



Palliative Care and Hospice: A Review for the Hematology/Oncology Practitioner

Stephanie Abel, PharmD
PGY-1 Pharmacy Practice Resident
Medical University of South Carolina, Charleston, SC



Palliative care and hospice currently are buzzwords in the oncology community. The American Society of Clinical Oncology (ASCO) published a Clinical Consensus Statement in 2012 urging oncologists to consider palliative care at the time of diagnosis of metastatic cancer or at any time in those with a high symptom burden.¹ The National Comprehensive Cancer Network (NCCN) Palliative Care Guidelines suggest that palliative care begin at cancer diagnosis in concordance with disease-directed, life-prolonging therapies.² The utilization of palliative care and hospice services is increasing and will likely continue as patient and caregiver outcomes improve, satisfaction with these services increases, and proposed economic benefits are realized.¹ This article defines palliative and hospice care, summarizes recent evidence regarding the benefit of these services, identifies symptoms that palliative care addresses, and summarizes the pharmacist's role in providing palliative care services.

Definitions

Palliative care is comprehensive patient and family care focusing on the relief of distressing symptoms of a chronic illness.² This is accomplished by incorporating psychosocial and spiritual care individualized to

patients' and families' needs, values, beliefs, and cultures. Goals of palliative care include anticipating, preventing, and reducing the suffering of the patient and family, in addition to supporting the best quality of life throughout the course of the disease.²

Hospice care focuses on the patient's quality of life as opposed to length of life. The goal of hospice care is to provide humane and compassionate care for patients during the late phases of an incurable disease so that they may live as fully and comfortably as possible.³ Hospice care and palliative care are very similar in that they both seek to provide the patient with the best possible quality of life. However, patients must have an estimated prognosis of 6 months or less to qualify for hospice care services in the United States. In essence, all hospice care is palliative care but not all palliative care is hospice. Palliative care can be provided during all stages of chronic disease and should not be equated to end-of-life (EOL) care. If the patient lives longer than 6 months, they may still participate in hospice care as long as their prognosis does not extend beyond 6 months. The philosophy of hospice is to accept death as the final stage of life. Hospice services neither hasten nor postpone death and promote treating the patient as a whole person rather than just treating a disease.³



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Overview of Recent Evidence

Temel and colleagues⁴ conducted a study of 151 adult patients with newly diagnosed metastatic non-small-cell lung cancer (NSCLC) who were randomized to receive early palliative care (PC) in addition to standard oncology care or to solely receive standard oncology care. Patients were recruited from a single outpatient clinic in Massachusetts. The intervention arm received a baseline PC assessment and an outpatient follow-up visit at least monthly with a multidisciplinary PC team. The primary outcome was change in quality of life (QOL) at 12 weeks based on the Trial Outcome Index (TOI), which consisted of the sum of scores from the Lung Cancer Subscale (LCS) and the Functional Assessment of Cancer Therapy-Lung (FACT-L). The FACT-L evaluates several aspects of QOL and the LCS is a subscale of the FACT-L that evaluates seven symptoms specific to lung cancer. The FACT-L scale is validated and has been used extensively for QOL assessment in patients with lung cancer.⁵ Secondary outcomes included mood assessments and incidence of aggressive EOL care defined as chemotherapy within 14 days of death, lack of hospice care, or hospice admission ≤ 3 days before death.

When comparing QOL, the PC intervention group had significantly higher scores in the FACT-L, TOI, and LCS ($p = .03$, $.009$, and $.04$, respectively). The PC intervention group had fewer depressive symptoms as measured by the Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire 9 (PHQ-9; $p = .01$). HADS and PHQ-9 are both validated scales and are commonly used to measure the outcomes assessed in this study.^{6,7} At the time of analysis of EOL care, 105 patients (70%) had died. Aggressive EOL care was more common in the standard oncology care group compared with the PC group (54% versus 33%, $p = .05$). Although patients in the PC group had less aggressive EOL care, the patients in this arm survived 2.7 months longer than those in the standard oncology care group ($p = .02$).⁴

Gade and colleagues⁸ at Kaiser Permanente randomly assigned 512 seriously ill patients receiving care in the hospital at three sites within the United States to receive either usual care (UC) or usual care plus an interdisciplinary palliative care service (IPCS). The percentage of patients with a cancer diagnosis was 27.3% and 34.4% in the IPCS and UC groups, respectively. The primary outcomes were to assess patient satisfaction, clinical outcomes assessed by overall survival, and cost of care for 6 months after hospital discharge. The IPCS treatment arm reported greater satisfaction with their care experience ($p = .04$). There was no statistically significant difference between groups in median survival from study enrollment and death during the study period ($p = .08$ for both measures). The total mean health costs were \$6,766 lower in the IPCS group ($p < .001$). In addition, patients in the IPCS arm had significantly fewer intensive care unit readmissions (IPCS: $n = 12$, usual care: $n = 21$, $p = .04$).

Palliative care models are not uniform in the literature, and although many models have been assessed, a benefit has been shown despite a lack of standardization. In addition, no studies to date have shown harm in any form to patients from a palliative care or hospice care intervention. Many national and international organizations have adopted a positive stance on the use of palliative care and hospice care in chronic illness and at the end of life based on the benefits observed in clinical trials.¹

Symptoms Addressed by Palliative Care

There are several symptoms (**Table 1**) that patients should be assessed for during each visit that may have an impact on their QOL. Many of these symptoms may be treated with both nonpharmacologic and pharmacologic measures and can be valuable interventions made by the pharmacist on the team. The NCCN and World Health Organization (WHO) offer thorough and complete resources that provide guidance on treatment options to address these symptoms.

Role of the Pharmacist

Medication therapy management is a large part of symptom management in palliative care, and, therefore, pharmacists have the potential to make a great impact on this area of care. Some traditional aspects that apply to most areas of pharmacy practice apply in palliative care, including assessing medication appropriateness, reviewing medication profiles, counseling

Table 1. Symptoms to Assess at Each Patient Encounter^{2,9}

Pain	Malignant bowel obstruction
Dyspnea	Fatigue/weakness/asthenia
Anorexia/cachexia	Insomnia/sedation
Nausea/vomiting	Delirium
Constipation	Hiccups

patients and caregivers, and providing drug information. Patients who are approaching the end of life may not tolerate adverse drug reactions and have an increased risk of iatrogenic complications. In addition, medications that prove to be ineffective for the patient need to be identified and modified quickly because time and goals of care may be of the essence.¹⁰ Pharmacists should keep in mind the patient's current goals of care, condition, tolerance of current regimen, and financial situation when performing a medication profile review. Medication administration issues may arise and the pharmacist can provide valuable input as to methods of administration, compounding options, and appropriate agent selection individualized to patient-specific circumstances.

Patient and caregiver education is of the utmost importance in palliative care. Medication regimens are only as effective as the patient's and caregiver's understanding of and adherence to the therapeutic plan. A patient's concern for symptom management may be clouded by concern about addiction, side effects, the social stigma associated with taking many medications, or financial barriers.¹⁰ Taking the time to understand the potential barriers to adherence, educating the patient and caregiver, and providing expertise to help navigate these medication-related issues can influence the success of a medication regimen.

In addition to patient education, the pharmacist can provide invaluable education to the healthcare team. As noted above, patient barriers to effective symptom management exist. Similarly, barriers to effective symptom management and pain control are present within the healthcare system as well as within the healthcare team. Healthcare professionals may have inadequate knowledge to assess and manage pain, fear of patient addiction or tolerance, concern for side effects of analgesics, or concern about regulation of controlled substances. Barriers to effective pain management also exist within the healthcare system. Insurance companies may inadequately reimburse for pain assessment and treatment and may not cover the best pain management agents for the patient. The medications also may be too expensive even if the patient has insurance and therefore may not be feasible options. Treatment availability may be limited or access may be restricted. Not all of these barriers can be addressed immediately, but keeping them in mind while providing patient care may help avoid potential problems.¹¹ The pharmacist is well suited to help identify and address these issues to improve patient outcomes.

Conclusion

Palliative care focuses on treating the whole person and not just the disease state. Hospice care utilizes the principles of palliative care in a patient population with a prognosis of less than 6 months to live. Palliative care services have been shown in the literature to provide benefit

to patients by improving QOL, providing less aggressive EOL care, decreasing healthcare costs, and prolonging survival. The pharmacist can play an integral role on a palliative care team or a general oncology team as an advocate for palliative care. In addition to general pharmacy practice services, the pharmacist can educate the patient, caregiver, and healthcare team about medication options, adherence, and barriers to adherence. The pharmacist can help assess symptoms at each encounter, assess efficacy of the current regimen, and make pharmacologic and nonpharmacologic recommendations throughout the course of palliative care treatment. 

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Food and Drug Administration Drug Approval Processes: Speedier Access to New Treatments

Caitlin N. Swann, PharmD

PGY2 Hematology/Oncology Pharmacy Resident

Cleveland Clinic, Cleveland, OH

Recently, there have been changes in the U.S. Food and Drug Administration's (FDA's) drug approval process to make important therapies available to patients sooner than ever before.¹ This article reviews the various pathways developed by the FDA to expedite the drug approval process. Specifically, priority review, accelerated approval, fast-track designation, and the breakthrough therapy designation will be discussed along with examples of drugs that have gone through these programs.

