Hematology/Oncology Pharmacy Association

# HOPA News

Volume 12, Issue 3, 2015

## Bridging the Gap Between Clinical and Specialty Pharmacy Services

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Regulatory agencies and insurance companies favor restricted drug distribution systems to dispense specialty drugs that make up much of the armamentarium of antineoplastic agents used today. From the U.S. Food and Drug Administration's perspective, specialty pharmacies limit the distribution of high-risk specialty medications to pharmacies that have the most experience complying with complicated risk evaluation and mitigation strategy programs.[1] From a payer perspective, specialty pharmacies create economies of scale while simplifying the distribution of expensive medications, thus reducing costs to insurance companies.[2]

As specialty drug prices balloon, cost containment has become increasingly important to insurance companies. It is estimated that in 2008, $54 billion was spent on specialty medications, accounting for 25%–30% of overall medical costs to health plans.[1] National drug expenditure forecasts for 2014 predicted growth in specialty drugs of 13%–24%.[3] Perhaps unsurprisingly, oncology practice is heavily impacted by specialty pharmacy because many antineoplastic agents fall into this high-cost, high-risk category.

In response, hospital systems have increasingly developed their own specialty pharmacies to capitalize on the financial opportunities that specialty pharmacy offers. According to an article published in *Pharmacy and Therapeutics,* hospital systems are hoping to purchase specialty medications at 340B prices, then bill insurance companies for the higher, nondiscounted cost.[4] At least one hospital-based specialty pharmacy program has reported revenue of $7.5 million during the first year.[5] Although the incentive to start a specialty pharmacy exists, health-system administrators will need to integrate specialty pharmacy into preexisting practice models to prevent fragmentation of care.

When a specialty pharmacy is being developed, one challenge is the lack of an official definition of *specialty pharmacy,* and services vary significantly between institutions.[3] There are no mandatory certificates for accreditation, which also is problematic. There are, however, accrediting bodies that hospital systems may voluntarily seek out. Both the Accreditation Commission for Health Care and URAC (formerly the Utilization Review Accreditation Commission)

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Send administrative correspondence or letters to the editor to HOPA, 8735 W. Higgins Road, Suite 300, Chicago, IL 60631, fax 847.375.6497, or e-mail info@hoparx.org. *HOPA News* is published by the Hematology/Oncology Pharmacy Association.



provide standards for performance. URAC's measures are available online[6] and focus mainly on medication adherence for nonspecialty medications; overall patient satisfaction; and distributive functions such as accurate dispensing, on-time delivery, and call center performance. URAC has not yet established a measure for specialty medication adherence.

In 2010 the National Comprehensive Cancer Network (NCCN) published a task force report on the potential advantages and risks of using specialty pharmacies to distribute oncology therapeutic agents.[3] Potential advantages include appropriate selection of medication, increases in adherence, avoidance of unnecessary drug costs, and increasing patient and provider satisfaction.[3,7]

However, if the specialty pharmacy is not operated by the hospital system, patient care may be compromised by lack of access to a patient's electronic medical record, poor communication between providers and the specialty pharmacy, and a breakdown in the drug's chain of custody because medications often are delivered to a patient's home.[3]

The University of Illinois at Chicago (UIC) recently published its approach to integrating existing clinical pharmacy with specialty pharmacy services.[8] In the UIC model, the clinical pharmacist provides services for one-half day per week. The specialty pharmacy has pharmacists, prior authorization specialists, students, and residents to staff its 24-hour call center.

The clinical pharmacist serves on the care team and interfaces with the specialty pharmacy, bridging a gap in care that NCCN warns may occur with the introduction of specialty pharmacy services. When the provider writes a prescription, the clinical pharmacist evaluates the order for appropriateness, then sends the fill to the specialty pharmacy if the patient does not have contraindications to therapy. The clinical pharmacist also coordinates any other education the patient may need, such as injection technique training. Meanwhile, some of the responsibilities of the specialty pharmacy include verifying prescription benefits, assisting with referrals to prescription assistance programs, and sending prior authorizations appeal forms to the clinical pharmacist for justification.

If permitted, the specialty pharmacy processes the fill for the patient's first visit with the clinical pharmacist. The clinical pharmacist continues therapeutic drug monitoring. The specialty pharmacy continues to monitor the patient for adherence and adverse effects through the use of clinical surveys, which are reported to the clinical pharmacist. The clinical pharmacist can then discuss alternate treatment options with the attending physician, if needed.

Utilizing an integrated clinical and hospital-based specialty pharmacy model offers the advantage of sharing electronic medical records, fostering closer collaboration between providers and specialty pharmacy because of closer geographic proximity, and ensuring proper storage of medications by direct delivery to clinics. Development of such models will be increasingly important as healthcare systems seek to develop their own specialty pharmacies.

