) was substantially shorter for SC rituximab (5–7 minutes) compared to IV rituximab (range: 2.6–3 hours). For each cycle beginning with cycle 2, a higher proportion of patients who received SC administration spent less than 2 hours in a chair or bed receiving rituximab than those who received IV rituximab (27%–56% SC vs. <1%–5% IV).[12] Likewise, an Irish study compared the cost of administering IV trastuzumab with that for administering SC trastuzumab. The study calculated substantial cost savings to institutions in the following areas: fewer materials used to prepare patients for the medication (e.g., IV placement), fewer materials used to compound SC versus IV trastuzumab, and less healthcare provider time required for patient supervision.[15] If SC rituximab and SC trastuzumab become more widely used, their proven efficacy and efficiency may encourage future development of more SC oncology medications. ●●

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# Evaluation of AHCC Supplementation to Clear High-Risk Human Papillomavirus Infections: A Bench-to-Bedside Approach *(continued from p. 11)*

*in vitro* efficacy of AHCC in clearing HR-HPV DNA, which was then translated into HR-HPV infection clearance in about 40%–60% of patients in the pilot studies. This AHCC supplementation was well tolerated, with no side effects reported. The mechanism of immune modulation by AHCC was determined to be through reduction of interferon beta levels, which has been noted with other chronic viral infections. The results of this study give clinicians a blueprint for formulating a strategy for other bench-to-bedside research and have helped identify a possible therapeutic strategy in this unmet area of need in prevention of cervical cancer. ●●

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# Board Update

## Summer Reflections

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I hope that all of you have taken time over the course of the summer to recharge and spend time with your friends and family. HOPA is grateful for the many hours that you, our members, dedicate to ensure that the organization can represent the high ideals that you all establish in your chosen roles. This year's annual conference was a great launching pad for our activities, but it was only the beginning of the work HOPA members will complete over the coming months.

In late May and early June, the American Society of Clinical Oncology annual meeting provided multiple points of engagement for HOPA's leaders and members. During the conference we were able to connect with a number of new and existing supporters and sit down with several collaborative partners, including the Oncology Nursing Society and the National Community Oncology Dispensing Association. I hope that if you were at the meeting, you had the chance to attend HOPA's member meet-up at City Winery on the Chicago Riverwalk. It was a great time to catch up with old friends and meet new ones. I am thankful to my fellow board members and committee leaders who gave so many hours to ensure that this meeting was productive.

In late May we also learned that our request to develop a preparatory and recertification course was granted by the Board of Pharmacy Specialties. We are very excited for the opportunity to build on our offerings of Board Certified Oncology Pharmacist (BCOP) education. Our goal is to have in place by the time of our 2020 annual conference a course that will open a clear path for early-career professionals to achieve BCOP status while also giving established professionals the credits they need to recertify and maintain their standing. Our dedicated group of HOPA volunteer leaders and HOPA staff members will ensure that the new preparatory course meets the high expectations of our members.

In June we partnered with the Academy of Managed Care Pharmacy to develop and launch "A Value of Cancer Care Forum: Pharmacy's Call to Action" in Washington, DC. The forum provided a platform for pharmacists seeking to engage with other healthcare professionals, concerned parties in industry, and members of the payer community to advance the delivery of value-based care at their institutions. A white paper now in development will document best practices and ideas that emerged from the forum. While in DC, HOPA members also attended our annual HOPA Hill Day, an all-day advocacy event where our members help deliver important information on pharmacy issues to their legislators on Capitol Hill. More than 30 HOPA members and staff members delivered key messages supporting the concept of oral chemotherapy parity, illustrating the problem of drug waste and its associated financial burdens, and educating legislators on patients' need for access to biosimilars.

In July, I was able to take some time to be with my family on beautiful Table Rock Lake in the Ozarks—a family vacation tradition that we all look forward to. It is during times like these that I can recharge and reflect on what is important. Those of us in clinical practice know how important it is to take care of ourselves and how often that seems to be low on our list of priorities. I encourage you to think about it this way: unless we take care of ourselves, we can't be the best providers of high-quality care to our patients.