Priority Review Versus Standard Review

To be eligible for priority review, a drug must treat a serious condition and provide a significant improvement in safety or effectiveness compared to standard treatment.¹ A major benefit of this designation is that the FDA will review and make a decision on the drug approval application within 6 months, compared with 10 months under the standard review process. Those drugs granted priority review will also receive additional attention and resources from the FDA during the evaluation phase.

Accelerated Approval

The advantage of undergoing accelerated approval is that a drug may be approved based on a surrogate endpoint that is likely to predict a clinical benefit without having to demonstrate the clinical benefit itself.¹ With accelerated approval, drugs can be approved much faster than the time it would take to demonstrate the drug's impact on morbidity or mortality. To qualify for accelerated review, the drug must be used for a serious or life-threatening condition for which acceptable treatments are lacking. In conjunction with accelerated approval, the FDA requires the sponsors to agree to conduct postapproval studies to verify that a clinical benefit has been demonstrated. If the study results confirm a clinical benefit, the FDA will convert the accelerated approval to traditional approval. If these studies fail to demonstrate a clinical benefit, the FDA may withdraw their approval of the agent, as was the case with ponatinib.

Ponatinib (Iclusig®), which is a tyrosine kinase inhibitor indicated for the treatment of chronic myeloid leukemia (CML) and Philadelphia positive (Ph+) acute lymphocytic leukemia (ALL) resistant or intolerant to other tyrosine kinase inhibitors, was approved in December 2012.² During the initial phase 2 approval trial of this agent, a complete cytogenetic response was demonstrated in 46% of patients, while a major cytogenetic response was shown in 56% of patients, and a major molecular response was observed in 34% of patients.³ In addition, a subset of patients with the T315I mutation demonstrated even greater benefits from the drug, with 70% achieving a major cytogenetic response.³ The presence of the T315I mutation confers resistance to all previously tested tyrosine kinase inhibitors; ponatinib was shown to be the exception. Approval of ponatinib would provide a much needed treatment option for patients with this particular genetic mutation.

The FDA granted accelerated approval of ponatinib with the understanding that additional studies would be performed to confirm its benefit on morbidity and mortality and to further evaluate its safety.⁴ At the time of approval, the initial study results demonstrated a favorable risk profile for ponatinib. Unfortunately, as the data matured, the frequency of serious and life-threatening blood clots and severe narrowing of blood vessels increased from 9% in the initial reports to at least 27% in the most recent results.⁵ The FDA suspended the marketing and sales of ponatinib on October 31, 2013. During this time, the FDA analyzed the potential benefit in the subset of patients in whom this agent may still possess a favorable risk/benefit ratio, specifically those with the T315I mutation. Ponatinib was not commercially available but could be obtained through a patient-specific investigational new drug (IND) or expanded access registry program. In December 2013 the FDA announced the reauthorization of marketing and sales of the drug with several new safety measures in place. A revised Risk Evaluation and Mitigation Strategy (REMS) highlights the cardiovascular risks associated with ponatinib as well as the new indications for its use. The indications are now limited to specific groups of patients: adults with T315I-positive CML or Ph+ ALL, and adults with chronic, accelerated, or blast-phase chronic myeloid leukemia or Ph+ ALL when no other tyrosine kinase inhibitor therapy is indicated. The commercial distribution of the drug resumed in mid-January 2014. Ponatinib is an example of how the accelerated approval process is meant to provide patients access to potentially life-saving treatments as soon as possible, while at the same time protecting the public from situations in which the actual risks outweigh the perceived benefits of treatment.

Fast Track Designation

The fast track designation also promotes expedited approval for drugs.⁶ In this program, sponsors of the drug will have frequent interactions with the FDA to discuss the drug's development plan and field any questions about the process. If the FDA grants a drug fast track designation status, the sponsor may file certain portions of the marketing application before submitting the complete application in a process known as rolling review. Fast track designation may be requested at any stage during drug development. To qualify for the fast track designation, the drug must be intended for the treatment of a serious or life-threatening disease or condition and it must demonstrate the potential to address unmet medical needs for the intended disease or condition. An unmet medical need exists when available therapy does not address the treatment or diagnosis of a condition. The defining criteria or type of information needed to prove the drug addresses an unmet medical need depend on how far along in the process this expedited status is requested. For example, in nonclinical models, the rationale behind the mechanism of action or other pharmacologic data may be considered sufficient if the drug is early in the development

phase. In contrast, if the drug is in the later stages of development and there are clinical data available, then this clinical data should be used to justify the potential to address an unmet need.

Breakthrough Therapy Designation

Breakthrough therapy designation is the newest FDA drug approval category, which was signed into law in 2012.⁶ This designation provides all of the same features that the fast track designation does but also allows for added guidance from the FDA. For drugs granted this designation, the FDA forms a multidisciplinary team that meets with the sponsor of the drug to provide advice in designing trials that will gather the necessary data efficiently to expedite the commercial approval of the drugs. In addition, the FDA will assign a senior manager to the approval application, along with a crossdisciplinary project lead from their review team to act as a liaison with the sponsor throughout the development process.

For a drug to receive the breakthrough therapy designation, the drug must meet certain criteria.⁶ It must be used to treat a serious condition or disease associated with morbidity and mortality, and it must have the potential to have a substantial impact on day-to-day functioning. In contrast to the fast track designation, this designation does not require an absence of available treatments for the disease or condition. Ideally, this designation can be used for drugs that demonstrate substantial improvements over existing therapies when measured using one or more clinically significant endpoints. These endpoints refer to those that measure effects on morbidity or mortality or on the presence and severity of symptoms caused by the disease. This is in contrast to the various forms of nonclinical information (e.g., theoretical or mechanistic rationale, early nonclinical data) required for fast track designation.

This new program is beginning to demonstrate an impact on drug development. In January 2013, the first two drugs to receive breakthrough designations were announced.¹ Both designations were awarded to Vertex Pharmaceuticals, which was seeking to expand the use of their cystic fibrosis drug ivacaftor (Kalydeco[®]). As of November 8, 2013, 92 requests for breakthrough designations had been made, of which 30 were granted, 47 were denied, and 15 were still under review. The first drug with the breakthrough designation to be granted FDA approval was obinutuzumab (Gazyva[®]). It was approved on November 1, 2013, for use in combination with chlorambucil in patients with treatment-naïve chronic lymphocytic leukemia (CLL).⁷ The initial study that led to FDA approval of this drug was a phase 3, open-label study of 356 patients with previously untreated CLL.^{7,8} The study reported improvements in the primary endpoint of progression-free survival, which was 23 months with obinutuzumab plus chlorambucil versus 11.1 months with chlorambucil alone ($p < .0001$). The overall response rate was increased in the combination arm when compared with chlorambucil alone (76% versus 32.1%). Last, the median duration of response was 15.2 months versus 3.5 months, favoring the combination arm. The most common grade 3 or 4 adverse events for patients who received obinutuzumab in combination with chlorambucil compared with chlorambucil alone were infusion-related reactions during the first infusion (21% versus 0%), thrombocytopenia (11% versus 3%), and neutropenia (34% versus 16%), although the higher incidence of neutropenia did not correspond with an increased rate of infections in the obinutuzumab plus chlorambucil arm.

Following obinutuzumab's approval, another drug received FDA approval under the accelerated approval program after being granted breakthrough therapy designation. Ibrutinib (Imbruvica[®]) received FDA approval on November 13, 2013, for patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.⁹ The drug made it through FDA review in just 4 months. Accelerated approval was granted based on the results of a phase 2 study that enrolled 111 previously treated patients with MCL.^{9,10} The primary endpoint was the overall response rate, with 66% of patients demonstrating this. Furthermore, 17% of patients achieved a complete response and 49% of patients achieved a partial response. The median duration of response was 17.5 months. Bleeding events, including bruising of any grade, occurred in 48% of patients, and 5% of these were grade 3 or higher. Treatment-emergent grades 3 or 4 cytopenias occurred in 41% of patients and 25% had grades 3 or 4 infection. As a condition of accelerated approval, the FDA required that the sponsor submit 24-month follow-up data for all patients in this single-arm trial. The sponsor must also submit the results of a randomized controlled trial comparing ibrutinib in combination with bendamustine plus rituximab to bendamustine plus rituximab alone in patients with newly diagnosed MCL.

Summary

There are several FDA programs available to expedite the process of drug development and review to make potentially life-saving treatment options available to patients sooner.^{1,6} Along with the benefits of these programs, there are limitations. It is possible for a drug to make it to market before it has demonstrated safety and effectiveness. According to the FDA, there are stringent measures in place that require aggressive review from multidisciplinary teams representing both the FDA and the drug sponsor.⁶ The key component necessary for all of these programs is effective and timely communication between the sponsor and the FDA. The benefits of these programs have been demonstrated with the expedited approvals of drugs such as obinutuzumab and ponatinib, which were both made available to patients in a relatively short time. **Table 1** summarizes the unique aspects of each approval pathway.³ Any healthcare professional can and should report adverse effects caused by any medication—new or old—through the MedWatch section on the FDA's website.¹¹ The new FDA approval pathways have the potential to greatly impact the treatment of cancer. Drugs are being approved faster than ever, meeting the needs of many cancer patients. 

