



USP <800>: Hazardous Drugs—Handling in Healthcare Settings

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What Is USP?

The United States Pharmacopeial Convention (USP) is a “scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements manufactured, distributed, and consumed worldwide.” USP publishes general chapters in the National Formulary (NF); those numbered under 1,000 contain standards that can be enforced by the U.S. Food and Drug Administration (FDA). These standards are used in more than 140 countries across the globe.¹

USP issues a bimonthly online journal, the *Pharmacopeial Forum* (PF), in which proposed revisions to USP-NF are published for public review and comment. PF is a free, online-only resource available to the public after a one-time registration to the USP website.¹



What Is USP <800>?

USP <800> is the newest chapter of the USP-NF and is designed to “guide the handling of hazardous drugs in healthcare settings.”² USP <800> builds on previously published chapters USP <795> and USP <797>, which address sterile and nonsterile compounding practices. Although seemingly comprehensive in nature, these two chapters fail to address the growing concern of exposure to hazardous drugs. USP <800> states that “there is no acceptable level of personal exposure to hazardous drugs.”² As such, this chapter provides guidelines for the minimization of exposure across the continuum of healthcare settings.

The chapter addresses all aspects of handling hazardous drugs, including receipt, storage, transportation, preparation, dispensing, and administration. The list of hazardous drugs can be found in the National Institute for Occupational Safety and Health (NIOSH) Alert.³

Contents

Highlights from Lymphoma and Myeloma 2014.....	2	Board Update.....	10
Recalls, Withdrawals, and Safety Alerts from the FDA.....	4	The Challenges of Working on Behalf of Our Patients.....	11
The Resident’s Cubicle: A Tale of Two Residents: Exploring a PGY2 Residency.....	6	Drug Update: Belinostat.....	12
Changes in Labeling, Indications, and Dosage Forms.....	7	Drug Update: Idelalisib.....	15
		Drug Update: Pembrolizumab.....	18



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What Is Next for USP <800>?

Due to the significance of the comments received in response to the initial publication of USP <800> in the May/June 2014 issue of *PF*, USP announced on October 13, 2014, that the chapter would undergo revision prior to formal introduction into the NF. The updated General Chapter <800> proposal will reflect new and revised guidance documents, respond to stakeholder input, and improve clarity of General Chapter <800>.

The revised proposal is tentatively projected to be published in *Pharmacoepial Forum*, 41(2) [Mar.–Apr. 2015].⁴

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Highlights from Lymphoma and Myeloma 2014: An International Congress on Hematologic Malignancies

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New targets and debates on appropriate therapies came to the forefront during Lymphoma and Myeloma 2014: An International Congress on Hematologic Malignancies, which took place in New York, NY, October 23–25, 2014.

Since its inception in 2000, the conference has become one of the largest international meetings on hematologic disorders. During the course of 3 days, an interdisciplinary group of clinicians discussed basic science, new therapies, and existing data on the treatment of multiple myeloma, chronic lymphocytic leukemia (CLL), and lymphomas. The following are summaries of selected congress presentations.

Novel Agents: What Will Be Available in the Next Few Years?

Kenneth Anderson, MD, concluded that with the advent of new therapies and specific targeting of the tumor microenvironment, multiple myeloma would become a chronic illness with sustained complete responses in a significant number of patients. Anderson highlighted several new agents under investigation, including monoclonal antibodies, antibody-drug conjugates, and vaccines against multiple myeloma-specific peptides.

Elotuzumab, a monoclonal antibody directed against signaling lymphocyte activation molecule (SLAMF7 or CS1), has been well tolerated in patients during phase 1 and 2 trials. Infusion reactions have been mitigated using premedications. Early trials show overall response rates ranging from approximately 27% as a monotherapy to 84% when given in combination with lenalidomide and dexamethasone. Ongoing phase 3 trials will examine this combination for both initial therapy and in relapsed or refractory disease.

Another monoclonal antibody in development, daratumumab, targets CD38. Early, small studies show marked decreases in M-protein and positive results in overall response rates in the

majority of patients. Phase 3 studies will examine daratumumab both as a monotherapy and in combination with lenalidomide/dexamethasone. Another anti-CD38 monoclonal antibody—SAR650984—also is in development.

Induction Therapies in Transplant-Eligible Patients with Multiple Myeloma

Tomer Mark, MD, discussed how to approach treatment in transplant-eligible patients with multiple myeloma in the era of novel therapies. Based on available data, Mark said combinations of novel agents lead to deeper responses pretransplant, which tend to translate into better responses posttransplant.

As a result of trials with combinations such as CyBORd (cyclophosphamide, bortezomib, dexamethasone), BiRD (clarithromycin, lenalidomide), and VRD (bortezomib, lenalidomide, dexamethasone), Mark suggested that any three-drug combination may be an appropriate choice for initial therapy. According to Mark, the similar response over time with the various first-line treatment strategies indicate that many good induction therapies exist and that the choice should be tailored to the patient.

In addition, Mark noted that carfilzomib may enhance initial response rates and decrease minimal residual disease (MRD). Mark cited two studies in which the majority of patients were MRD negative with the addition of carfilzomib. Progression-free survival in these patients was between 89% and 91% at 3 years and 18 months, respectively. At this point, however, Mark cautioned that little is known regarding how stem cell transplant may negate initial differences in response, consequences of long-term use, or implications for subsequent therapies.

Ibrutinib: Analysis of Its Pivotal Data

Richard Furman, MD, one of the primary authors on many initial ibrutinib trials and the CLL cochair for the congress, reviewed current data on the Bruton's tyrosine kinase (BTK) inhibitor and offered insights from his vast experience with the drug.

Furman noted that as more and more data are published, both response rate results and adverse effect profiles will continue to evolve. One take-home point from this session was that achieving best response was time dependent, and the proportion of patients with either complete or partial responses tended to increase during follow-up. The proportion of patients with a partial response with lymphocytosis also decreased as data matured.

In terms of side effects, atrial fibrillation became one notable effect during the RESONATE trial. In this trial, overall rates of atrial fibrillation were 5% with 3% reported at grade 3 or above. Furman said that additional data are needed to fully elucidate true clinical relevance—especially for the grade 3 or above reactions.

Also of concern with the administration of ibrutinib is the possible increased bleed risk. In the RESONATE trial, 44% of patients in the ibrutinib arm experienced bleeding. Grade 3 or 4 bleeds, however, occurred in only 1% of patients who experienced bleeding. The direct effect of BTK on platelets, as well as other off-target effects currently being explored, could modulate this bleed risk, Furman said.

Another particularly troublesome side effect of ibrutinib is the relatively high rate of diarrhea experienced by patients. Furman noted that this effect is reversible and generally only symptomatic when food is present in the stomach. He suggested patients take ibrutinib at night and avoid eating after ingesting the drug. A dose reduction also may be necessary, if diarrhea continues.

Idelalisib: Analysis of Its Pivotal Data


Jeff Sharman, MD, summarized available data on idelalisib, which recently received U.S. Food and Drug Administration approval, and also offered suggestions on when to use the medication in therapy.

In the United States, idelalisib is indicated for relapsed CLL in combination with rituximab in patients for whom rituximab alone would be appropriate therapy due to other comorbidities. In addition, idelalisib may be used as monotherapy in relapsed follicular lymphoma or relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic therapies. European indications also include idelalisib as first-line therapy for CLL patients with a 17p deletion or TP53 mutation and who are not suited for chemoimmunotherapy.

The drug also carries four black box warnings: fatal and/or serious hepatotoxicity, fatal and/or serious and severe diarrhea, fatal and serious pneumonitis, and fatal and serious intestinal perforation. Deaths from each of these adverse effects occurred in studies at a rate of less than 1%.

Based on indications, available data, and side effect profile, Sharman proposed several situations in which idelalisib might be a good therapeutic choice versus ibrutinib. He suggested idelalisib for CLL patients receiving rituximab and those on blood thinners with a history of atrial fibrillation, with pre-existing renal insufficiency, and possibly a 17p deletion. In contrast, Sharman recommended using ibrutinib in patients with abnormal liver function, history of bowel difficulties, lung issues, or when monotherapy is preferred.

Although not a comprehensive review, presentations from the congress are available for free download. For additional information and to download slides, visit www.imedex.com/lymphoma-myeloma-conference. Slides may be found by clicking on the archives link from the home page.

Next year's congress is scheduled for October 22–24, 2015, at the Waldorf Astoria Hotel in New York, NY. 

Recalls, Withdrawals, and Safety Alerts from the FDA

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Darbepoetin Alfa (Aranesp) Recall in Non-U.S. Countries

Amgen has issued a voluntary recall of darbepoetin alfa 500-mcg pre-filled syringes distributed outside of the United States. This is because of the presence of visible particles that were observed in certain lots during a routine quality exam. There have been no adverse events reported. Darbepoetin alfa distributed in the United States has not been impacted by the recall.