For many of us, patients are at the center of everything we do. Cancer doesn't take time off, but we hope to give our patients the opportunity to live better lives with this diagnosis. To that end, HOPA has continued to build on the relationships that we have initiated with patient advocacy organizations and other professional societies. Development of our Time to Talk Immuno-Oncology initiative is well under way, and the process includes participants from Cancer Support Community (https://www.cancersupportcommunity.org), the Society for Immunotherapy of Cancer (https://www.sitcancer.org/home), the Oncology Nursing Society (https://www.ons.org), and the Advanced Practitioner Society for Hematology and Oncology (https://www.apsho.org). I encourage you to take advantage of the extensive resources that these organizations offer to improve patient care. I also ask you to stay tuned for the release of a comprehensive toolkit that will bring many of the most effective tools together in one place.

I can't say this often enough, but in closing I thank you all again for your strength of conviction and the service that you provide in your position and as a member of HOPA. HOPA is a great example of how an engaged membership and the power of collaboration can truly make a difference. ●●

Fulphila®
(pegfilgrastim-jmdb) injection

# The First FDA-approved Biosimilar for Neulasta® (pegfilgrastim)

## INDICATION

Fulphila® is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Fulphila® is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

## IMPORTANT SAFETY INFORMATION

Do not administer Fulphila® to patients with a history of serious allergic reactions, including anaphylaxis, to pegfilgrastim or filgrastim.

Splenic rupture, including fatal cases, can occur following the administration of pegfilgrastim products. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Fulphila®.

Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Fulphila® for ARDS. Discontinue Fulphila® in patients with ARDS.

Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure and can recur within days after discontinuation of initial anti-allergic treatment. Permanently discontinue Fulphila® in patients with serious allergic reactions to any pegfilgrastim or filgrastim products.

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue if sickle cell crisis occurs.

Glomerulonephritis has been reported in patients receiving pegfilgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after withdrawal of pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose-reduction or interruption of Fulphila®. White blood cell counts of 100 x $10^9$/L or greater have been observed in patients receiving pegfilgrastim products. Monitoring of CBCs during therapy with Fulphila® is recommended.

Capillary leak syndrome has been reported after granulocyte colony-stimulating factor (G-CSF) administration, including pegfilgrastim products, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

The G-CSF receptor, through which pegfilgrastim and filgrastim products act, has been found on tumor cell lines. The possibility that pegfilgrastim products act as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim products are not approved, cannot be excluded.

Aortitis has been reported in patients receiving pegfilgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology and discontinue Fulphila® if aortitis is suspected.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone imaging results.

The most common adverse reactions (≥ 5% difference in incidence) in placebo-controlled clinical trials are bone pain and pain in extremity.

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**FULPHILA®** (pegfilgrastim-jmdb) injection, for subcutaneous use Initial U.S. Approval: 2018 Brief summary. See package insert or full prescribing information.

### INDICATIONS AND USAGE

#### Patients with Cancer Receiving Myelosuppressive Chemotherapy

Fulphila is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia *[see Clinical Studies].*

Limitations of Use

Fulphila is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

### CONTRAINDICATIONS

Fulphila is contraindicated in patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products *[see Warnings and Precautions].* Reactions have included anaphylaxis *[see Warnings and Precautions].*

### WARNINGS AND PRECAUTIONS

#### Splenic Rupture

Splenic rupture, including fatal cases, can occur following the administration of pegfilgrastim products. Evaluate for an enlarged spleen or splenic rupture in patients who report left upper abdominal or shoulder pain after receiving Fulphila.

#### Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) can occur in patients receiving pegfilgrastim products. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving Fulphila, for ARDS. Discontinue Fulphila in patients with ARDS.

#### Serious Allergic Reactions

Serious allergic reactions, including anaphylaxis, can occur in patients receiving pegfilgrastim products. The majority of reported events occurred upon initial exposure. Allergic reactions, including anaphylaxis, can recur within days after the discontinuation of initial anti-allergic treatment. Permanently discontinue Fulphila in patients with serious allergic reactions. Do not administer Fulphila to patients with a history of serious allergic reactions to pegfilgrastim products or filgrastim products.

#### Use in Patients with Sickle Cell Disorders

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disorders receiving pegfilgrastim products. Discontinue Fulphila if sickle cell crisis occurs.