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Table 1. FDA Approval Pathways

	Priority Review	Accelerated Approval	Fast Track	Breakthrough Therapy
Procedure	Upon receipt of application; Clinical team leader of FDA review team makes recommendation	At time of clinical studies; Sponsor requests during meetings	Any time before marketing approval; Product sponsor requests designation; FDA grants if criteria are met (within 60 days)	At time of IND or later but sponsor requests no later than phase 2 meeting
Criteria	Major advance in treatment or treatment for which no adequate therapy exists	Serious or life-threatening conditions and potential to address unmet medical needs	Serious or life-threatening conditions and potential to address unmet medical needs	Serious condition Preliminary clinical evidence indicates the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies.
Benefit during development		Approval based on surrogate endpoint likely to translate to a clinically meaningful outcome	More frequent FDA communication	More intensive communication and guidance from FDA
Benefit during review	Expedited review (6 months compared to 10 months)		Rolling review	Crossdisciplinary team assigned to aid in review process
Post approval requirement		Studies to confirm clinical benefit		

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HOPA Weighs in on FDA Proposal to Reschedule Hydrocodone Combination Products

Jordan Wildermuth, MSW, Health Policy and Advocacy Manager

In October, Janet Woodcock, MD, director of the Center for Drug Evaluation and Research, issued a press release on behalf of the U.S. Food and Drug Administration (FDA) stating its intent to submit a formal recommendation to the U.S. Department of Health and Human Services (HHS) to reclassify hydrocodone combination products from Schedule III to Schedule II. The decision comes after years of concern by the FDA regarding the abuse and misuse of opioid products. After the recommendation is reviewed by HHS, a final decision on the appropriate scheduling of hydrocodone combination products will be made by the Drug Enforcement Agency.

HOPA's pain management workgroup convened in September 2013 to evaluate requests for HOPA's support of issues related to access to pain medication for cancer patients and respond to legislative, regulatory, and industry changes and practices to ensure the responsible use of pain medications while maintaining access to pain medications for cancer patients. The workgroup, with the support of the Health Policy Committee, concluded that reclassifying hydrocodone combination products would negatively affect the appropriate management of pain and the patient's quality of life.

HOPA determined that two responses were appropriate for this issue. The first was an opportunity to sign on to a letter addressed to HHS submitted by the Pain Care Forum, a coalition of which HOPA is a member. The Pain Care Forum's mission is to "balance the

fundamental rights of patients and clinicians with the challenge of risk containment for opioid misuse, abuse, and addiction associated with medical prescribing and use of controlled substances." The letter outlined a three-part proposal that included maintaining hydrocodone combination products in Schedule III, changing the limits on prescriptions for Schedule III medications so that a telephone prescription for hydrocodone-containing products would not exceed a 10-day supply, and limiting the total amount of medication available through the original prescription plus refills to no more than a 90-day supply.

The second response was to send a letter from HOPA to HHS to bring focus to the patient and, more specifically, how pain affects the cancer patient. Among other points discussed in HOPA's letter, it was noted that until Schedule II narcotics are available through e-prescriptions, oncology patients, while battling cancer and the side effects of treatments, would have to travel to their physician's office to obtain a hard-copy prescription. For patients living in rural areas, the nearest oncologist office may be several hours away from the patient's home. HOPA stated that the rescheduling of hydrocodone combination products to Schedule II is likely to cause more access to care problems rather than solving the drug diversion/abuse problem.

For more information about HOPA's advocacy activities, visit www.hoparx.org/health-policy. 

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Board Update

Niesha Griffith, RPh MS FASHP, HOPA President



Well, it certainly has been an interesting winter! If nothing else, we have all learned a lot about weather systems caused by the “polar vortex” and the “pineapple express.” Personally, I have had just about enough of the snow and cold; however, I know we have been spared here in Ohio compared with those on the East Coast or even those in the South, who are just not prepared to deal with this kind of weather.

I was not pleased to hear that Punxsutawney Phil, the world’s most famous furry forecaster, popped out of his burrow and predicted 6 more weeks of winter. I was, however, very pleased to hear that Buckeye Chuck (no relation to Phil) did not see his shadow. I do realize that this is not a scientific exercise, but Chuck only lives an hour away from Columbus, so I have decided he probably knows best regarding what’s in store for us Buckeyes. After dealing with below-zero temperatures and weekly snow storms, I think we are all looking for some good news wherever we can find it!

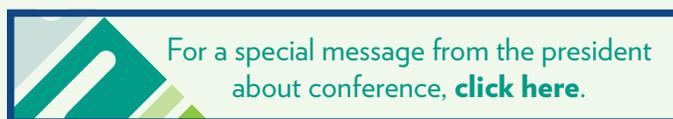
HOPA Annual Meeting

Speaking of good news, our annual meeting is less than a month away! This year, our conference is expected to draw more than 800 pharmacists from all over the world—nearly half of our entire HOPA membership. Our conference educational programs have been developed with an eye toward providing a variety of cutting-edge sessions that serve the needs of both new and seasoned oncology pharmacists.

We will hold two preconference workshops: Oncology 201, covering topics such as bladder, uterine, and thyroid cancer; and a program for oncology residency and preceptor program development.

We will kick off the conference on Wednesday afternoon with the John G. Kuhn Keynote Lecture. This year features our very own John Kuhn (a founding member and our first HOPA president), and Kevin E. O’Connor, who is an author, executive coach, and professional speaker. John and Kevin will reflect on the current state of oncology pharmacy, how far HOPA has come as an organization, and what the future may hold for both our profession and the organization.

Many of our nation’s leading experts in hematology/oncology pharmacy will share their knowledge via educational and interactive sessions featuring a wide range of topics, including new and emerging therapies, controversies in care, and clinical pearls. New this year are two research sessions: developing and submitting a high-quality research proposal and conducting research on clinical service development and evaluation. Breakout sessions will address chemotherapy dosing in obese patients, updates on closed-system transfer devices, and the use of chemotherapy during pregnancy, among others. Our lobbyists from Drinker Biddle & Reath will provide an update on legislative issues affecting HOPA and a review of our health policy priorities and activities.



Several networking events will offer attendees an opportunity to expand their professional contacts. Our exhibit hall will be filled with the premier providers of pharmaceutical products, devices, and delivery systems. As always, our members will have an opportunity to review the latest in completed research during the poster sessions. All conference information, including session descriptions and a list of exhibitors, is available at Conference Web Central on the HOPA website. Be sure to check it out!

Scope of Hematology/Oncology Pharmacy Practice

In a previous board update, I mentioned that the *Scope of Hematology/Oncology Pharmacy Practice* was complete and available on our website. Since that time, an abbreviated version has been accepted for publication in the *Journal of Oncology Pharmacy*. I want to offer a big thank you and congratulations to Lisa Holle and Laura Michaud for spearheading this publication and producing a document to increase awareness of our profession in the hematology/oncology community.

Industry Relations Council

In the spirit of good news, I am happy to report that we now have 14 Industry Relations Council (IRC) members. We had five new members sign on since January (Bayer, Boehringer-Ingelheim, Helsinn Therapeutics, Lilly Oncology, and Seattle Genetics). Thank you to all of the IRC members for their continued support of HOPA.

Miscellaneous Updates

In late November, a work group met to begin developing a HOPA guideline that will address medication therapy management for oral anticancer agents. In February, the work group editors submitted their outline, references, and presentations to the medical writer to compose the first draft. Members will have an opportunity to review and comment on the guideline in spring/summer 2014. The *HOPA Investigational Drug Service Best Practice Standards* is now in production and will be available for member comment in April 2014.

HOPA is in the final stages of completing two issues briefs, which are also expected to be released as early as this spring. One will focus on pain management in cancer patients, while the other identifies measures for preventing counterfeit medications from entering our secure supply chains.

The Volunteer Activity Center is open until March 31. Please sign in and let us know whether you would be interested in participating in any HOPA committees.

The board is suggesting a number of bylaws changes to support our new leadership development plans. Among these proposals will be a name change for the Nomination and Awards Committee and a term change for board members. Watch for the notification of the revisions to be posted on our website for a 45-day member comment period.

HOPA 10th Anniversary Gala

Last, but certainly not least, to recognize the founding of HOPA 10 years ago, we will host the HOPA 10th Anniversary Gala on the evening of Friday, March 28, at The Chicory, which is just a 5-minute walk from the conference hotel. The event will feature a buffet dinner of Creole cuisine, an open bar, and live entertainment provided by some of New Orleans' finest jazz musicians. During this festive evening, we will raise money for the HOPA Research

Fund and recognize those individuals who were instrumental in the founding and shaping of this great organization. Tickets are available online at hoparx.org or by calling 1.877.HOPARX1.

As this is my last board update, I want to take this opportunity to thank the HOPA Board, staff, IRC, and all of you—our dedicated members—for your help and support during the past year. I am excited about all of our accomplishments and growth. We now have 2,093 members, more than 150 members than this time last year!