<http://www.fda.gov/Safety/Recalls/ucm410011.htm>

Everolimus (Afinitor)

The warnings and precautions section for everolimus has been updated to include the risk of *Pneumocystis jiroveci* pneumonia (PJP), which may be associated with concomitant corticosteroids or other immunosuppressive agents. Consider the administration of PJP prophylaxis when these agents are used concomitantly.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm258494.htm>

Docetaxel

The package labeling for docetaxel has been updated to include information on the alcohol content of some docetaxel formulations. There have been cases of alcohol intoxication reported. Consideration on the ability to drive, operate machinery, or perform other activities that require skill and alertness should be taken into account after receiving an infusion.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm396551.htm>

Ruxolitinib (Jakafi)

Updates have been made to the warnings and precautions—risk of infection section of the package insert for ruxolitinib. Patients should be evaluated for risk factors of tuberculosis, and those who are at high risk for latent infection should be tested prior to initiating ruxolitinib. The prescribing information within the warnings and precautions section also has been revised to include the risk of myelofibrosis symptom exacerbation following the interruption or discontinuation of ruxolitinib. Myelofibrosis symptoms may return to pretreatment levels over a time frame of approximately 1 week following interruption or discontinuation and have included respiratory distress, multiorgan failure, disseminated intravascular coagulation, hypotension, or fever. Patients may require the drug to be restarted or the dose to be increased in these instances. When possible, consideration should be made to taper the dose gradually. Patients should be educated to not interrupt or discontinue ruxolitinib therapy on their own without consulting a healthcare practitioner.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm377314.htm>

Ado-Trastuzumab (Kadcyla)

Hemorrhagic events have been reported in clinical trials of ado-trastuzumab. Some of the events were fatal, and some included respiratory, central nervous system, and gastrointestinal hemorrhage. Cases occurred in patients with or without known risk factors for bleeding. Additional monitoring should be considered if concomitant anticoagulation or antiplatelet therapy is necessary.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm409252.htm>

Triptorelin (Trelstar) and Leuprolide Acetate (Lupron)

Updated warnings and precautions include the potential for androgen deprivation therapy to prolong the QT/QTc interval. Risks versus benefits should be considered in patients with congestive heart failure, congenital long QT syndrome, or frequent electrolyte abnormalities, or who are taking concomitant meds known to prolong the QT interval. Correct electrolyte abnormalities and consider periodic monitoring of EKGs and electrolytes.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm347049.htm>

Axitinib (Inlyta)

Cardiac failure was noted in 2% of patients receiving axitinib for renal cell carcinoma in a clinical trial compared with 1% in patients receiving sorafenib. Some of the cases were reported to be fatal. Patients should be monitored for signs and symptoms of cardiac failure during therapy with axitinib.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm372723.htm>

Peginterferon Alfa-2b (Sylatron)

Information on dosing peginterferon alfa-2B in patients with moderate or severe renal impairment or end-stage renal disease (ESRD) has been included in the dosing and administration section of the package insert. A 25% dose reduction is recommended in patients with moderate renal impairment (CrCl 30–50 mL/min/1.73m²), and a 50% dose reduction is recommended for patients with severe renal impairment (CrCl < 30 mL/min/1.73m²) or those with ESRD on dialysis.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm314604.htm>

Bevacizumab (Avastin)

The warnings and precautions have been updated to include data from cervical cancer studies. The incidence of gastrointestinal (GI) perforation in patients with persistent, recurrent, or metastatic cervical cancer occurred in 3.2% of patients treated with bevacizumab. All of the patients who developed GI perforation had previously received pelvic radiation. The incidence of GI-vaginal fistulae formation was 8.2% in cervical cancer patients who received bevacizumab, all of

whom had a history of prior pelvic radiation, compared with 0.9% in control patients. The incidence of non-GI vaginal, vesical, or female genital tract fistulae was reported in 1.8% of cervical cancer patients receiving bevacizumab versus 1.4% in control patients. In addition, an increased risk of venous thromboembolic events may occur in patients with persistent, recurrent, or metastatic cervical cancer who receive bevacizumab. The incidence of \geq grade 3 venous thromboembolism (VTE) in those receiving chemotherapy in combination with bevacizumab was 10.6% versus 5.4% in those receiving chemo alone. Bevacizumab should be permanently discontinued in patients with grade 4 VTE, including pulmonary embolism.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm287610.htm>

Lenalidomide (Revlimid)

The risk of arterial thromboembolism has been added to the black box warnings and the warnings and precautions section of the package labeling for lenalidomide. There is an increased risk of myocardial infarction and stroke in patients with multiple myeloma receiving lenalidomide with dexamethasone. Because of the increased risk of thrombotic events in patients receiving lenalidomide in combination with dexamethasone, the administration of thromboprophylaxis is recommended.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm299519.htm>

5-HT₃ Receptor Antagonists

The risk of serotonin syndrome has been added to the warnings and precautions section of the package inserts for all 5-HT₃ receptor antagonists. Most cases have occurred concomitantly with other serotonergic agents (e.g., SNRIs, SSRIs, MAOIs, methylene blue, tramadol, lithium, mirtazapine, and fentanyl), and some cases have resulted in fatalities. Patients should be monitored for signs or symptoms of serotonin syndrome, especially when used in combination with other serotonergic drugs.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm418818.htm>

Clofarabine (Clolar)

The warnings and precautions section of the prescribing information for clofarabine has been updated. The update includes the risk of hemorrhage. There have been serious and fatal reports, including pulmonary, cerebral, and gastrointestinal hemorrhage, the majority of which occurred in patients with thrombocytopenia. Platelets and coagulation parameters should be monitored. The warnings and precautions section also includes the risk of enterocolitis, which has been reported most commonly within 30 days of combination therapy. Some of the cases have been serious and fatal and have included *C. difficile* colitis, cecitis, and neutropenic colitis. Patients should be monitored for signs or symptoms of this complication. Last, clofarabine should be discontinued if patients develop exfoliative or bullous rashes. The risk of skin reactions, including serious and fatal cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, has been reported with the drug.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm338244.htm>

Nilotinib (Tasigna)

The drug interactions section of the prescribing information has been updated and identifies nilotinib as a moderate CYP3A4 inhibitor. Concomitant administration of agents that are metabolized by CYP3A4 may lead to increased concentrations. Dose adjustment of agents that CYP3A4 substrates and that have a narrow therapeutic index may be necessary.

ISMP Medication Safety Alerts

July 17, 2014 (Volume 19, Issue 14)

A recent overdose with oral lomustine was reported to the Institute for Safe Medication Practices (ISMP). The patient inadvertently took an equivalent of three cycles of lomustine at one time after thinking the pharmacy had dispensed a single dose. There have been at least five similar errors with lomustine reported by the ISMP, where more than one dose was dispensed and taken. The ISMP recommends that prescribers, pharmacists, nurses, insurers, manufacturers, and the U.S. Food and Drug Administration follow several safe practices for oral lomustine therapy, including the following:

Prescribers

1. On the prescription, specify that only a single dose should be dispensed.
2. Discuss with the patient that a single dose should be taken no sooner than every 6 weeks.
3. Review and provide written instructions for the patient. Remind the patient that he or she should not assume he or she should be taking all the capsules in the bottle. The patient should compare the prescriber's written instructions with the pharmacy label, and he or she needs to call if there are any questions prior to taking a dose.

Pharmacists

1. Program alerts into order entry systems to prevent errors (e.g., allowing only a single dose to be entered).
2. Dispense only a single dose per filled prescription. Call the prescriber if multiple doses have been prescribed.
3. Ensure patients receive counseling when picking up new prescriptions and refills for lomustine.
4. Supply written drug education materials to patients that include information about dispensing only a single dose per fill. Verify the written drug education materials are consistent with the labeled instructions.
5. Enhance labels with bold font or all capital letters.
6. Avoid filling lomustine prescriptions via mail order or specialty pharmacies unless patient counseling can occur by phone prior to dispensing the drug.

Nurses

1. Reinforce education on taking only a single dose for those patients being discharged on lomustine therapy.

Insurers

1. Do not approve more than a single-dose supply for outpatient lomustine prescriptions.

Manufacturer

1. Enhance label warnings to dispense only enough capsules for one dose.

FDA and Manufacturer

1. Require distribution of medication guides to patients receiving lomustine.

A Tale of Two Residents: Exploring a PGY2 Residency

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Oncology pharmacy is a highly specialized field, necessitating the pursuit of PGY2 oncology pharmacy residency positions for new practitioners. The American Society of Health-System Pharmacists' website currently lists more than 80 sites offering a PGY2 in oncology pharmacy, up 76% from 2010. Sites offering PGY2s include academic centers, community hospitals, outpatient clinics, Veterans Affairs medical centers, and others. When pursuing an oncology pharmacy residency program, residents have to consider factors such as program size, rotation structure, specialties of the practice site, and residency requirements, and make sure they coincide with their career goals.

The increase in specialized PGY2 pharmacy residency opportunities is not unique to the oncology field. In 2014, 795 PGY2 positions were available for pharmacists pursuing residency training in one of 26 specialties. With so many options, why are increasing numbers of PGY1 residents focusing on PGY2 residencies in oncology?

Stephanie's Journey

My exposure to oncology began in elementary school. My mom was diagnosed with stage III breast cancer at the age of 39, and I remember her being worn out and taking plenty of naps. However, I was not truly aware of the severity of her illness at the time. Looking back today as a healthcare professional, my perception surrounding her treatment has changed. My mom underwent a lumpectomy, mastectomy, and reconstructive surgery. She endured weeks of radiation and several cycles of chemotherapy. Her healthcare team, consisting of oncologists, surgeons, nurses, and pharmacists, worked together to provide her with a treatment plan that allowed her to function in her everyday life and that has kept her cancer free for 14 years. This treatment plan not only accounted for the care my mom received, but it also included care for our family. She never seemed as sick as she truly was. When I reflect on the care my mom received, I realize the practitioners who specialize in oncology care for the whole patient as well as their family and friends.