#### Glomerulonephritis

Glomerulonephritis has occurred in patients receiving pegfilgrastim products. The diagnoses were based upon azotemia, hematuria (microscopic and macroscopic), proteinuria, and renal biopsy. Generally, events of glomerulonephritis resolved after dose reduction or discontinuation of pegfilgrastim products. If glomerulonephritis is suspected, evaluate for cause. If causality is likely, consider dose reduction or interruption of Fulphila.

#### Leukocytosis

White blood cell (WBC) counts of 100 x $10^9$/L or greater have been observed in patients receiving pegfilgrastim products. Monitoring of complete blood count (CBC) during pegfilgrastim therapy is recommended.

#### Capillary Leak Syndrome

Capillary leak syndrome has been reported after G-CSF administration, including pegfilgrastim products, and is characterized by hypotension, hypoalbuminemia, edema and hemoconcentration. Episodes vary in frequency, severity and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

#### Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which pegfilgrastim products and filgrastim products act has been found on tumor cell lines. The possibility that pegfilgrastim products act as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which pegfilgrastim products are not approved, cannot be excluded.

#### Aortitis

Aortitis has been reported in patients receiving pegfilgrastim products. It may occur as early as the first week after start of therapy. Manifestations may include generalized signs and symptoms such as fever, abdominal pain, malaise, back pain, and increased inflammatory markers (e.g., c-reactive protein and white blood cell count). Consider aortitis in patients who develop these signs and symptoms without known etiology. Discontinue Fulphila if aortitis is suspected.

#### Nuclear Imaging

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive



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bone imaging changes. This should be considered when interpreting bone imaging results.

## ADVERSE REACTIONS

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

- Splenic Rupture *[See Warnings and Precautions]*
- Acute Respiratory Distress Syndrome *[See Warnings and Precautions]*
- Serious Allergic Reactions *[See Warnings and Precautions]*
- Use in Patients with Sickle Cell Disorders *[See Warnings and Precautions]*
- Glomerulonephritis *[See Warnings and Precautions]*
- Leukocytosis *[See Warnings and Precautions]*
- Capillary Leak Syndrome *[See Warnings and Precautions]*
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells *[See Warnings and Precautions]*
- Aortitis [see Warnings and Precautions]

### Clinical Trials Experience

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

Pegfilgrastim clinical trials safety data are based upon 932 patients receiving pegfilgrastim in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n =56) received pegfilgrastim after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.

The following adverse reaction data in Table 2 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m$^2$ every 21 days (Study 3). A total of 928 patients were randomized to receive either 6 mg pegfilgrastim (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American, or other.

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo-controlled clinical trials are bone pain and pain in extremity.

**Table 2. Adverse Reactions with ≥ 5% Higher Incidence in Pegfilgrastim Patients Compared to Placebo in Study 3**

| Body System Adverse Reaction | Placebo (N = 461) | Pegfilgrastim 6 mg SC on Day 2 (N = 467) |
|---|---|---|
| Musculoskeletal and connective tissue disorders | | |
| Bone pain | 26% | 31% |
| Pain in extremity | 4% | 9% |

*Leukocytosis*

In clinical studies, leukocytosis (WBC counts > 100 x 10$^9$/L) was observed in less than 1% of 932 patients with non-myeloid malignancies receiving pegfilgrastim. No complications attributable to leukocytosis were reported in clinical studies.

### Immunogenicity

As with all therapeutic proteins, there is a 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 pegfilgrastim in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Binding antibodies to pegfilgrastim were detected using a BIAcore assay. The approximate limit of detection for this assay is 500 ng/mL.

Pre-existing binding antibodies were detected in approximately 6% (51/849) of patients with metastatic breast cancer. Four of 521 pegfilgrastim-treated subjects who were negative at baseline developed binding antibodies to pegfilgrastim following treatment. None of these 4 patients had evidence of neutralizing antibodies detected using a cell-based bioassay.