I look forward to supporting HOPA's efforts in my final year on the board as past president and in the future as an active member. I sincerely hope to see many of you in New Orleans for the meeting.

Here's looking forward to a memorable 10th anniversary, successful meeting, and warm spring! 



ANNIVERSARY GALA CELEBRATING SUCCESS

March 28, 2014  New Orleans, LA

Join us for a special evening as HOPA marks its 10th anniversary with Celebrating Success: HOPA's 10th Anniversary Gala. Enjoy a fun evening as we celebrate HOPA's accomplishments, recognize key people instrumental in founding HOPA, and raise money to fund oncology pharmacy research and education. This is an occasion you won't want to miss!

Silent Auction Added!

Festivities will take place at The Chicory, once the largest coffee warehouse in the country, which is just a 5-minute walk from the conference hotel. The ticket price includes a buffet dinner featuring Creole cuisine and an open bar. Tickets are available through online registration or you may download a registration form from the HOPA website.

Thank you to our Gala sponsors

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Recalls, Withdrawals, and Safety Alerts from the FDA

Recalls

ForeCYTE Breast Health Test and Mammary Aspiration Cytology Test (MASCT)

Atossa Genetics Inc. initiated a voluntary recall to remove the ForeCYTE Breast Health Test and the Mammary Aspiration Specimen Cytology Test (MASCT) device from the market. Atossa is removing the ForeCYTE Breast Health Test and the MASCT device from the market to address U.S. Food and Drug Administration (FDA) concerns about the current instructions for use (IFU), certain promotional claims used to market these devices, and the need for FDA clearance for certain changes made to the nipple aspirate fluid specimen collection process identified in the current IFU. To date, Atossa is unaware of any adverse incidents or injuries associated with the use of the ForeCYTE Breast Health Test, the MASCT device, or the processing method currently identified in the IFU.

www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm370784.htm

Specialty Medicine Compounding Pharmacy Certain Unexpired Compounded Sterile Products: Recall—Particulate Matter Found in Vials

Specialty Medicine Compounding Pharmacy is voluntarily recalling all lots of certain unexpired human and veterinary sterile products to the consumer level due to particulate matter found in vials of a compounded dextrose injection product dispensed to a local hospital. Further testing and analysis of the medication is being conducted. If there is microbial contamination in products intended to be sterile, patients are at risk for serious, potentially life-threatening infections. The recalled products were distributed to hospitals and consumers located only within Michigan from July 1, 2013, through October 19, 2013. No products were distributed out of state. For a detailed list of affected products visit www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm371563.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

MedStream Programmable Infusion Pump and Refill Kits by Codman & Shurtleff: Class 1 Recall—Drug Over Infusion

FDA and Codman & Shurtleff, Inc., notified healthcare professionals of the class 1 recall of MedStream Programmable Pump and MedStream Refill Kit due to air in the pump reservoir, which may release a higher dosage of drug than expected, leading to drug overdose. This product may cause serious adverse health consequences, including low blood pressure (hypotension), an abnormally slow heart rate (bradycardia), loss of consciousness, and death.

www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm371988.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

Nature's Pharmacy and Compounding Center Sterile Compounded Products: Recall—Lack of Sterility Assurance

Nature's Pharmacy and Compounding Center of Asheville, NC, is voluntarily recalling all lots of sterile products compounded by the pharmacy that are not expired to the consumer level. The product will

be in the form of an injectable drug or an eye drop. The recall is being initiated due to concerns associated with quality control procedures that were observed during a recent FDA inspection and present a potential risk to sterility assurance.

www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm375412.htm

Hematology/Oncology Approvals and Safety Notifications

Inclusig (Ponatinib): Drug Safety Communication—Increased Reports of Serious Blood Clots in Arteries and Veins

The FDA is investigating an increased frequency of reports of serious and life-threatening blood clots and severe narrowing of blood vessels (arteries and veins) in patients taking the leukemia chemotherapy drug Inclusig (ponatinib). Data from clinical trials and postmarket adverse event reports show that serious adverse events have occurred in patients treated with Inclusig, including heart attacks resulting in death, worsening coronary artery disease, stroke, narrowing of large arteries of the brain, severe narrowing of blood vessels in the extremities, and urgent surgical procedures to restore blood flow. The FDA is actively working to further evaluate these adverse events and will notify the public when more information is available.

www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm370971.htm

ISMP Medication Safety Alert!

- **November 14, 2013 (Volume 18, Issue 23):** Management of overfill volume for chemotherapy is critical to ensure patients receive full doses of their medications. Healthcare organizations should develop standardized preparation methods for consistency.
- **December 12, 2013 (Volume 18, Issue 25):** There is confusion regarding the need to use 10-ml syringes for flushing and locking via vascular access devices, including implanted ports and peripherally inserted central catheter lines. Bard Access Systems is updating their information to state that, with the exception of a 1-ml prefilled syringe, and once patency is assured, medication administration with smaller diameter syringes can occur.

Changes in Safety Labeling

Arzerra (Ofatumumab) Injection

Changes to ofatumumab labeling include the following:

- Reactivation of hepatitis B virus (HBV) with some reports of fulminant hepatitis, hepatic failure, and death; all patients should be screened for HBV before starting treatment with ofatumumab.
- Tumor lysis syndrome can occur with ofatumumab.
- Progressive multifocal leukoencephalopathy (PML) resulting in death has occurred with ofatumumab. PML should be considered in patients with new onset of or changes in pre-existing neurological signs or symptoms.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm372685.htm

Tasigna (Nilotinib) Capsules

The following changes to nilotinib labeling have occurred:

- Avoid food 2 hours before and 1 hour after taking a dose of nilotinib.
- Electrolyte, calcium, and magnesium blood levels should be tested before initiating and periodically during treatment with nilotinib.
- Sudden deaths have occurred in 0.3% of chronic myeloid leukemia patients treated with nilotinib.
- Nilotinib can cause increases in serum lipase, and those patients with a history of pancreatitis may be at greater risk.
- Avoid administration with agents that are strong CYP3A4 inhibitors, or antiarrhythmic medications (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine, and sotalol) and other medications that may prolong the QT interval. Therapy with nilotinib should be interrupted if treatment with any of these agents is started.
- Lower doses of nilotinib should be used in patients with mild to severe hepatic impairment due to increased nilotinib exposure.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm182234.htm

Gemcitabine Injection 38 mg/mL

The following change has been made to gemcitabine labeling:

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Discontinue gemcitabine if CLS develops during therapy.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm371309.htm

NEUPOGEN (Filgrastim)

The following changes have been made to filgrastim labeling:

- Thrombocytopenia has been reported in patients receiving NEUPOGEN. Platelet counts should be monitored closely.
- Information on Amgen's Lactation Surveillance Program has been added.
- Splenomegaly has been added to the adverse reaction section according to postmarketing experience.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm219032.htm

Alimta (Pemetrexed for Injection)

The following change has been made to pemetrexed labeling:

Reports of immune mediated hemolytic anemia have occurred with pemetrexed used as a single agent or in combination with other agents.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm371329.htm

Gleevec (Imatinib Mesylate) Tablets

The following change has been made to imatinib mesylate labeling:

Gleevec can cause fetal harm when administered to a pregnant woman.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm255333.htm

Lupron Depot (Leuprolide Acetate for Depot Suspension) and Lupaneta Pack (Leuprolide Acetate for Depot Suspension; Norethindrone Acetate Tablets)

The following labeling change has been made:

There have been postmarketing reports of convulsions in patients on leuprolide acetate therapy. These included patients with and without concurrent medications and comorbid conditions.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374019.htm

Zaltrap (Ziv-Aflibercept) Injection

The following labeling change has been made to ziv-aflibercept:

Monitor proteinuria by urine dipstick analysis or urinary protein creatinine ratio (UPCR) for the development or worsening of proteinuria during Zaltrap therapy. Patients with a dipstick of =2+ for protein or a UPCR greater than 1 should undergo a 24-hour urine collection.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374591.htm

Abraxane Injectable Suspension (Paclitaxel Protein-Bound Particles [Albumin-Bound])

The following labeling change has been made to Abraxane:

Cardiovascular: There have been reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block with Abraxane. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm359951.htm

Nexavar (Sorafenib)

The following labeling changes have been made to sorafenib:

- Osteonecrosis of the jaw.
- Impairment of thyroid-stimulating hormone suppression in differentiated thyroid carcinoma; Sorafenib impairs exogenous thyroid suppression.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm280363.htm

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319233.htm

Revlimid (Lenalidomide) Capsules

The following labeling change has been made to lenalidomide:

Lenalidomide should not be used to treat people who have chronic lymphocytic leukemia unless they are participants in a controlled clinical trial, due to increased mortality risk.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm299519.htm

Xalkori (Crizotinib) Capsules

The following labeling changes have occurred with crizotinib:

- Drug-induced hepatotoxicity with fatal outcome occurred in two (0.2%) of the 1,225 patients treated with crizotinib across three main clinical trials.
- Severe, life-threatening, or fatal interstitial lung disease/pneumonitis can occur in patients treated with crizotinib.
- QTc prolongation can occur in patients treated with crizotinib.
- Symptomatic bradycardia can occur in patients receiving crizotinib.