My personal experience sparked an interest in a career in oncology that has grown with my professional experiences. As a student, I learned about oncology medications and their place in therapy during pharmacotherapeutics and pharmacology. I was surprised that much of the curriculum was focused on supportive care, and I realized pharmacists can play a large part in improving a patient's quality of life as they receive chemotherapy. I completed an intern rotation in bone marrow transplant with a team guiding patients through high-dose chemotherapy and life-saving transplants. I was fascinated with the complexity of treatment regimens. There are many opportunities for

pharmacists to make interventions related to chemotherapy, antibiotics, and supportive care. While following the palliative care team as a resident, I interviewed many patients and their families regarding pain and symptom management. I enjoyed developing relationships with patients while helping improve their quality of life as they persevered through difficult situations. Even though oncology pharmacy is considered a specialty, I have learned that there are many different opportunities for pharmacists in the oncology field, and that is one reason why I am excited to pursue a PGY2 oncology pharmacy residency.

These experiences only scratch the surface of potential opportunities for pharmacists in oncology pharmacy. There are endless chances for pharmacists who specialize in oncology to affect the lives of patients. PGY2 programs offer rotations in inpatient oncology, outpatient oncology, infectious disease in the immunocompromised population, pediatric oncology, bone marrow transplantation, and palliative care. Because of the specialized nature of an oncology pharmacist, a PGY2 residency offers an opportunity for young pharmacists to explore the specialty and better understand the expanding roles pharmacists can play in oncology. I look forward to building on my experiences in oncology, as well as the foundation built during PGY1 pharmacy practice residency, through a PGY2 oncology pharmacy residency.

Nicole's Journey


I became interested in pursuing a PGY2 in oncology pharmacy for several reasons. I first became involved in oncology while working as an oncology pharmacy technician at a Veterans Affairs medical center. My science-minded side enjoyed learning about complex chemotherapy regimens and compounding, while my outgoing side enjoyed meeting with patients and their families. As a technician, each morning I would evaluate the infusion center schedule, review the regimens and organize my supplies, and then prepare the chemotherapy as patients arrived. I wanted to know everything and was constantly asking the pharmacists "Why?" Why this regimen? Why were there different doses? Why do we have premedications? When I delivered chemotherapy, if time permitted, I would stop and chat with patients. I loved being able to sit with patients and hear about their adventures. Throughout my experiences as an intern, and now as a pharmacy practice resident, I continue to see oncology-related issues from different perspectives, not just from the perspective of an oncology pharmacist.

I find there are dynamic opportunities within the oncology pharmacy field. Oncology pharmacists have the possibility to work in the outpatient setting as a clinician, the inpatient setting as part of the healthcare team, or in a combination of the two. In either setting, the pharmacist

has an opportunity to develop a relationship with patients and encourage them to take an active role in their health care. Some patients may feel that it is them versus the insurance company or the healthcare system as a whole. Numerous new oral chemotherapy agents have emerged on the market, creating a daunting experience for the patient when high costs and difficult dosing regimens are involved. Pharmacists can advocate for the patient, motivate patients when they are discouraged, provide alternatives and education, and act as a conduit between the doctor and insurance provider.

I've always loved a difficult puzzle, and I view patients with complex medical issues as a great challenge. On paper, two patients may seem very similar in their diagnosis, past medical history, and medication profile. However, their response to treatment and medication tolerance can vary greatly. Each patient's case is like a puzzle with pieces made from their medications, response to treatment, comorbidities, insurance coverage, and personal beliefs. A clinical oncology pharmacist must be able to collaborate with the patient's healthcare team to fit the pieces together to help provide optimal patient care.

As new agents enter the market at incredible speeds, the field of oncology pharmacy is continuously evolving. Treatments that were once considered the gold standard are being used in combination with new therapies, or in some cases, are being replaced altogether. I am excited to stay up to date on new medications, guidelines, and clinical trials published at an ever-increasing pace. I will be able to evaluate the data to determine whether study results support a change in clinical practice that would apply to my clinical setting and can take what I learn to help educate the team and patients. I continue to ask "why" to my preceptors and feel a PGY2 specializing in oncology will help me develop the skills needed to find the answers.

Each candidate has his or her own reasons for pursuing a PGY2 pharmacy residency. For me, I enjoy that oncology pharmacy is a great combination of oncology, critical care, infectious disease, internal medicine, cardiology, and more. Opportunities within the field will allow me to be an advocate for patients, a problem solver, a collaborative member of the healthcare team, and a life-long learner. 

Changes in Labeling, Indications, and Dosage Forms

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Herceptin® (trastuzumab)

On June 30, 2014, the U.S. Food and Drug Administration (FDA) approved changes in the labeling. These included the addition of data from an 8-year follow-up study on the comparison of 1 year versus 2 years of trastuzumab, the addition of the statement to not extend adjuvant treatment beyond 1 year, and the deletion of some data that were erroneously carried over from one of the trials included in the original label.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/103792Orig1s5313,s5318ltr.pdf

Afinitor® (everolimus)

On July 1, 2014, the FDA approved labeling changes that included the addition of information regarding opportunistic infections, some additions to the adverse effects section, and some minor formatting changes.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/022334Orig1s025,203985Orig1s007ltr.pdf

Beleodaq™ (belinostat)

On July 3, 2014, the FDA approved belinostat for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. For more information on this new drug, please see the article on belinostat in this newsletter.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/206256Orig1s000ltr.pdf

Vantas® (histrelin acetate)

On July 8, 2014, the FDA approved the addition of QT/QTc interval effect information to the package labeling.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/021732Orig1s019ltr.pdf

Lupron® (leuprolide acetate)

On July 10, 2014, the FDA approved the addition of QT/QTc interval effect information to the package labeling.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/019010Orig1s037ltr.pdf

Kadcyla® (ado-trastuzumab emtansine)

On July 11, 2014, the FDA approved labeling changes and the issuance of a "Dear Healthcare Provider" letter regarding cases of severe hemorrhage seen with the use of Kadcyla®.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/125427Orig1s033ltr.pdf

Zydelig® (idelalisib)

On July 23, 2014, the FDA approved idelalisib for the treatment of patients with relapsed follicular lymphoma and patients with small lymphocytic lymphoma. For more information on this new drug, please see the article on idelalisib in this newsletter.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/205858Orig1s000ltr.pdf

Iclusig® (ponatinib)

On July 24, 2014, the FDA approved additional labeling information to be included that provides information from the clinical pharmacology studies.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/203469Orig1s009ltr.pdf

Jakafi® (ruxolitinib)

On July 25, 2014, the FDA approved labeling additions listing drug interactions when used concomitantly with strong CYP4503A4 inhibitors. The revised labeling also includes overall survival data from the results of a 3-year follow-up on the phase 3 studies.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/202192Orig1s006ltr.pdf

Imbruvica® (ibrutinib)

On July 28, 2014, the FDA approved the addition of two indications to the package labeling. The additions are for patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and for those with CLL with the 17p deletion.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205552Orig1s001ltr.pdf

Halaven® (eribulin mesylate)

On August 1, 2014, the FDA approved changes to the labeling to include updates in the adverse events section.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/201532Orig1s009ltr.pdf

Inlyta® (axitinib)

On August 1, 2014, the FDA approved the addition of cardiac failure events to the warnings and precautions section of the labeling.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/202324Orig1s002ltr.pdf

Velcade® (bortezomib)

On August 8, 2014, the FDA approved changes to the labeling with regard to the drug's safety, dosing, administration, and efficacy in the treatment of relapsed multiple myeloma.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/021602Orig1s038ltr.pdf

Emend® (aprepitant; fosaprepitant)

On August 12, 2014, the FDA approved an addition to the drug interaction section that lists the possibility of neurotoxicity when used in combination with ifosfamide.

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/021549Orig1s024,022023Orig1s011ltr.pdf

Rituxan® (rituximab)

On August 12, 2014, the FDA approved labeling changes that included information on tumor lysis syndrome as well as additional information on overdosing of rituximab.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/103705Orig1s5432ltr.pdf

Avastin® (bevacizumab)

On August 14, 2014, the FDA approved the addition of an indication to the label. Bevacizumab is now indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125085Orig1s301ltr.pdf

Ifex® (ifosfamide)

On August 28, 2014, the FDA approved the rewording of a portion of the drug interaction section.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/019763Orig1s019ltr.pdf

Avastin® (bevacizumab)

On August 30, 2014, the FDA approved the addition of the incidence data of posttreatment vascular events to the section on adverse reactions.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125085Orig1s297ltr.pdf

Vectibix® (panitumumab)

On August 30, 2014, the FDA approved the addition of information regarding mucocutaneous reactions to the adverse effects and warnings and precautions sections of the labeling.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125147Orig1s194ltr.pdf

Keytruda® (pembrolizumab)

On September 4, 2014, the FDA approved pembrolizumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600-mutation positive, a BRAF inhibitor. For more information on this new drug, please see the article on pembrolizumab in this newsletter.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125514Orig1s000ltr.pdf

Campath® (alemtuzumab)

On September 5, 2014, the FDA approved the addition of a section reporting the results of required postmarketing QT testing to the product labeling.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/103948Orig1s5150,s5143ltr.pdf