### Postmarketing Experience

The following adverse reactions have been identified during post approval use of pegfilgrastim products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Splenic rupture and splenomegaly (enlarged spleen) *[see Warnings and Precautions]*
- Acute respiratory distress syndrome (ARDS) *[see Warnings and Precautions]*
- Allergic reactions/hypersensitivity, including anaphylaxis, skin rash, and urticaria, generalized erythema, and flushing *[see Warnings and Precautions]*
- Sickle cell crisis *[see Warnings and Precautions]*
- Glomerulonephritis *[see Warnings and Precautions]*
- Leukocytosis *[see Warnings and Precautions]*
- Capillary Leak Syndrome *[see Warnings and Precautions]*
- Injection site reactions
- Sweet's syndrome, (acute febrile neutrophilic dermatosis), cutaneous vasculitis
- Aortitis *[see Warnings and Precautions]*

## USE IN SPECIFIC POPULATIONS

### Pregnancy

Risk Summary

Although available data with Fulphila or pegfilgrastim product use in pregnant women are insufficient to establish whether there is a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, there are available data from published studies in pregnant women exposed to filgrastim products. These studies have not established an association of filgrastim product use during pregnancy with major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal studies, no evidence of reproductive/developmental toxicity occurred in the offspring of pregnant rats that received cumulative doses of pegfilgrastim approximately 10 times the recommended human dose (based on body surface area). In pregnant rabbits, increased embryolethality and spontaneous abortions occurred at 4 times the maximum recommended human dose simultaneously with igns of maternal toxicity (see Data).

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

Data

Human Data

Retrospective studies indicate that exposure to pegfilgrastim is without significant adverse effect on fetal outcomes and neutropenia. Preterm deliveries have been reported in some patients.

*Animal Data*

Pregnant rabbits were dosed with pegfilgrastim subcutaneously every other day during the period of organogenesis. At cumulative doses ranging from the approximate human dose to approximately 4 times the recommended human dose (based on body surface area), the treated rabbits exhibited decreased maternal food consumption, maternal weight loss, as well as reduced fetal body weights and delayed ossification of the fetal skull; however, no structural anomalies were observed in the offspring from either study. Increased incidences of post-implantation losses and spontaneous abortions (more than half the pregnancies) were observed at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

Three studies were conducted in pregnant rats dosed with pegfilgrastim at cumulative doses up to approximately 10 times the recommended human dose at the following stages of gestation: during the period of organogenesis, from mating through the first half of pregnancy, and from the first trimester through delivery and lactation. No evidence of fetal loss or structural malformations was observed in any study. Cumulative doses equivalent to approximately 3 and 10 times the recommended human dose resulted in transient evidence of wavy ribs in fetuses of treated mothers (detected at the end of gestation but no longer present in pups evaluated at the end of lactation).

### Lactation

Risk Summary

There are no data on the presence of pegfilgrastim in human milk, the effects on the breastfed child, or the effects on milk production. Other filgrastim products are secreted poorly into breast milk, and filgrastim products are not absorbed orally by neonates. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fulphila and any potential adverse effects on the breastfed child from Fulphila or from the underlying maternal condition.

### Pediatric Use

The safety and effectiveness of pegfilgrastim have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature. Use of pegfilgrastim in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma [see Clinical Pharmacology and Clinical Studies].

### Geriatric Use

Of the 932 patients with cancer who received pegfilgrastim in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over. No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

## OVERDOSAGE

Overdosage of pegfilgrastim products may result in leukocytosis and bone pain. Events of edema, dyspnea, and pleural effusion have been reported in a single patient who administered pegfilgrastim on 8 consecutive days in error. In the event of overdose, the patient should be monitored for adverse reactions [see Adverse Reactions].

## NONCLINICAL TOXICOLOGY

### Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenesis studies have been performed with pegfilgrastim products.

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

## PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Advise patients of the following risks and potential risks with Fulphila:

- Splenic rupture and splenomegaly
- Acute Respiratory Distress Syndrome
- Serious allergic reactions
- Sickle cell crisis
- Glomerulonephritis
- Capillary Leak Syndrome
- Aortitis

Instruct patients who self-administer Fulphila using the single-dose prefilled syringe of the:

- Importance of following the Instructions for Use.
- Dangers of reusing syringes.
- Importance of following local requirements for proper disposal of used syringes.