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm295722.htm

Votrient (Pazopanib) Tablets

The following change has been made to the adverse reactions section of pazopanib labeling:

Arthralgia, muscle spasms

www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303649.htm

Highlights from the 36th Annual CTRC-AACR San Antonio Breast Cancer Symposium (SABCS)

Bobbie Quach, PharmD Student

Meghana V. Trivedi, PharmD PhD BCOP

Assistant Professor

University of Houston College of Pharmacy, Houston, TX

Bisphosphonates in Breast Cancer

Adjuvant Bisphosphonate Reduces Bone Recurrence and Improves Survival in Postmenopausal Women with Early Breast Cancer¹

During the past 15 years, numerous randomized controlled trials have shown conflicting clinical benefits in the use of adjuvant bisphosphonate therapy in breast cancer. To address this, a meta-analysis of 36 randomized controlled trials was conducted to compare bisphosphonate versus no bisphosphonate in the adjuvant setting. The primary outcomes were time to recurrence, time to first distant recurrence, and mortality. In all 17,709 women (pre- and postmenopausal) included in the study, a significant reduction in bone recurrence (10-year gain: 1.5%) was observed with the use of bisphosphonates. When the analysis was restricted to 11,306 postmenopausal women, the reduction in bone recurrence with bisphosphonate therapy was even higher (10-year gain: 2.9%). In the analysis of bone recurrence by menopausal status, use of adjuvant bisphosphonates significantly reduced bone recurrence in postmenopausal women (hazard ratio [HR] = 0.66) but not in premenopausal women (HR = 0.93). There was a significant delay in breast cancer recurrence and non-bone distant recurrence in postmenopausal women taking bisphosphonates; this difference was not seen when premenopausal women were also included in the analysis. In evaluating mortality in postmenopausal women, adjuvant bisphosphonate use significantly reduced breast cancer mortality (10-year gain: 3.1%) and all-cause mortality (10-year gain: 2.3%). Although the difference in breast cancer mortality was significant with bisphosphonates in all women, this was primarily driven by the majority of postmenopausal women. In summary, adjuvant bisphosphonates in postmenopausal women significantly reduced the risk of bone recurrence (risk reduction of 34%) and improved survival (risk reduction of 17%) irrespective of the type of bisphosphonate and osteoporosis versus cancer dose, ER positivity, node status, and presence/absence of chemotherapy.

No Advantage of Postneoadjuvant Zoledronic Acid in Primary Breast Cancer²

The NaTaN (Neo-Adjuvant Trial Add-On) study evaluated the effects of postneoadjuvant treatment with zoledronic acid in patients without pathological complete response (pCR) after anthracycline-taxane-based chemotherapy for primary breast cancer. Patients were randomized within 3 months, 1 year, 2 years, or 3 years after surgery to receive intravenous (IV) zoledronic acid 4 mg with 1,000 mg calcium and 880 international unit (IU) vitamin D daily versus observation. For the first 6 months, zoledronic acid was administered every 4 weeks for the first six doses, every 3 months for the following 2 years (eight doses), and every 6 months for the last 2.5 years (five doses). Primary outcome was event-free survival (EFS); reported secondary outcomes were overall survival (OS), EFS in subgroups, and toxicity. An interim analysis was conducted with a nonprotocolled Bayesian futility analysis with a 15% futility

boundary for the likelihood the results will become statistically significant. The probability of success was <6%; therefore, results were considered final and released. No EFS improvements were seen for patients given 5-year zoledronic acid postneoadjuvant therapy (HR = 0.960, 95% confidence interval [CI]: 0.709–1.30; $p = .7885$) in comparison to the control group. EFS benefits were not seen in any of the subgroup analyses. Similarly, no significant difference in OS ($p = .4082$) was noted. In addition, serious adverse events occurred more often in the treatment group (60 events) compared with the observation group (21 events). Although this first randomized postneoadjuvant zoledronic acid treatment study did not improve outcomes in patients without pCR after neoadjuvant chemotherapy, several postneoadjuvant treatment options are currently under investigation, such as rucaparib (PARP-inhibitor) in triple-negative breast cancer (BRE09-146), trastuzumab emtansine in HER2+ disease (OT1-1-06), and palbociclib in HR+/HER2- disease (OT2-6-11).

Aromatase Inhibitors (AIs): Breast Cancer Prevention

Anastrozole for Prevention in Postmenopausal Women at High Risk³

The International Breast Cancer Intervention Study II (IBIS-II) trial, a multicenter, randomized, placebo-controlled study, assessed the efficacy of anastrozole versus placebo in 3,864 postmenopausal women who do not have breast cancer but have an increased risk of developing breast cancer. Increased risk was determined by age, family history, type (atypia/lobular carcinoma in situ), breast density, or if the Tyrer-Cuzick model indicated a 10-year risk of breast cancer greater than 5%. The updated data with a median follow-up of 5 years were presented at the meeting. A 53% reduction in breast cancer was seen in the anastrozole treatment group (95% CI: 0.32–0.68; $p < .0001$). In addition, significant reductions were also seen in ductal carcinoma in situ (DCIS; 70% reduction, HR = 0.30 [0.12–0.74]), all invasive breast cancer (50% reduction, HR = 0.50 [0.32–0.76]), and ER+ invasive breast cancer (58% reduction, HR = 0.42 [0.25–0.71]), but not in ER-invasive breast cancer. Compliance was similar in anastrozole and placebo groups with few dropouts due to side effects. Musculoskeletal events (63.9% versus 57.8%) and vasomotor/gynecological adverse effects (56.8% versus 49.4%) were common and significantly higher in the anastrozole group compared with placebo. Currently, the IBIS-II trial provides evidence to support the use of anastrozole for prevention in high-risk postmenopausal women. The long-term follow-up of these patients will determine the full scope of benefits and risks of anastrozole.

AI: Adverse Effects Management

Exercise Interventions to Alleviate Aromatase Inhibitors' Arthralgia⁴

AIs are standard of care for hormone receptor-positive breast cancer;

however, side effects, such as arthralgia, result in poor adherence and early discontinuation. The HOPE (Hormone and Physical Exercise) study examined 121 postmenopausal stage I-III breast cancer patients who were taking an AI for at least 6 months and experienced at least mild arthralgia defined by pain score >3 on the Brief Pain Inventory-Short Form (BPI). The BPI measured worst pain, pain severity, and pain interference at baseline, 6, and 12 months reported on a scale of 0–10 (mild pain = 3–4, moderate pain = 5–7, severe pain = 8–10). The patients were randomized to the exercise group ($n = 61$) or usual care group ($n = 60$). The year-long exercise program consisted of a twice weekly supervised strength training session comprising six common strength-training exercises (8–12 repetitions, three sets) and 2.5 hours/week of moderate aerobic exercise with heart rate monitors to determine intensity. At baseline both controls and exercisers reported similar BPI scores with the worst pain at a pain score of 6 (moderate pain). After 12 months, women randomized to exercise had a significant (20%) decrease in their worst joint pain score, while the usual care control group had only a 3% decrease ($p = .017$). Women who had 80% or higher adherence to the exercise plan had greater benefits compared with women who had $<80\%$ adherence to exercise plans. This preliminary study showed clinical benefit with the use of exercise to reduce pain level from AI-induced arthralgias in breast cancer survivors; therefore, this regimen may lead to improvements in AI adherence, quality of life, and mortality risks. Additional analyses are in progress to further evaluate the benefits of this exercise intervention.

Als: Preemptive Symptom Management May Improve Adherence⁵

The COBRA (Consortium on Breast Cancer Pharmacogenomics) investigators analyzed the patient-reported symptoms prior to AI initiation and after discontinuation to determine if a patient's baseline symptoms may impact persistence with AI treatment. The ELPh (Exemestane and Letrozole Pharmacogenetics) trial randomized 503 postmenopausal women with early stage ER+ breast cancer to exemestane 25 mg PO daily ($n = 248$) or letrozole 2.5 mg PO daily ($n = 252$) for 2 years. Every 1, 3, 6, 12, and 24 months, quality of life and serum hormone concentration data were collected. Quality of life assessments evaluated depression (CESD), anxiety (HADS-A), sleep (PSQI), and symptoms (BCPT). Overall, 31.2% participants discontinued treatment due to toxicity (60 patients taking letrozole and 80 patients on exemestane). Poor sleep (45%, OR = 1.91, $p = .002$), feeling tired (58%, OR = 1.76, $p < .001$), and forgetfulness (46%, OR = 1.66, $p = .015$) were significant adverse effects associated with early AI treatment discontinuation. A significant correlation ($p = .007$) was seen between baseline symptom burden and AI discontinuation in 1 year. In conclusion, the ELPh study suggested that up-front evaluation and management of initial symptoms might help improve adherence to AI therapy by managing these symptoms before they become problematic and also identifying patients at higher risk of treatment discontinuation in order to enable appropriate interventions.