Xtandi® (enzalutamide)

On September 10, 2014, the FDA approved the addition of a new indication for the treatment of patients with metastatic castration-resistant prostate cancer.

www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/203415Orig1s003ltr.pdf

Thalomid® (thalidomide)

On September 12, 2014, the FDA approved modifications to the risk evaluation and mitigation strategy (REMS) for thalidomide.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/020785Orig1s054ltr.pdf

Revlimid® (lenalidomide)

On September 12, 2014, the FDA approved modifications to the REMS for lenalidomide.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/021880Orig1s039s040ltr.pdf

Pomolyst® (pomalidomide)

On September 12, 2014, the FDA approved modifications to the REMS for pomalidomide.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/204026Orig1s004ltr.pdf

Clolar® (clofarabine)

On September 15, 2014, the FDA approved the additions of hemorrhage, enterocolitis, and skin reactions to the warnings and precautions section of the labeling. Hyponatremia also was added to the postmarketing experience section.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/021673Orig1s023ltr.pdf

Docetaxel

On September 17, 2014, the FDA approved revisions to the highlights, warnings and precautions, and adverse reactions sections to be consistent with the most recent revisions to the product labeling. There also was information added regarding the use of docetaxel in pediatric patients. There were some general editorial changes made to the product label.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/203551Orig1s002ltr.pdf

Zofran®; Zuplenz® (ondansetron)

On September 18, 2014, the FDA approved the addition of information regarding the risk of serotonin syndrome to the product labeling.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/020007Orig1s046ltr.pdf

Anzemet® (dolasetron mesylate)

On September 18, 2014, the FDA approved the addition of information regarding the risk of serotonin syndrome to the product labeling.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/020623Orig1s012ltr.pdf

Sancuso® (granisetron)

On September 18, 2014, the FDA approved the addition of information regarding the risk of serotonin syndrome to the product labeling.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/022198Orig1s012ltr.pdf

Aloxi® (palonosetron)

On September 18, 2014, the FDA approved the addition of information regarding the risk of serotonin syndrome to the product labeling.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/022233Orig1s005ltr.pdf

Tasigna™ (nilotinib)

On September 25, 2014, the FDA approved updates made to the drug interactions section of the labeling based on the final results of the CAMN107A2128 study.

www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/022068Orig1s019ltr.pdf



HOPA **11th** **ANNUAL CONFERENCE**
March 25–28, 2015
JW Marriott Austin • Austin, TX
Early bird deadline is February 9, 2015

Board Update

Michael Vozniak, PharmD BCOP, HOPA President



Happy new year! This time of year is hectic and exciting for everyone as we return to our normal routines after a busy holiday season. It also is a time when numerous “Top Events of the Year” lists are published and discussed on the radio, in press, and on social media. I figured why should HOPA be any different?

The following is my Top 10 List of HOPA Highlights for 2014 (in no particular order as they all are important):

1. The HOPA 10th Annual Conference in New Orleans breaks attendance records.
2. The 2nd Annual Fall Practice Management Course saw growth in the number of participants.
3. HOPA held the first mini-HOPA Hill Day in September.
4. HOPA’s Industry Relations Council (IRC) grew in participation and sponsorship levels.
5. The Health Policy Committee introduced two new issue briefs: Pain Management and Counterfeit Drug Prevention.
6. HOPA supported the passage of HR 4190!
7. My mentor and friend, Moe Schwartz, won the HOPA Award of Excellence.
8. HOPA published the *Scope of Hematology/Oncology Pharmacy Practice* document.
9. HOPA published our first best practice standard, *HOPA Investigational Drug Service Best Practice Standards*.
10. Countless number of outstanding members volunteered their time and efforts for the advancement of our profession!

Although there are numerous other highlights from the past year that were not included above, this reflection is helpful to recognize all that HOPA has accomplished in 2014. It also is a good time to look ahead and see what the organization needs to achieve this year.

Strategic Planning

HOPA’s strategic plan was last reviewed and updated in November 2012. Typically, strategic plans are updated or revised approximately every 3–5 years. In consideration of this and based on the progress HOPA has made toward fulfilling its strategic objectives, HOPA’s Board of Directors has decided to undergo strategic planning in 2015. The board of directors and key stakeholders participated in an in-person strategic planning session in January 2015.

HOPA has contracted Marsha Rhea, president, Signature i, LLC, to serve as HOPA’s strategic planning consultant. Signature i utilizes a methodology called forward design, which is a “systematic and creative process for exploring an organization’s current and future context, analyzing strategic issues and opportunities, inviting aspirations for design, and then using this learning to inspire an organization’s future.”

Before creating Signature i, Rhea was a senior futurist with the Institute for Alternative Futures, where she honed an aptitude for environmental scanning, scenario planning, visioning, and strategy

development for associations, governments, and businesses. In her career as an association executive, Rhea has held executive positions in the American Society of Association Executives (ASAE), as director of education and then executive vice president of the foundation; the National Recycling Coalition as executive director; and the American Subcontractors Association as vice president of communications and education. Signature i specializes in not for profits and associations.

The board’s intention is to share the new HOPA strategic plan at the annual conference in March.

HOPA’s Collaborative Efforts

Throughout 2014, HOPA engaged and worked with numerous organizations to advance our goals and the care of oncology patients. Our collaborative efforts have spanned from working with pharmacy organizations such as the American Society of Health-System Pharmacists (ASHP) and the American College of Clinical Pharmacy to working with nonpharmacy organizations such as the American Society of Clinical Oncology and Oncology Nursing Society. In addition, our efforts have extended to organizations such as Medscape and the Institute for Safe Medication Practices. HOPA recognizes the importance of establishing partnerships with outside organizations so that we may improve cancer patient care and provide professional development opportunities for our members.


HOPA has taken steps to become a member of the Joint Commission of Pharmacy Practitioners (JCPP). JCPP is comprised of 11 pharmacy organizations, and their vision statement is “Pharmacists will be the healthcare professionals responsible for providing patient care that ensures optimal medication therapy outcomes.” The HOPA Board of Directors determined this organization would be a great conduit to solidify existing relationships with other pharmacy organizations and help us to form new relationships with other pharmacy organizations. HOPA has been accepted into “observation” status and is expected to attend four meetings before being reviewed for full membership. The observation status is a great opportunity for HOPA to better understand JCPP and evaluate whether it is in HOPA’s best interest to formally join, if invited. I attended their last meeting in November in Alexandria, VA. My attendance gave me a much better understanding of what other pharmacy organizations are working on and what is impacting them. It also gave me a better perspective on what opportunities there may be to collaborate with JCPP and the individual member organizations.

In other exciting news, HOPA learned in late December that our organization has been accepted into the Patient Access to Pharmacists’ Care Coalition. The mission of the coalition “is to develop and help enact a federal policy proposal that would enable patient access to, and payment for, Medicare Part B services by state-licensed pharmacists in medically underserved communities.” Concisely, this is the coalition that is pushing for passage of HR 4190 legislation. Some notable coalition members include the American Public Health Association, ASHP, American Association of Colleges of

Pharmacy, American Society of Consultant Pharmacists, and several community pharmacy companies, such as Albertsons, CVS Caremark, and Walgreens, to name a few. HOPA will partner with the coalition to see how we can help drive the passage of this legislation as we enter a new congressional year. During HOPA's Hill Day in September, pharmacists' provider status was one of the main topics we discussed with the congressional offices. I hope the momentum continues!

HOPA's 11th Annual Conference

Believe it or not, HOPA's 11th Annual Conference is a short time away! Conference registration is open. Our Program Committee has planned another outstanding conference that includes three different preconference offerings. We are excited to hold the conference in Austin, TX, and are looking forward to having a great meeting. Please check Conference Web Central at www.hoparx.org for more information.

Best wishes to everyone for a happy and healthy 2015! 

The Challenges and Rewards of Working on Behalf of Our Patients

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I had been told that during the course of my career I would encounter patients who would impact me in such a way that I would never forget them and they would even transform the way I work. I was fortunate enough to meet one such individual during the first year of my first job as a clinical pharmacist in an outpatient oncology clinic. This is the story of Ms. X and how meeting her truly changed my perspective on the role of a clinical pharmacist, my passion for the care of oncology patients, and my life.

Ms. X was a delightful woman in her 60s who had a textbook case of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer: she was a healthy, lifelong nonsmoker with aggressive disease and had an impressive, but short-lived, response to initial treatment. At the time of her disease progression her physician asked me to investigate ways in which we could gain access to ceritinib, an investigational second generation ALK-inhibitor that was in phase 1 trials at the time. In my pursuit to obtain this medication for Ms. X, I contacted the drug company to apply for an individual compassionate use trial and enroll Ms. X in an expanded treatment protocol. In the midst of this process, the U.S. Food and Drug Administration approved ceritinib. The next 3 weeks included a flurry of activity as I worked tirelessly to gain access to the drug for Ms. X. I vividly remember the day I received a call from one of the many specialty pharmacies I had reached out to, informing me that they had access to the drug and would be able to ship a prescription to Ms. X the next day! I could barely contain my excitement as I called Ms. X to give her the great news. The joy I felt that day had nothing to do with me or the time I had spent working to gain access to this drug for Ms. X. The emotions I experienced—excitement, joy, and relief—were focused solely on Ms. X.