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# Ensuring Healthcare Worker Safety When Handling Hazardous Drugs

*This is a joint position statement from the Oncology Nursing Society and the Hematology/Oncology Pharmacy Association.*

Hazardous drugs (HDs) are chemicals that demonstrate one or more of the following characteristics: carcinogenicity, genotoxicity, teratogenicity, reproductive toxicity, or organ toxicity. In addition, newer drugs with a structural or toxicity profile that mimics an agent known to be hazardous by one of the aforementioned criteria also should be treated as such (National Institute for Occupational Safety and Health [NIOSH], 2016). Any HD handling activity can result in exposure for healthcare workers (HCWs), as documented in a multitude of case reports and studies throughout the medical literature. Exposure to HDs has been associated with acute symptoms (e.g., nasal sores, hair loss, skin rash), adverse reproductive outcomes (e.g., infertility, miscarriage), genetic changes (e.g., chromosomal aberrations, sister-chromatid exchanges), and an increased occurrence of cancer (Centers for Disease Control and Prevention [CDC], 2019).

The Occupational Safety and Health Administration (OSHA, 1986) acknowledged the occupational risks of HDs and issued recommendations for their safe handling over 30 years ago. Updated guidelines from NIOSH and professional societies subsequently have been published (NIOSH, 2016; Polovich & Olsen, 2018; Power & Coyne, 2018). All guidelines address the need for HD-related policies and procedures, education and training, and safe-handling precautions in settings in which HDs are present. Safe-handling precautions include the use of engineering controls, safety equipment, safe work practices, and personal protective equipment (PPE). When used appropriately and consistently, recommended precautions reduce occupational HD exposure (NIOSH, 2004).

Occupational HD exposure can be minimized by a comprehensive HD safe-handling program based on a hierarchy of controls (Connor & McDiarmid, 2006). When a hazard cannot be eliminated, engineering controls are recommended to control exposure. For antineoplastic HDs, engineering controls must be used in a way consistent with expertise within consensus guidelines of United States Pharmacopeia (USP) chapters. Administrative controls are the next level of protection and include safe-handling policies and procedures, hazard communication, education, and medical surveillance of those who potentially are exposed. Finally, PPE that has been tested for use with HDs provides barrier protection for workers. PPE includes gowns, gloves, eye and face shields, and respirator protection, depending on the HD-handling activities. Both employers and employees must share the responsibility for HD safe handling.

It is the position of the Oncology Nursing Society and the Hematology/Oncology Pharmacy Association that

- Settings in which hazardous drugs (HDs) are present will establish evidence-based policies and procedures for safe handling that comply with regulatory requirements and standards.
- Settings in which HDs are present will ensure that PPE indicated for handling HDs is available to all staff to minimize exposure.
- Settings in which antineoplastic HDs are prepared and administered will provide and maintain primary engineering controls such as biologic safety cabinets and compounding aseptic containment isolators in conjunction with secondary engineering controls such as buffer rooms or segregated compounding areas consistent with USP chapters.
- Settings in which antineoplastic HDs are administered will ensure the use of supplemental engineering controls at the point of both compounding and administration when the dosage form allows.
- Settings in which HDs are present will provide education and training specific to each staff member whose work puts them at risk for exposure to HDs. Education, training, and competency evaluation will include the risks of exposure, including the reproductive and developmental effects, the recommended precautions for specific handling activities, safe handling of contaminated patient excreta, proper disposal of contaminated waste, and how to handle acute exposure.
- Settings in which HDs are present will protect the rights of staff who are trying to conceive, are pregnant, or are breast feeding to engage in alternative duty that does not require HD handling.
- Settings in which HDs are present will ensure that patients who receive these drugs and their caregivers receive education about safe handling to minimize unintended exposure in both the institutional and home setting.
- Settings in which HDs are present will ensure that HD waste is disposed of according to regulatory guidelines and in a manner that protects staff and the environment.
- Settings in which HDs are present should engage in medical surveillance of staff.
- Settings in which HDs are present should conduct surface wipe testing as a measure of exposure control to aid in the continuous process improvement for handling HDs.
- Our professional societies support and encourage continued research and the generation of new knowledge about the risks of HD exposure and the efficacy of risk reduction strategies
- Our professional societies will continue to explore evidence-based strategies for mitigation of risk associated with handling HDs and share recommendations with our respective members.
- Our professional societies support and encourage compliance with all of the NIOSH recommendations, USP compounding standards, and regulatory requirements.
- Our professional societies support and encourage advocacy efforts to make recommendations and standards into enforceable laws that best protect staff and the environment.

Approved by the Oncology Nursing Society Board of Directors, July 2019
Approved by the Hematology/Oncology Pharmacy Association Board of Directors, August 2019

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