HER2+ Breast Cancer

Pathological Complete Response (pCR) Correlates with Survival Advantage in HER2+ Breast Cancer⁶

The initial findings of the Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO) trial presented at SABCS in 2011 showed that the pCR rate was significantly higher in

the combination lapatinib plus trastuzumab arm compared with the single therapy with either lapatinib or trastuzumab. The updated survival analyses presented at the 2013 meeting demonstrated that patients who achieved pCR had significantly better EFS and OS compared with no pCR irrespective of treatment arm. At a median follow-up of 4 years, there was a significant increase in EFS in patients who experienced pCR in comparison to no pCR (HR = 0.8 [0.22–0.63], $p = .0003$). In evaluating OS, a 65% reduction (HR = 0.35 [0.15–0.70], $p = .005$) in death risk was seen in patients who had pCR compared with patients who did not. A greater difference in EFS and OS between pCR and no pCR was seen for hormone receptor-negative breast cancer. No differences in EFS or OS were noted between the treatment arms; however, the NeoALTTO study was not powered to detect modest differences in survival. This question will be addressed by the ALTTO trial, which will be presented next year. Although the data are promising, it might be still premature to use the combination anti-HER2 therapy as a standard of care because of increased risk of adverse effects and lower adherence to therapy with the combination therapy even in hormone receptor-negative cancer. The standard of care in the neoadjuvant setting still remains chemotherapy and trastuzumab. Follow-up analysis will occur over the next 2.5 years. The results from this study also support the FDA's accelerated approval process in the neoadjuvant setting based on the pCR data.

Neoadjuvant Lapatinib Plus Trastuzumab in Combination with Chemotherapy: Similar pCR Rates, More Toxicities, and Less Adherence Compared with Trastuzumab Only⁷

The TRIO-US B07 was a randomized phase 2 trial comparing the efficacy and safety of neoadjuvant lapatinib plus trastuzumab, lapatinib alone, and trastuzumab alone in HER2+ stage I-III breast cancer. Women were randomized into three treatment arms: trastuzumab ($n = 34$), lapatinib ($n = 36$), or combination lapatinib plus trastuzumab ($n = 58$) for 21 days followed by six cycles of Docetaxel 75 mg/m² and carboplatin AUC 6 IV every 3 weeks. Biopsies were collected at baseline, after run-in cycle, and at surgery, with pCR rate as the primary endpoint. Although pCR was higher in lapatinib plus trastuzumab arm (52%) compared with trastuzumab (47%) or lapatinib (25%) arms as shown by other groups, the difference was only statistically significant when comparing the combination with lapatinib. Combination therapy was associated with higher incidence of diarrhea compared with trastuzumab; whereas cardiac events were not significantly different in lapatinib plus trastuzumab arm compared with trastuzumab only. Completion of therapy was significantly lower in the combination therapy (73%) and lapatinib (72%) groups compared with trastuzumab (100%). The lack of benefit from the combination therapy over the trastuzumab only arm, which has been observed in several other studies (e.g., NeoALTTO, TBCRC 006), may be due to a short therapy with anti-HER2 agents.

Novel Agents in Breast Cancer

Src Inhibitor: Dasatinib⁸

In a randomized study, 120 patients with ER+, HER2- breast cancer were treated with either letrozole plus dasatinib or letrozole alone as first-line therapy for metastatic disease. Time to progression was doubled from 9.7 months to 20.1 months when dasatinib was added to letrozole. This was despite no clinical benefit based on tumor size and

symptoms. These findings suggest a role of dasatinib in overcoming resistance to AIs. Dasatinib might be an attractive candidate for further investigation in this setting because it also did not greatly increase the toxicity profile of the AI.

Anti-VEGF Receptor-2 Antibodies: Ramucirumab⁹

Ramucirumab, a recombinant human IgG1 monoclonal antibody that binds the extracellular domain of VEGF receptor-2, was investigated as a first-line therapy in combination with docetaxel for HER2- metastatic breast cancer. Progression-free survival was not significantly better in docetaxel plus ramucirumab compared with docetaxel alone (HR = 0.88; $p = .08$). Ongoing molecular analysis from this study may reveal biomarkers for ramucirumab response.

PARP Inhibitors: Veliparib^{10,11} and BMN 673¹²

Veliparib plus carboplatin every 3 weeks plus weekly paclitaxel therapy for a total of 12 weeks followed by AC (four cycles of doxorubicin plus cyclophosphamide [every 2–3 weeks]) regimen was tested in comparison to weekly paclitaxel followed by AC in an adaptive trial with 116 high-risk HER2- patients.¹⁰ There was a significant increase in the estimated pCR rate from 22% to 33% when veliparib plus paclitaxel were added to the neoadjuvant regimen. The increase in the estimated pCR rate was primarily observed in triple negative breast cancer (26% versus 52%) and not in hormone receptor-positive and HER2- breast cancer (14% versus 19%). Unfortunately, the relative contributions of veliparib and carboplatin could not be determined based on the study design. In a second smaller study, veliparib was tested in 20 stage IV breast cancer patients who were BRCA 1 or 2 carriers.¹¹ At least partial response was seen in 14 of 20 patients. Another PARP inhibitor, BMN 673, was also tested in patients with deleterious germline BRCA 1 and 2 mutations.¹² Partial response was achieved in 8 of 18 patients treated with BMN 673. Both veliparib and BMN 673 remain attractive candidates for further investigation in breast cancer.

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The Resident's Cubicle

Alex Shillingburg, PharmD

Clinical Specialist BMT/Hematologic Malignancy

WVU Healthcare, Morgantown, WV

Surviving the Interview Season

It's open season for potential residency candidates and new job seekers. This edition of The Resident's Cubicle will focus on tips to help PGY2 oncology residents survive the impending interview season. There are three facets of the interview season that have a significant impact on the oncology resident's life: traveling to and preparing for job interviews, keeping up with residency responsibilities while absent from work for interviews and travel, and interviewing oncology residency candidates to take your place in your program the following year.

Preparing for the Job Interview

The time has come to find a place to work for an indefinite period of time. Many things need to play into this decision, such as location, family circumstances, fit with the mission and atmosphere of the institution, and the job responsibilities. Here are some tips that are important enough to reiterate even though they should be second nature after all the interviewing over the past few years to get to this point.

1. **Talk.** It may seem silly, but to figure out if you would be a good fit, you need to be engaged during your interview. If you don't engage, not only will you seem dull, but you won't be able to get a good sense of the organization. Talk to the cab driver, the cashier in the lunch line, and the receptionist. Everyone you meet can help mold your opinion of a place. Don't talk over your interviewers, but be sure to take advantage of every chance to interact. You are only there for a short period and want to gather as much information as you can to make an informed decision.
2. **Be real.** Be yourself and be honest. It should go without saying to absolutely not falsify any information and to be honest about your personality. Don't be the person you think they want; be who you are. You will thank yourself later when the real you fits well in your new position!
3. **Dress smart.** Put your absolute best foot forward for your first impression. There is no need to be a fashionista, but always wear a matching freshly pressed suit; wear clean, unscuffed shoes; and keep hair, facial hair, nails, and accessories well-groomed, neat, and tasteful.
4. **Never be late.** Plan for weather-related delays, especially in the winter.
5. **Be interested.** Ask plenty of questions to which you genuinely want answers. Nothing turns someone off more than interviewing a candidate who doesn't want to be there. Nonverbal cues send very strong signals. Sit up straight, lean in slightly, make eye contact, and smile.

During your interview you will make connections with professionals in your future field and, trust me, you *will* see them again. Oncology pharmacy is a small world, and it never hurts to have friends in many institutions.

One aspect of job interviewing that will differ drastically from residency interviewing will be the inconsistent timeline. This is often the most frustrating part of the job search for PGY2 residents. There will not be a magical match day when you find out with which institution you were matched. There will not be a tight 6-week timeline for interviews. You will likely find that some places may take weeks to months to evaluate and interview all of their candidates. Job offers could be made to you before you even go to other interviews, and they may expect an answer quickly. Navigating this very unpredictable timeline will require difficult life decisions, often without all of the pieces of the puzzle in front of you. My best advice to you is to be professional. Be upfront with your intentions, respect the institution's time frame as well as your own, and don't accept a job expecting to reject it if a better one comes along. If your top institution has not made an offer yet and you need to give other places an answer, it is not unreasonable to contact human resources to ask if they have filled the position or know when they will begin making offers. Deciding whether to take a good offer or to turn it down to gamble on an offer from your dream job is difficult. Unfortunately there is no right answer, but be prepared for these situations to arise and take care not to burn bridges.

Keeping Up During Your Absence

Don't assume that your responsibilities to your residency will be absolved when you are away for an interview. Regardless of the number of days missed for interviews, residents should expect to be held accountable for their residency expectations during this time. That's not to say that you should cancel interviews or that special accommodations cannot be made for extra days away from the residency. The best way to address missed days is to keep open and upfront communication with your residency program director and your preceptors during this time. It is likely that they will know how many positions you have applied for because you may be asking them for recommendations, but be forthcoming with interview dates and travel plans as soon as possible. Adjustments may need to be made to make up presentations or activities after a rotation has ended. Topic discussions may be concentrated during specific times during rotations to maximize learning with limited days on rotation. Additional activities may be necessary if significant patient care time is missed, but the resident's learning experience should not be impacted by excessive absences.