Prior to this experience, I did not fully appreciate all of the challenges surrounding the prescribing of oral chemotherapy or realize how vital the role of a pharmacist could be in the process. Providing appropriate clinical review and patient education were obvious needs, but navigating a complex network of insurance providers and specialty pharmacies were challenges I had not anticipated. As the clinical pharmacist working in the outpatient oncology clinic, I was in an ideal position to coordinate the efforts of many members of the healthcare team in the provision of oral chemotherapies. The physician looked to me to assist in procurement of this new oral chemotherapy agent. The patient and her family counted on me to answer questions and provide education about her new medication. The insurance company and specialty pharmacies valued my ability to act as a liaison for both the patient and physician.

In recent months, I have transitioned to a new position within my institution that allows me to focus my efforts on the care of patients receiving oral chemotherapy. As the oral chemotherapy clinical pharmacist, I serve as a liaison between the patient, physician, insurance company, and specialty pharmacy. This unique position provides me with the ability to counsel patients, coordinate prior authorizations and refills, and collaborate with physicians to ensure appropriate monitoring and dose adjustments of oral chemotherapy. I value the relationships I have developed with my patients and their families, and I look forward to going to work every day because I know I will significantly affect the care of my patients. My experience with Ms. X allowed me to see the need for a pharmacist devoted to oral chemotherapy management, and I count myself incredibly lucky to have been afforded the opportunity to turn my vision into a reality. 

Belinostat (Beleodaq®)

Class: Histone deacetylase inhibitor

Indication: Relapsed or refractory peripheral T-cell lymphoma

Dose: 1,000 mg/m² intravenous infusion over 30 minutes once daily on days 1–5 of a 21-day cycle; can be repeated every 21 days until disease progression or unacceptable toxicity

Dose modifications: Decrease dosage by 25% (750 mg/m²) for absolute neutrophil count nadir < 0.5 × 10⁹/L and/or platelet count < 25 × 10⁹/L and any Common Terminology Criteria for Adverse Events grade 3 or 4 reaction. Starting dose should be reduced to 750 mg/m² in patients known to have the UGT1A1* allele.

Common adverse effects: Nausea, fatigue, pyrexia, anemia, and vomiting

Serious adverse effects: Pneumonia, pyrexia, infection, anemia, increased creatinine, thrombocytopenia, and tumor lysis syndrome

Drug interactions: Primarily metabolized by UGT1A1, so strong UGT1A1 inhibitors should be avoided

Belinostat for Relapsed Peripheral T-Cell Lymphoma

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Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of generally rare but aggressive malignancies derived from mature (postthymic) T cells and natural killer (NK) cells, and represents approximately 10%–15% of all non-Hodgkin lymphomas (NHLs).¹ The World Health Organization (WHO) classifies PTCL into more than 20 histological subtypes, the most common being PTCL not otherwise specified (PTCL-NOS). Most adult patients are diagnosed with PTCL at a median age of 60 years.¹ Even though the subtype anaplastic lymphoma kinase (ALK)-positive PTCL has a more favorable prognosis, PTCL, as a whole, generally is an aggressive disease with poor clinical outcomes characterized by refractory or early relapsed disease to initial therapy.^{1,2} With conventional chemotherapy, the median overall survival (OS) for PTCL is 9–42 months, and in the absence of hematopoietic stem-cell transplantation, treatment for relapsed or refractory PTCL usually is palliative.^{1–3}

Although the etiology is unknown, chromosomal translocations, infections, environmental factors, immunodeficiency states, and chronic inflammation are associated with the development of PTCL.⁴ PTCL is a neoplasm of mainly the lymph nodes with the origin of various

lymphoid neoplastic tumor cell lines and is characterized by the unregulated progressive clonal expansion of T cells or NK cells arising from an accumulation of genetic lesions, modulating proto-oncogenes, or tumor-suppressor genes and resulting in cell immortalization.⁵

There is no consensus on the standard front-line therapy for PTCL due to a lack of prospective randomized, controlled trial evaluation for the disease. In the absence of the first-line treatment, most PTCL patients are treated with the current standard combination chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) that is extrapolated from data demonstrating efficacy in B-cell lymphoma. The largest case series investigating traditional chemotherapy regimens included 153 patients with relapsed or refractory peripheral T-cell lymphoma who were treated at the British Columbia Cancer Agency from 1976 to 2010.⁶ Median OS was 3.7 months for the group as a whole and 6.5 months for those who received chemotherapy. Rates of second progression-free survival (PFS) and OS at 3 years were 16% and 7%, respectively. Among the 78 patients treated after 2001, the median second PFS and OS after relapse were 4.6 and 6.7 months, respectively, and did not differ from the group as a whole. These results confirm the relapsing and refractory nature and poor prognosis of PTCL even with traditional chemotherapy.

With favorable data from previous clinical trials, the U.S. Food and Drug Administration (FDA) granted accelerated approval for pralatrexate injection (Folotyn®)⁷ in September 2009, romidepsin (Istodax®)⁸ in June 2011, and most recently, belinostat (Beleodaq®)^{9,10} in July 2014, each as a single agent for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. As demonstrated from their respective clinical trials, pralatrexate may be preferred in patients with a history of cardiac arrhythmia (particularly ventricular arrhythmia),⁷ romidepsin may be preferred in patients intolerant to mucositis,⁸ and belinostat may be preferred as a reasonable first-line treatment in patients with baseline thrombocytopenia (<100,000/μL).^{9,11}

Belinostat is a histone deacetylase (HDAC) inhibitor that has demonstrated favorable antitumor response rates and duration of response in relapsed or refractory PTCL during a phase 2 trial. HDAC catalyzes the removal of acetyl (CH₃CO) groups from the lysine residues of histones and some nonhistone proteins; therefore, HDAC inhibition induces histone acetylation, leading to increased active expression of tumor suppressor genes, resulting in accumulation of acetylated histones and other proteins, and causing cell-cycle arrest, cell differentiation, and apoptosis.^{12–14} In vitro, belinostat demonstrates pan-HDAC inhibition and preferential antineoplastic cytotoxicity toward tumor cells compared with normal cells at nanomolar concentrations of <250 nM.^{9,11,14}

The accelerated FDA conditional approval of belinostat was based on data from 129 patients with relapsed or refractory PTCL (R/R PTCL) in a pivotal open-label, single-arm, international phase 2 clinical trial conducted at 62 centers from December 2008 to March 2014 (CLN-19 BELIEF study). The study enrolled a cohort of patients with relapsed or refractory measurable PTCL confirmed by central pathology review (CPRG), adequate organ function, platelet count ≥50,000/μL, failure of at least one or more prior systemic therapies, and no prior

HDAC inhibitor therapy. The study's patient population had a median of 2 (range 1–8) prior therapies (CHOP and CHOP-like), and 23% of the patients had prior stem cell transplants. All patients received belinostat 1,000 mg/m² intravenous (IV) infusion for 30 minutes on days 1–5 of a 21-day cycle until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR), including both complete response (CR) and partial response (PR). Tumor response was assessed by Cheson 2007 criteria. Secondary endpoints included safety, efficacy parameters (e.g., time to response, duration of response [DoR], time to progression, and survival), and population pharmacokinetics.^{9,11}

A total of 120 patients with CPRG confirmed R/R PTCL ($n = 120$) were included in the efficacy analysis. The ORR was 26% ($n = 31$; 10% CR; 16% PR). The median time to response was 5.6 weeks (range 4.3–50.4). The median DoR was 8.3 months; the longest DoR was 29.4 months. For the subgroup of patients with CPRG-confirmed PTCL and baseline platelets $\geq 100,000/\mu\text{L}$ ($n = 100$), ORR was 28% (CR 11%; PR 17%).^{9,11}

The most common grade 3 or 4 adverse reactions were thrombocytopenia (7%), neutropenia (13%), anemia (11%), dyspnea (6%), pneumonia (6%), and fatigue (5%). The most common serious adverse reactions ($>2\%$) were pneumonia, pyrexia, infection, anemia, increased creatinine, thrombocytopenia, and multiorgan failure. Belinostat was well tolerated with a low incidence of myelosuppression. Patients with platelets $<100,000/\mu\text{L}$ ($n = 17$) were able to tolerate belinostat with 98% dose intensity. There are no contraindications to administering belinostat, but there are several precautions and warnings that should be noted. Belinostat may cause hepatic toxicities, and liver function tests should be monitored prior to the start of each cycle. Patients with advanced stage disease or high tumor burden are at increased risk for tumor lysis syndrome (TLS) and appropriate precautions should be taken to monitor for metabolic disturbances associated with TLS. Serious and fatal infections can occur with belinostat therapy, and patients with an active infection should not receive therapy. Patients with a history of extensive chemotherapy may be at higher risk of life-threatening infections, and close monitoring for neutropenia should be performed.¹¹

Belinostat is categorized as pregnancy category D. It is teratogenic and may cause embryofetal death because the drug targets actively dividing cells. Females with reproductive potential should avoid becoming pregnant while undergoing treatment with belinostat.¹¹