Keep in mind when scheduling interviews that middle-of-the-week dates will require more time off for travel but may not be avoidable. Be sure to maintain an up-to-date agenda during this time, and always inform the organizer of any meetings or presentations you will miss. Try to reschedule to keep your original commitments and work with colleagues to help cover any duties you have scheduled such as precepting students, teaching classes, or maintaining operational responsibilities. These things can often be easily addressed in advance, but will reflect extremely poorly on you if forgotten.

Managing PGY2 Candidate Interviews at Your Program

Regardless of your role in these interviews—dinner host, tour guide, or planned one-on-one interview—do not discount their importance. Even though you may be leaving in a few short months, do not forget that the candidate who matches will graduate from the same program you did. You should have pride in your program and work to ensure that the candidate who will replace you is the best fit for your program.

These interviews can also take a significant amount of time from your day depending on your interview responsibilities, which you should consider while managing your to-do list for that day. It can also be very exhausting to be consistently “on” if you are with the candidate for long periods of time throughout the day. It is crucial to be as engaged during the last few minutes while walking them out as you were in the morning when they first stepped foot in the building. Your excitement and professionalism will leave an impression with the candidate, and you want that impression to be that you are prompt, cordial, respectful of them, and proud to be graduating from your program.

Be prepared with three or four questions to ask each candidate so that you have an equal basis on which to compare. Remember to take notes of their responses, questions they asked you, and your

impression. You will be surprised by how many faces you will see during these months, and you will need your notes to jog your memory come rank time. Don't be surprised if you don't get to all of your questions because the candidate may be prepared with a continuous stream of his or her own questions for you. Almost everyone will advise them to talk to the current resident. You are in the midst of the program they are interested in and the most relatable source of information. Be sure to be truthful but keep in mind that this is not the time to vent your frustrations. You represent your institution and your program. It is appropriate to talk about recommendations for improvements, but complaining or trash-talking will only reflect poorly on you.

In summary, this time will be very busy and will require oncology residents to continually switch gears and refocus from interviewer to interviewee. Always be mindful of the situation you are in and maintain a professional attitude. Through all the stress and commotion, this is also an extremely exciting time with big changes and opportunities on the horizon. Explore every option, keep an open mind, and stay excited about the novelty of new people, cities, and jobs. You have worked hard to get to this point. Be proud of your accomplishments!



HOPA By-Laws Amendments: Member Comment Period

After accepting recommendations from the HOPA Leadership Task Force and conducting a thorough legal review, the HOPA Board of Directors is proposing several by-laws amendments and seeking member comment. The proposed changes will

- provide greater consistency and clarity in the language used throughout the document as well as language that reflects current practice
- increase the board terms for at-large members, secretary, and treasurer from 2 years to 3 years

- change the current Nominations & Awards Committee to a Nominations & Leadership Development Committee with expanded leadership development responsibilities.

Please visit the HOPA website (www.hoparx.org) to review the proposed amendments, a crosswalk of the proposed amendments, and the implementing resolution that would be needed to implement amendments to board terms. A 45-day member comment period is open between February 21 and April 8, 2014. Please send comments, questions, or concerns to board@hoparx.org no later than close of business April 8, 2014.



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Ibrutinib (Imbruvica™)

Class: Bruton's tyrosine kinase inhibitor

Indication: Treatment of patients with mantle cell lymphoma who have received at least one prior therapy

Dose: 560 mg (four 140-mg capsules) taken orally once daily

Dose modifications: Interrupt therapy for the following toxicities: grade 3 or greater neutropenia with infection or fever, or any grade 3 or greater nonhematologic or grade 4 hematologic toxicities. Upon resolution of toxicity to grade 1 or lower, reinstitute therapy at the starting dose. If the toxicity recurs, reduce the dose by 140 mg (one capsule) daily. A second dose reduction of 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue therapy.

Common adverse effects (≥20% incidence): Thrombocytopenia, neutropenia, anemia, diarrhea, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting, and decreased appetite

Warnings and precautions: Increased risks of hemorrhage (consider holding at least 3–7 days pre- and postsurgery, depending on bleeding risk), infection, myelosuppression, renal toxicity, secondary primary malignancies, and embryo-fetal toxicity have been reported. Avoid use in patients with baseline hepatic impairment.

Drug interactions: Substrate of CYP3A4; avoid concurrent use with strong CYP3A4 inhibitors and inducers; modify dose with moderate CYP3A4 inhibitors.

Ibrutinib for Mantle Cell Lymphoma

Bryan Do, PharmD

PGY1 Pharmacy Practice Resident

UMass Memorial Medical Center, Worcester, MA

Mantle cell lymphoma (MCL) represents one of the many subtypes of B-cell non-Hodgkin's lymphomas (NHLs) and accounts for approximately 6% of the more than 69,000 new cases of NHL diagnosed each year.¹ MCL arises from a translocation of chromosomes 11 and 14 (t[11;14]) causing an overexpression of cyclin D1, a protein that regulates cell division and growth.^{2,3} This mutation results in defective B lymphocytes, leading to bone marrow destruction, lymphadenopathy, and gastrointestinal complications.³

MCL typically affects older men, with a median survival range of 3–5 years.³ Although a number of patients will have indolent disease and may undergo watchful waiting, most patients present with advanced stage III/IV disease requiring aggressive treatment. Initial management for MCL typically involves induction chemotherapy with a modified R-CHOP regimen or R-HyperCVAD followed by stem cell rescue.⁴ However, many patients will require second-line therapy as a result of relapsed or refractory disease. Novel targeted therapies are

under investigation and have shown to alter disease progression in B-cell malignancies.⁵

Ibrutinib (Imbruvica™, Pharmacyclics, Inc.) is a novel oral tyrosine kinase inhibitor that received accelerated approval by the U.S. Food and Drug Administration (FDA) on November 13, 2013, for the treatment of MCL in patients who have received at least one prior therapy.⁶ Ibrutinib covalently binds to Bruton's tyrosine kinase, impairing B-cell antigen receptor signaling and disrupting the proliferation and survival of malignant B-cells.⁷

Ibrutinib initially demonstrated activity in MCL during a phase 1 dose-escalation study that enrolled nine patients with MCL. Seven of the nine patients (78%) with relapsed or refractory MCL achieved a clinical response to therapy, either a partial response (PR) or complete response (CR) as defined by the Revised International Working Group Criteria. Ibrutinib was well tolerated, with the most common adverse events reported being self-limiting grade 1 and 2 diarrhea, nausea/vomiting, fatigue, and myalgia.⁸

The safety and efficacy of ibrutinib in MCL was evaluated during a phase 2 international open-label study of 111 patients with relapsed or refractory MCL. Enrolled patients had received at least one prior therapy with no partial or better response to the previous regimen, or had disease progression despite treatment. Participants received 560 mg ibrutinib taken orally daily until disease progression. The primary endpoint was the rate of overall response (ORR) and the secondary endpoints included response duration, progression-free survival (PFS), overall survival (OS), and safety. The median age of patients enrolled was 68 years, with 86% having intermediate- to high-risk disease. Of the 111 patients who received ibrutinib, 75 patients (68%) responded to therapy, with 52 patients (47%) experiencing a PR and 23 patients (21%) experiencing a CR. Patients had an estimated median response duration of 17.5 months (range: 0.0–19.6; 95% confidence interval [CI]: 15.8–not reached). The estimated PFS was 13.9 months (range: 0.7–21.4; 95% CI: 7.0–not reached); the median OS rate was not reached during follow-up but was estimated to be 58% at 18 months.⁹

Ibrutinib was well tolerated during the phase 2 trial. The most common adverse effects (≥20% of patients, all grades) were diarrhea, fatigue, nausea, peripheral edema, dyspnea, constipation, upper respiratory tract infection, vomiting, and decreased appetite. Grade 3 or 4 hematologic adverse events included neutropenia (16%), thrombocytopenia (11%), and anemia (10%). Grade 3 or 4 nonhematologic events occurring in ≥5% of patients included pneumonia (7%), skin infections (5%), diarrhea (6%), fatigue (5%), and abdominal pain (5%). Eight patients (7%) discontinued treatment due to adverse events and 14% required dose reductions.^{8,9}

The FDA-approved dose for ibrutinib is 560 mg orally once daily (four 140-mg capsules). Therapy should be held for any grade 3 or greater nonhematologic toxicity, grade 3 or greater neutropenia with infection or fever, or grade 4 hematologic toxicity. After the toxicity has resolved to grade 1 or baseline, ibrutinib therapy may be reinitiated at the starting dose. If toxicities reoccur, the dose should be reduced by one capsule (140 mg per day). If symptoms persist following two

dose reductions, discontinue ibrutinib. Ibrutinib is metabolized primarily by the CYP3A4 enzyme system. Coadministration of ibrutinib with moderate and strong CYP3A4 inhibitors should be avoided. During short-term use of strong CYP3A4 inhibitors (antifungals and antibiotics taken for <7 days), ibrutinib therapy may be interrupted. Unavoidable concurrent use of moderate CYP3A4 inhibitors may be managed with an ibrutinib dose decrease to 140 mg. Concurrent use of ibrutinib with strong CYP3A4 inducers (phenytoin, St. John's wort, carbamazepine) can significantly decrease plasma concentrations of ibrutinib by up to tenfold and should be avoided. Capsules should be taken whole with a full glass of water. Administration with food increases medication exposure approximately twofold compared with administration after overnight fasting.¹⁰