There are insufficient data to recommend a dose of belinostat in patients with moderate to severe hepatic impairment because these patients were excluded from clinical trials. Belinostat can cause fatal hepatotoxicity and treatment may be interrupted or discontinued based on the severity of the hepatic toxicity. No dose recommendations are available for patients with moderate to severe renal insufficiency (creatinine clearance ≤ 39 mL/min). The absolute neutrophil count (ANC) should be $\geq 1.0 \times 10^9/\text{L}$ and the platelet count $\geq 50 \times 10^9/\text{L}$ before the start of each cycle and prior to resuming treatment following a toxicity. If a patient experiences a nadir ANC $0.5 \times 10^9/\text{L}$ or platelet count $25 \times 10^9/\text{L}$, the dosage of belinostat should be decreased by 25%. Belinostat should be discontinued in patients who have recurrent ANC nadirs $0.5 \times 10^9/\text{L}$ or platelet count nadirs $25 \times 10^9/\text{L}$ after two dose reductions. Belinostat

also should be reduced by 25% for any Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 adverse reactions. For nausea, vomiting, and diarrhea the dose should be modified only if the duration of these symptoms is ≥ 7 days with supportive management. It is recommended to discontinue belinostat for recurrence of CTCAE grade 3 or 4 adverse reactions after two dose reductions.¹¹

Belinostat primarily is metabolized by hepatic UGT1A1 and strong inhibitors of UGT1A1 are expected to increase exposure of the drug. Patients with genetic polymorphisms (e.g., UGT1A1*28 allele) have reduced UGT1A1 enzyme activity, which could lead to decreased clearance of belinostat. The starting dose of belinostat should be reduced to 750 mg/m² in patients who have the UGT1A1*28 allele to minimize toxicities. Belinostat also undergoes metabolism by hepatic enzymes CYP2A6, CYP2C9, and CYP3A4 to form belinostat amide and belinostat acid. In vitro studies demonstrated belinostat and its metabolites inhibited the metabolic activities of CYP2C8 and CYP2C9, but concurrent administration of belinostat and warfarin in cancer patients did not increase plasma exposure of either R-warfarin or S-warfarin.¹¹

Belinostat is supplied as a 500-mg lyophilized powder in a single-use vial. Each vial should be reconstituted with 9 mL of sterile water for injection to create a 50-mg/mL solution. Belinostat is administered as an IV infusion over 30 minutes, but if patients experience infusion site pain or other symptoms attributable to the infusion, the infusion time may be extended to 45 minutes. Use of a 0.22-micron in-line filter is recommended. Patients should be counseled on the possibility of serious bleeding due to low platelet counts and the likelihood that this drug will cause neutropenia and anemia. Patients should notify their physician if they experience any unusual bleeding or bruising, fatigue, pyrexia, nausea, and vomiting.¹¹

As an effective salvage agent, belinostat provides an additional option for treating R/R PTCL in patients who are relapsed or refractory to previous traditional chemotherapy. As a condition of the accelerated FDA approval, a dose-finding trial of belinostat as well as another trial comparing the efficacy of belinostat used in combination with CHOP versus CHOP alone are required.¹⁰ The BelCHOP phase 3 clinical study is expected to enroll as many as 28 patients by the end of 2014, and the second part of the confirmatory trial is expected to be initiated in the first half of 2015. Belinostat has a relatively low adverse drug reaction profile and may be a preferred agent for patients with baseline thrombocytopenia. With many advances in lymphomas, novel agents with unique mechanisms offer new treatment paradigms for relapsed or refractory T-cell lymphomas.

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HOPA Volunteer Activity Center Now Open!

Members interested in becoming involved in association activities or volunteering for one of the 2015-2016 committees or work groups can now visit the HOPA Volunteer Activity Center on the HOPA website to review current opportunities. Volunteers also may provide a list of their skills and interests that the organization will use when seeking participants for future opportunities. If you would like to serve on a 2015-2016 committee, visit today and tell us how you would like to be involved!

Idelalisib (Zydelig®)

Class: Phosphatidylinositol 3-kinase inhibitor

Indication: Treatment of relapsed chronic lymphoid leukemia in combination with rituximab in patients who single-agent rituximab would be considered appropriate therapy due to comorbidities. Treatment of relapsed follicular B-cell non-Hodgkin lymphoma or relapsed small lymphocytic relapsed following at least two prior systemic therapies

Dose: Maximum starting dose 150 mg orally twice daily

Dose modifications: Doses of idelalisib should be held for aspartate aminotransferase/alanine transaminase (AST/ALT) $>5 \times$ the upper limit of normal (ULN), bilirubin $>3 \times$ ULN, any severity of symptomatic pneumonitis, severe diarrhea or diarrhea requiring hospitalization, absolute neutrophil count $<0.5 \times 10^9/L$, platelets $<25 \times 10^9/L$. Doses of idelalisib can be reinitiated at a lower dose of 100 mg twice daily after liver function tests return to $<1 \times$ ULN, diarrhea resolves, neutrophils are $>0.5 \times 10^9$, or platelets are $>25 \times 10^9$. Therapy should be discontinued permanently if AST/ALT $>20 \times$ ULN, bilirubin $>10 \times$ ULN, or life-threatening diarrhea occurs.

Common adverse effects: Diarrhea, pyrexia, fatigue, cough, pneumonia, abdominal pain, chills, rash, neutropenia, hypertriglyceridemia, hyperglycemia, AST/ALT elevations

Serious adverse effects: Severe cutaneous reactions, anaphylaxis

Black box warning: Hepatotoxicity, severe diarrhea and colitis, fatal/serious pneumonitis, and fatal/serious intestinal perforation have been reported.

Drug interactions: Idelalisib is a substrate of CYP3A4, P-glycoprotein, and UGT1A4. Idelalisib also inhibits CYP2C19, CYP2C8, CYP3A4, and UGT1A1. Coadministration with medications that are strong CYP3A4 inducers and substrates should be avoided.

Idelalisib in the Treatment of Relapsed Chronic Lymphocytic Leukemia

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Idelalisib (Zydelig®, Gilead) is a first-in-class phosphatidylinositol 3-kinase inhibitor (PI3K) that was approved on July 23, 2014, by the U.S. Food and Drug Administration (FDA) for use in the treatment of relapsed chronic lymphocytic leukemia (CLL) in combination with rituximab in patients who would have been otherwise treated with rituximab alone.^{1,2} With the earlier approval of ibrutinib, idelalisib was the second targeted medication approved for the treatment of CLL in 2014.³ This medication also was granted accelerated approval for the treatment of relapsed

follicular B-cell non-Hodgkin lymphoma (FL) and small lymphocytic lymphoma in patients who have received previous therapy with at least rituximab and an alkylating agent.^{1,2}

The PI3K kinase family includes lipid kinases central to normal cellular functions.⁴ The PI3K pathway is activated when an antigen binds to a B-cell antigen receptor (BCR), a transmembrane receptor involved in the survival of malignant B cells. This activation leads to the phosphorylation of CD19 and B-cell adapter protein and the recruitment of various downstream signaling mediators responsible for cell proliferation, survival, and motility.^{4,5} Activated PI3K produces the second messenger phosphatidylinositol 3,4,5-triphosphate (PIP₃) to recruit other proteins to the membrane of the B cell and activates Bruton's tyrosine kinase (BTK) and protein kinase B (Akt). This pathway determines the occurrence of several downstream events, including calcium mobilization and cell division.⁴ The utilization of the PI3K pathway in cancer therapy has been complicated by the existence of four catalytic isoforms: α and β , which are widely expressed in many tissues, and γ and δ , which are more specific to hematopoietic cells.⁶ The PI3K δ isoform primarily is expressed in circulating leukocytes and lymphoid tissues and has been shown to be essential for B-cell survival, migration, and proliferation in animal models.^{6,7} B cells deficient in PI3K δ have been found to be more prone to apoptosis and less likely to transform into malignant or hyperactive states.⁴ Idelalisib specifically targets and inactivates the PI3K δ isoform, interrupting the downstream signaling of the BCR. This disruption induces apoptosis in B cells in a time- and dose-dependent manner regardless of the presence of common negative genomic prognostic factors. Preclinical and clinical studies have demonstrated that idelalisib shows selective cytotoxicity to malignant B cells compared with normal B cells, as well as normal natural killer (NK) and T cells.^{4,6,8}

The indication for treatment of CLL was based on a phase 3 trial of 220 patients with relapsed CLL who were not eligible to receive chemotherapy due to other comorbidities.⁸ Patients in this trial were randomized to receive either idelalisib and rituximab or placebo and rituximab. This study was stopped early after an interim analysis demonstrated a significant difference between the two groups in progression-free survival (PFS), reaching at least 10.7 months with the idelalisib combination compared with 5.5 months with rituximab alone—a 24-week PFS rate of 93% compared with 46%, respectively (adjusted hazard ratio [HR] = 0.15; 95% confidence interval [CI]: 0.08–0.28; $p < .001$). In addition, the rate of overall survival at 12 months was significantly higher in the idelalisib group compared with the placebo group (92% versus 80%; 95% CI: 0.09–0.86; $p = .02$). Overall response (OR) was 81% in patients who received idelalisib compared with 13%, in patients who received placebo (OR 29.92, $p < .001$).⁸ Of those patients meeting inclusion criteria, 169 underwent at least one post-baseline imaging assessment to assess response to treatment, and imaging results showed a significantly greater proportion of patients in the idelalisib group with at least a 50% reduction in lymphadenopathy (93%; 95% CI: 85–97 versus 4%; 95% CI: 1–10). Lymphocytosis had been associated with idelalisib monotherapy in previous studies; however, during this study, the degree and duration of lymphocytosis was blunted and shortened when idelalisib was

administered with rituximab, peaking at week 2 and resolving by week 12.⁸ A sustained lymphocytosis was seen at week 24 in the placebo group, coinciding with the completion of the rituximab.