Because ibrutinib is metabolized in the liver, significant increases in drug exposure are expected in patients with hepatic impairment. Patients with elevated hepatic enzymes (aspartate transaminase or alanine transaminase $\geq 3.0 \times$ upper limit of normal) were excluded from clinical trials; therefore, there is insufficient data to recommend a dose modification in patients with baseline hepatic impairment. Preliminary, ongoing pharmacokinetic data in patients with hepatic impairment indicate exposure is approximately sixfold higher in subjects with Child-Pugh B hepatic impairment ($N = 3$). Ibrutinib is minimally excreted (1%) renally and exposure is not altered in patients with a creatinine clearance >25 mL/min. Ibrutinib has not been studied in patients with a creatinine clearance <25 mL/min or in patients on dialysis. In geriatric patients, no overall differences in effectiveness were observed, though some adverse effects occurred more frequently (atrial fibrillation, hypertension, pneumonia, cellulitis, diarrhea, and dehydration).¹⁰

Patients with relapsed or refractory MCL have poor long-term outcomes and limited effective treatment options. Ibrutinib is a newly FDA-approved oral chemotherapy agent for the treatment of patients with refractory disease that appears to be well tolerated and has low rates of discontinuation. Because of the drug's accelerated approval, the FDA is requiring Pharmacyclics to submit 24 months of follow-up data to ensure patient safety is maintained during long-term use.⁶

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Pertuzumab (Perjeta®): FDA Approval for Neoadjuvant Breast Cancer

Brandi Anders, PharmD

PGY1 Pharmacy Resident

WVU Healthcare, Morgantown, WV

After lung cancer, breast cancer is the second leading cause of cancer-related death among women.¹ Approximately 20%–25% of breast cancers overexpress the growth-promoting receptor HER2 on the cancer cell surface.² The overexpression of HER2 contributes to cancer cell growth and survival and is associated with poor prognosis if untreated. The treatment of HER2-positive breast cancer consists of agents that target the overexpression of the HER2 receptor. Two targeted anti-HER2 monoclonal antibodies currently available include trastuzumab (Herceptin®) and pertuzumab (Perjeta®).

Trastuzumab was granted approval by the U.S. Food and Drug Administration (FDA) in November 2006 for the treatment of HER2-overexpressing breast cancer. Trastuzumab is a recombinant, humanized monoclonal antibody that binds to the extracellular domain of the HER2 protein. Upon binding, it inhibits the growth of tumor cells and mediates antibody-dependent cellular cytotoxicity in cancer cells overexpressing HER2.³ Pertuzumab (Perjeta®) is also a recombinant, humanized monoclonal antibody that is used in the treatment of HER2-positive breast cancer. Pertuzumab works by targeting the extracellular dimerization domain (Subdomain II) of the human epidermal growth factor receptor 2 protein (HER2), thereby blocking ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. As a result, pertuzumab inhibits ligand-initiated intracellular signaling, leading to cell growth arrest and apoptosis. In addition, pertuzumab also mediates antibody-dependent, cell-mediated cytotoxicity.⁴ Due to differing binding sites, trastuzumab and pertuzumab act complementarily and are used in conjunction with one another.

Pertuzumab was initially approved by the FDA in June 2012 for the treatment of HER2-positive metastatic breast cancer in combination with trastuzumab and docetaxel.⁵ On September 30, 2013, the FDA granted accelerated approval to pertuzumab for use in combination with trastuzumab and docetaxel in the neoadjuvant setting. Specifically, it was approved as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.⁵

The accelerated approval of pertuzumab for neoadjuvant treatment of HER2-positive breast cancer is based on the results of a randomized, multicenter, international, open-label phase 2 study in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere).⁶ In this study, 417 treatment-naïve women with confirmed HER2-positive operable breast cancer were randomly assigned (1:1:1) to receive one of four neoadjuvant regimens consisting of trastuzumab plus docetaxel, pertuzumab and trastuzumab plus docetaxel, pertuzumab and trastuzumab, or pertuzumab plus docetaxel. Trastuzumab, pertuzumab, and docetaxel were administered by

intravenous (IV) infusion every 3 weeks neoadjuvantly for a total of four cycles. Following neoadjuvant treatment, patients underwent surgery and three cycles of adjuvant FEC (fluorouracil, epirubicin, and cyclophosphamide) therapy every 3 weeks and then received concomitant trastuzumab every 3 weeks for 1 year. The primary endpoint for the study was pathological complete response in the breast, defined as the absence of invasive neoplastic cells upon examination of the primary tumor at surgery (ypT0/is).⁶

In May 2012, the FDA issued a draft guidance on the use of pathologic complete response (pCR) as an endpoint to support accelerated approval for medications used in the neoadjuvant treatment of high-risk, early stage breast cancer. Per the FDA, pCR is defined as the absence of invasive cancer in the breast and lymph nodes following completion of neoadjuvant systemic therapy (ypT0/is ypN0).⁷

Statistically significant improvements were seen in the rates of pCR in patients receiving trastuzumab and pertuzumab plus docetaxel, compared with patients receiving trastuzumab plus docetaxel. The pCR rates were 21.5% with trastuzumab plus docetaxel, 39.3% with trastuzumab and pertuzumab plus docetaxel, 11.2% with pertuzumab and trastuzumab, and 17.7% with pertuzumab plus docetaxel. The difference in pCR between the trastuzumab plus docetaxel (21.5%) and trastuzumab and pertuzumab plus docetaxel (39.3%) groups was 17.8% and was statistically significant (adjusted $p = .0063$, Cochran-Mantel-Haenszel test). The rates of pCR, as well as the magnitude of improvement, were higher in the subset of patients with hormone receptor–negative tumors than in those with hormone receptor–positive tumors.⁶

The most common adverse events associated with treatment with trastuzumab and pertuzumab plus docetaxel were alopecia, neutropenia, diarrhea, and nausea. Most adverse events were National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 1 or 2. The most common NCI-CTCAE grade 3 or higher adverse events were neutropenia, febrile neutropenia, leukopenia, and diarrhea.⁶ Other adverse reactions reported with the use of pertuzumab include left ventricular dysfunction, infusion-related reactions, hypersensitivity reaction, and anaphylaxis.⁴

The approval of pertuzumab additionally is supported by an open-label, phase 2, randomized, multicenter study in 225 patients with HER2-positive, operable, locally advanced, or inflammatory breast cancer (TRYPHAENA study).⁸ The primary objective of the study was to evaluate the safety and tolerability (primarily cardiac safety) of trastuzumab and pertuzumab when FEC or carboplatin is added to neoadjuvant treatment.⁸ According to results of the TRYPHAENA study, the combination of trastuzumab and pertuzumab generally was well tolerated regardless of whether it was given with anthracycline-based or carboplatin-based chemotherapy.

Pertuzumab contains two black box warnings for cardiotoxicity and embryo-fetal toxicity. The recommended dosing for pertuzumab as neoadjuvant treatment in breast cancer is 840 mg IV over 60 minutes followed by a maintenance dose of 420 mg over 30–60 minutes every 3 weeks for three to six cycles. Pertuzumab and trastuzumab may be administered in any order, but docetaxel should be administered after trastuzumab and pertuzumab. In the case of missed or delayed doses, if fewer than 6 weeks have elapsed since the last pertuzumab dose, the 420-mg maintenance dose can be administered. If more than 6 weeks have elapsed, the initial 840-mg dose should be administered, followed by the 420-mg maintenance dose every 3 weeks.⁴

The patient's left ventricular ejection fraction (LVEF) should be assessed at baseline and at regular intervals during treatment. If the LVEF drops below 40%, or is between 40% and 45% with $\geq 10\%$ decrease from baseline values, pertuzumab and trastuzumab should be held for at least 3 weeks and patients should be reassessed before re-initiating therapy. Patients also should be monitored for reactions and hypersensitivity during the infusion and for 30–60 minutes after each pertuzumab infusion. In the event that trastuzumab therapy is held, pertuzumab also should be held. If docetaxel therapy is discontinued, pertuzumab and trastuzumab therapy may be continued.⁴

The accelerated approval for pertuzumab is based on a demonstration of improved pCR. Currently, there are no data available to show an improvement in event-free or overall survival. Due to its accelerated approval, continued approval is dependent on a confirmatory trial demonstrating an improvement in disease-free survival. The confirmatory trial (APHINITY) is a phase 3 trial that currently has enrolled more than 4,800 patients.⁹ This trial compares the use of trastuzumab, pertuzumab, and chemotherapy with trastuzumab and chemotherapy in the adjuvant setting.⁹ The confirmatory trial should provide further data on efficacy, safety, and long-term outcomes with the use of pertuzumab in combination with trastuzumab and docetaxel in the neoadjuvant treatment of patients with HER2-positive breast cancer. Results are expected in 2016. The use of pertuzumab in combination with trastuzumab and docetaxel resulted in significant increases in pCR compared with the use of trastuzumab and docetaxel alone with a relatively mild adverse effect profile. The use of this combination offers a new and effective treatment option to patients with HER2 positive breast cancer in the neoadjuvant setting.

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