More than 90% of patients included in this study experienced some adverse effect, with similar events reported in both groups. Most adverse effects were reported as grade 2 or lower.⁸ The most common adverse effects experienced in the treatment arm of this study were pyrexia (29%), fatigue (24%), nausea (24%), chills (22%), and diarrhea (19%). The most common serious adverse events included various pneumonia, pyrexia, and febrile neutropenia. Based on the results presented in studies to date, idelalisib carries a boxed warning for potentially fatal liver toxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation.^{1,5}

The indications for the treatment of relapsed FL and small lymphocytic lymphoma in patients who have received previous therapy were based on a phase 2 trial evaluating the overall rate of response to therapy in 125 patients with indolent non-Hodgkin lymphoma refractory to treatment or who had experienced a relapse 6 months following therapy.⁶ This was a single-group, open-label study during which patients with a confirmed diagnosis of B-cell indolent non-Hodgkin lymphoma refractory to both rituximab and an alkylating agent received 150 mg of idelalisib twice daily. Therapy was continued until disease progression, the occurrence of unacceptable toxicities, or death. The study noted a 57% response rate (95% CI: 48–66) among the 125 patients, where 7% had a complete response, 50% had a partial response, and 1% had a minor response. Subgroup analyses rates of response were consistent, with favorable rates occurring regardless of demographics, disease, refractoriness, and prior regimens. The median time to response was 1.9 months (range 1.6–8.3 months), and the median duration of response was 12.5 months (range 0.03–14.8 months) with continued administration of idelalisib. With a median duration of treatment of 6.6 months (range 0.6–23.9 months) at the time of data cutoff, the median PFS was 11.0 months (range 0.03–16.6 months) and the median overall survival was 20.3 months (range 0.7–22.0 months).

Study investigators of this trial reported the adverse events that occurred in 10% of patients.⁶ Among those reported, the events that occurred most frequently were diarrhea (43%), nausea (30%), cough (29%), and pyrexia (28%). The events that were reported as grade 3 or higher most often were diarrhea (13%), pneumonia (7%), and dyspnea (3%). The most common laboratory abnormalities reported were neutropenia (27%) and elevations in serum alanine and aspartate aminotransferases (13%). Grade 3 or higher abnormalities included thrombocytopenia (6%) and anemia (2%). Twenty-five patients discontinued therapy with idelalisib due to adverse events, and the initial dose was reduced to 100 mg twice daily or 75 mg twice daily in 42 patients (34%). Grade 3 or higher diarrhea, colitis, or both occurred in 20 patients (16%) at a median of 6 months after initiation, and 14 of these cases resolved spontaneously after dose reduction or with a temporary interruption of therapy. Grade 3 or higher elevations in serum aminotransferase levels developed at a median of 6.3 weeks after the initiation of treatment (range 4–11 weeks), all of which were asymptomatic and resolved to grade 1 or less after interruption of therapy or a dose reduction.

The maximum recommended initial dose of idelalisib is 150 mg orally twice daily.² Idelalisib carries a boxed warning of fatal and serious toxicities, including liver toxicity, diarrheas and colitis, pneumonitis, and intestinal perforation, and is approved with a Risk Evaluation and Mitigation Strategy that includes a communication plan to ensure providers are fully aware of these risks.² Patients experiencing significant pneumonitis, hepatotoxicity, diarrhea, neutropenia, or thrombocytopenia may be advised to temporarily interrupt therapy until toxicities resolve, and if interrupted for severe or life-threatening toxicities, patients should receive a reduced dose of 100 mg twice daily upon reinitiation.² Treatment should be continued until disease progression or unacceptable toxicity.² Idelalisib currently is available as 150-mg and 100-mg tablets through specialty pharmacies and classified as a hazardous agent requiring appropriate handling and disposal. The tablets must be taken whole twice daily but may be taken without regard to food. This medication currently carries a pregnancy risk factor D due to adverse events noted in animal reproduction studies. Women with child-bearing potential should be advised to use effective contraception while taking idelalisib and for at least 1 month after discontinuation.²

Due to the novelty of idelalisib, a paucity of published data on drug interactions exists. The potential for several major drug interactions exists because idelalisib is a major substrate and strong inhibitor of CYP3A4. The area under the curve (AUC) of idelalisib was reduced by 75% when it was coadministered with a strong CYP3A4 inducer and increased 1.8-fold when coadministered with a strong CYP3A4 inhibitor.² Idelalisib also is a substrate of p-glycoprotein and UGT1A4, and weak inhibitor of CYP2C19, CYP2C9, and UGT1A1.² Administering idelalisib with strong CYP3A4 inducers should be avoided and patients should be monitored for toxicity when idelalisib is administered with CYP3A4 inhibitors.²

The successful response rates and acceptable toxicity profile seen with idelalisib demonstrate the therapeutic utility of targeting the BCR pathway in B-cell malignancies. The recent approval of ibrutinib, which targets BTK, is further evidence of this. Although current data on idelalisib are promising, maintaining indications will depend on the further studies' results for response rates and durability, survival, and long-term effects. Idelalisib currently is approved following initial therapies, but studies on its use earlier in cancer treatment as well as in combination with other agents to optimize the inhibition of the BCR pathway can be expected.

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Register for Optional Events at the 11th HOPA Annual Conference!

Come early to participate in HOPA Boot Camps! These sessions are designed to provide pharmacy practitioners who work with oncology patients an introductory overview of in-depth look at unique specialty areas within oncology pharmacy. Registration for optional events is now open at www.hoparx.org. These events are extra-fee events and are not included in the price of registration.

Wednesday, March 25

7:30–11:30 am

Oncology 301: Hematologic Malignancies (001) 0.4 CEUs

Larry Buie, PharmD BCOP; Jill Bates, PharmD MS BCOP; Jessica Duda, PharmD BCOP; Hillary Prescott, PharmD BCOP

Oncology 301 focuses on the management of hematologic malignancies. This is the third installment in a series of preconference boot camps that are designed to expose those with limited experience to the basics of oncology pharmacy practice while maintaining a level that is appropriate for seasoned practitioners in any oncology pharmacy practice setting. The disease states that will be discussed during this 4-hour preconference session include chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, and primary myelofibrosis.

Pediatric Oncology Bootcamp (002) 0.4 CEUs

Susannah E. Koontz, PharmD BCOP; Brooke Bernhardt, PharmD MS BCOP; Jennifer Thackray, PharmD BCPS; Heidi Trinkman, PharmD

This 4-hour course is designed to provide pharmacy professionals with a concise introductory overview to common cancers and hematologic disorders that occur in pediatric patients. Participants will be able to describe key fundamental concepts pertaining to the diagnosis, treatment, and monitoring of children with solid tumors, hematologic cancers, and nonmalignant hematologic disorders.

Lecture-based learning will be supplemented with patient case examples and ancillary handout materials to demystify how to care for younger patients. Whether you are a student or resident interested in pediatric hematology/oncology, a pharmacy practitioner or other medical professional new to the field, or are looking to prepare for the Board Certified Oncology Pharmacist (BCOP) examination, this course is a must for you!

9–11 am

Radiation for the Oncology Pharmacist (003) 0.2 CEUs

Karen Hoffman, MD MHS MPH; Makala Pace, PharmD RPh BCOP

This 2-hour course is designed to provide pharmacy professionals with a concise introductory overview of radiation and the management of radiation-induced toxicities in cancer patients. Participants will be able to describe key fundamental concepts pertaining to radiation therapy in cancer patients, including basics of radiation therapy, types of radiation, indications for radiation, and treatment of radiation-induced toxicities. Lecture-based learning will be supplemented with patient case examples and ancillary handout materials. Radiation therapy is one of the key modalities in the cancer therapy triad. If you are a student or resident interested in hematology/oncology, a pharmacy practitioner, or other medical professional new to the field, this course will enhance your current understanding of the integrative nature of cancer patient care.

HOPA is also pleased to offer attendees the opportunity to extend their learning with a special postconference course.

Saturday, March 28, 1–5 pm / Sunday, March 29, 8 am–Noon

Fundamentals of Hematopoietic Cell Transplantation

Presented by the National Marrow Donor Program (NMDP) and the American Society of Blood and Marrow Transplantation

The field of hematopoietic cell transplantation (HCT) continues to advance rapidly. This 8-hour training course is designed to provide practitioners with the skills and knowledge required to care for patients undergoing HCT. The course content will focus on the pharmacotherapy management of HCT patients. Practitioners, including pharmacists, pharmacy students and residents, registered nurses, advanced practice professionals, and hematology/oncology fellows, will derive benefit from this coursework. Registration for this postconference event is handled directly through NMDP and is separate from your HOPA conference registration.

For registration information, including pricing and continuing education information, and to view the full agenda and sample course materials, please refer to the registration site <http://www.cvent.com/d/k4qhqn>

Pembrolizumab (Keytruda™)

Class: Human programmed death receptor-1 (PD-1)-blocking antibody

Indication: Unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation-positive disease, a BRAF inhibitor

Dose: 2 mg/kg over 30 minutes every 3 weeks until disease progression or unacceptable toxicity

Dose modifications

Hold treatment for aspartate aminotransferase/alanine transaminase (AST/ALT) 3–5 × the upper limit of normal (ULN), total bilirubin 1.5–3 × ULN, pneumonitis (grade 2), colitis (grade 2), nephritis (grade 2), hypophysitis (grade 2), hyperthyroidism (grade 3), and any other severe treatment related adverse reaction (grade 3).

Discontinue treatment for AST/ALT > 5 × ULN, total bilirubin > 3 × ULN, pneumonitis (grade 3), colitis (grade 4), nephritis (grade 3), hypophysitis (grade 4), hyperthyroidism (grade 4), infusion reaction (grade 3), any life-threatening adverse reaction, any persistent grade 2 or 3 reaction that persists for 12 weeks after last dose, and any recurring grade 3 treatment-related adverse reaction.

Common adverse effects: Fatigue, hyperglycemia, hyponatremia, hypoalbuminemia, pruritus, nausea, cough, rash, decreased appetite, hypertriglyceridemia, hypocalcaemia, constipation, diarrhea, arthralgia, and peripheral edema

Serious adverse effects: Immune-mediated reactions such as hypothyroidism, pneumonitis, hyperthyroidism, colitis, hepatitis, hypophysitis, and nephritis

Drug interactions: No known clinically significant interactions

Blocking Programmed Death Receptor-1 in Melanoma: Pembrolizumab

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The number of patients diagnosed with melanoma is rapidly rising compared with other cancers, except for lung cancer in women.

Melanoma presents as localized (82%–85%), regional disease (10%–13%) or with distant metastases (2%–5%). The 5-year survival decreases by half when presenting with regional disease, while long-term survival with distant metastases is less than 10%. Different targeted therapies have been developed in recent years to treat metastatic melanoma. Ipilimumab stimulates T-cells but has many immune-mediated adverse effects. Overall survival (OS) with ipilimumab was 10.1% compared with placebo. Oral targeted therapies include vemurafenib, dabrafenib (BRAF V600-mutation inhibitors), and trametinib (MEK1 and MEK2 inhibitor). Although these targeted therapies have high initial response rates, about half of patients treated with these agents as monotherapy relapse within 6 months.¹

Pembrolizumab (Keytruda™) was granted accelerated approval by the U.S. Food and Drug Administration (FDA) on September 4, 2014, for advanced or unresectable melanoma that is not responsive to ipilimumab or, if eligible, a BRAF V600-mutation inhibitor.

Pembrolizumab opens the door to a novel mechanism of action against tumor cells by increasing the host immune response against tumor cells through the programmed death receptor-1 (PD-1) pathway. PD-1 regulates the host immune response by limiting the action and life span of killing T-cells and antigen-presenting cells (APC) where the receptor is commonly expressed. The PD-1 antibody disrupts the action of programmed death receptor-ligand-1 (PD-L1) on peripheral, and cytotoxic T-cells and programmed death receptor-ligand-2 (PD-L2) ligands on APCs. Blocking the action of the PD-1 receptor increases the life span and activity of cytotoxic T-cells against the tumor cells. PD-1 antibodies are particularly effective in environments where the PD-L1 and PD-L2 are overexpressed by tumor cells and macrophages. These environments include melanoma and solid tumors, such as lung and renal cell carcinoma. Pembrolizumab is a humanized monoclonal IgG4 antibody against the PD-1.²

Because of its effectiveness as an agent of last resort for the treatment of a cancer with low incidence, pembrolizumab received priority review and orphan product designation for melanoma. This approval is based on a phase 1 clinical trial that established its efficacy and safety and was presented as two studies based on the different cohorts involved.^{3,4} Although there are no results from a comparative clinical trial, previous trials established that a high percentage of patients who achieved tumor regression had a favorable safety profile.³ It was shown that pembrolizumab comes with a relatively low rate of systemic adverse effects, most of which are low grade.⁴

The efficacy and safety of pembrolizumab (formerly lambrolizumab) was investigated in a multicentered, open-label, randomized, dose-comparative, activity-estimating multicohort trial. Hamid and colleagues reported safety and tumor response in 135 advanced melanoma patients (KEYNOTE-0001).³ Patients with advanced melanoma were randomized to receive either pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks until unacceptable toxicity or symptomatic disease progression or rapidly progressive disease. The regimens were well tolerated, with adverse event rates similar in occurrence and severity between the two. The primary outcome was

confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST), which was 38%, with no significant difference in response based on prior ipilimumab therapy. The overall median progression-free survival (PFS) was longer than 7 months. These results support that pembrolizumab, at either dose, may be an effective treatment for patients who have progressed with ipilimumab therapy and have few effective treatment options available.³

Robert and colleagues continued the study of pembrolizumab in ipilimumab-refractory patients, also looking at their BRAF V600 mutation status.⁴ In the expansion cohort study, 173 patients with advanced melanoma were randomized to either 2 mg/kg or 10 mg/kg every 3 weeks. The ORR in both treatment arms was 26%. When split into subgroups based on BRAF V600 status, ORR in BRAF-wild type patients was 28% compared with 19% in BRAF-mutant patients. Most responses appeared before week 12. However, responses were reported as late as 11 months after initiation of therapy. Median response duration was not reached and is estimated to range from 6 to 37 weeks. Reduction of baseline lesion size appeared in 73% of patients and the PFS was 22 weeks. No significant improvement in OS was reported. The median number of days on therapy was 188 days and the most common reason for discontinuation of therapy was disease progression⁴

Both systemic and immunologic adverse reactions are possible with pembrolizumab.²⁻⁴ Systemic adverse effects include fatigue (47%), cough (30%), nausea (30%), pruritus (30%), rash (29%), decreased appetite (26%), constipation (21%), arthralgia (20%), diarrhea (20%), chills (14%), myalgia (14%), fever (11%), and vitiligo (11%). Most of the time, these generalized adverse effects are low grade and do not require intervention. Metabolic and laboratory abnormalities include hyperglycemia (40%), hyponatremia (35%), hypoalbuminemia (34%), hypertriglyceridemia (25%), hypocalcaemia (24%), and increased AST (24%). Immunologic effects, such as hypothyroidism (8.3%), pneumonitis (2.9%), hyperthyroidism (1.2%), colitis (1%), hepatitis (0.5%), hypophysitis (0.5%), and nephritis (0.7%) can progress to a higher grade where holding the dose or permanently discontinuing the medication may be necessary. High-dose systemic corticosteroid treatment can be used to treat immune-mediated adverse events. Typical doses were ≥ 40 mg of prednisone or equivalent per day followed by a taper.²

Pembrolizumab does not require dose adjustment based upon renal function, age, gender, tumor burden, or body mass index. Approximately 39% of the 411 patients were older than 65 years and no difference was reported when comparing the safety and efficacy of this drug with that seen in younger patients. There are no data for the use of pembrolizumab in pediatric patients.² Interruptions in pembrolizumab therapy are recommended for the following adverse events: grade 2 pneumonitis, grade 2 or 3 colitis, symptomatic hypophysitis, grade 2 nephritis, grade 3 hyperthyroidism, AST or ALT elevated 3–5 \times the upper limit of normal (ULN), total bilirubin elevated 1.5–3 \times the ULN, or any other severe or grade 3 treatment-related adverse reaction.² Resume treatment when the adverse reaction has recovered to grade 0 or 1. Permanently discontinue therapy for the following: any

life-threatening adverse reaction, grade 3 or 4 pneumonitis, grade 3 or 4 nephritis, AST or ALT $> 5 \times$ ULN or total bilirubin $> 3 \times$ ULN, grade 3 or 4 infusion-related reactions, inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalents per day within 12 weeks after the last dose, persistent grade 2 or 3 adverse reactions that do not recover to grade 0 to 1 within 12 weeks after last dose, or any severe or grade 3 treatment-related adverse reaction that recurs.²

The mean elimination half-life of pembrolizumab is 26 days and steady state is reached after 18 weeks. No significant drug interactions were reported.²

Pembrolizumab is supplied as a 50-mg powder vial. It is reconstituted with 2.3 ml of sterile water injected along the walls of the vial, but not directly on the lyophilized powder. The resulting concentration is 25 mg/ml. Swirl the vial slowly for approximately 5 minutes, but do not shake the vial. The reconstituted solution has a slightly opalescent, colorless to slightly yellow color. The solution is transferred to a 0.9% sodium chloride for a concentration between 1 mg/ml to 10 mg/ml, and some sites use a 50-mL bag. Reconstituted and diluted solutions have an expiration time of 4 hours at room temperature and 24 hours under refrigeration (2 °C–8 °C or 36 °F–46 °F). Pembrolizumab is administered intravenously over 30 minutes with an in-line, low-protein binding 0.2–5 micron filter.²

Patients should be advised of the possibility of immunologic adverse reaction with a broad range of symptoms. In addition, corticosteroid treatment may be required for immunologic reaction management. Pembrolizumab is considered pregnancy category D. Therefore, women of reproductive age should be counseled to use highly effective contraception during treatment and should continue for 4 weeks after treatment. Mothers should be advised not to breastfeed while on this medication.²

Pembrolizumab currently is in phase 2 and 3 ongoing trials for advanced melanoma. It also is currently being looked at for monotherapy as well as in combination for more than 30 types of cancers and has recently received breakthrough therapy designation for non-small cell lung cancer. We have the opportunity to continue to learn of completed trial results and pembrolizumab's expanded place in treatment algorithms.

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