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# Mentoring/Precepting Students and Residents During a PGY2 Residency

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The number of pharmacy learners, including students and residents, continues to increase within our profession. As of 2014, there are more than 130 pharmacy colleges and schools in the United States with an accredited or candidate professional degree program and an estimated graduating class of more than 14,000 students. In addition, more new practitioners are pursuing specialty residency training, including PGY2 oncology programs. According to the American Society of Health-System Pharmacists' Resident Matching Program statistics, there were 121 available PGY2 oncology positions among 75 total programs in 2014, up from 74 positions at 50 total programs in 2010.[1] As the number of pharmacy students and residents increases, it is vital that we prepare and utilize these learners appropriately to maximize educational experiences and organizational value.

## Layered Learning Practice Model

The Layered Learning Practice Model (LLPM) was developed at the University of North Carolina (UNC) Eshelman School of Pharmacy and UNC Hospitals to enhance patient care and provide new educational opportunities for student and resident learners. This innovative model of pharmacy practice mimics the medical model of active learning and features an attending pharmacist who is responsible for all aspects of a patient's care and residents (PGY1 or PGY2) and students who function as extenders to provide expanded clinical patient care services. In addition to clinical services, the attending pharmacist oversees student/resident education. In this model, learning is handled in a layered fashion from attending pharmacist to resident to student, providing opportunities for resident and student learners to be responsible for patient care on rotation. In addition, it affords the PGY2 resident opportunities to lead topic discussions and serve as preceptors for PGY1 residents and student pharmacists. Attending pharmacists benefit by gaining dedicated time for leadership, scholarship, and program expansion activities.

## PGY2 Resident Precepting Roles

In the LLPM, PGY2 residents can have a large impact on the education and development of PGY1 and student learners while freeing up attending pharmacists' time for high-level clinical activities. PGY2 residents have the necessary experience to fill all formal precepting roles such as direct instruction, modeling, coaching, and facilitating. For example, PGY2 residents may provide direct instruction by leading topic discussions. Rounding experiences and the subsequent opportunities to provide specific feedback and education allow the PGY2 resident to model and coach desired behaviors. In addition, PGY2 residents can serve as a coach and mentor for residents and students working on case presentations, rotation projects, or journal clubs. Ultimately, the PGY2 resident can facilitate independent experiences for other learners, such as patient monitoring and documentation. Under the LLPM, PGY2 residents develop the valuable skills necessary to serve as strong future preceptors.

## PGY2 Resident Benefits and Challenges

The development of nonclinical skills is essential for PGY2 residents to complement their direct patient care experiences. Expanding the skills necessary to function as an excellent preceptor is arguably one of the most important outcomes of residency training and can serve as the foundation of a resident's clinical practice. Benefits of mentoring and precepting learners as a PGY2 resident include sharpening these skills, freeing time for the attending pharmacist, and providing a high-quality learning experience for PGY1 residents and students. From an organizational perspective, PGY2 precepting can add efficiency to the training of learners. For example, utilizing a PGY2 resident to lead supportive care topic discussions allows an attending pharmacist to focus on patient care while allowing the preceptor to have more time and energy to focus on other projects.

Serving as a preceptor while completing a PGY2 residency can be challenging. Because PGY2 residents lack the same clinical experience as an experienced pharmacist they may be perceived as a less formal educator, which may negatively impact learner structure. Learner proximity of experience and coresident comradery could potentially adversely affect the PGY2 resident's influence and ability to successfully precept in the LLPM. Setting clear expectations regarding preparation and communication can help ensure a successful professional relationship between the PGY2 and the learner. Another key to successful PGY2 mentoring and precepting of learners is appropriate oversight and mentorship of the PGY2 resident. As a PGY2 resident, receiving feedback on your precepting skills from attending pharmacists ensures continued professional growth and development.

## PGY2 Resident Experience

As a PGY2 oncology resident at the University of Wisconsin Hospital and Clinics, an academic medical center that utilizes the LLPM, I have regular opportunities to work with various learner groups. From direct topic instruction to rounding facilitation, I use all four formal precepting models on a daily basis. Pre- and postrounding patient review has been one of the more fulfilling PGY2 residency experiences and allows me to work one on one with learners to sharpen their clinical

skills while enhancing my precepting skills. In addition, PGY2 residents serve as formal facilitators for PGY1 residents and pharmacy students for our triweekly "Resident Report" sessions. Resident Report is an opportunity for a learner to present clinical or administrative topics to the learner group via lecture and discussion. As a PGY2 resident, I help the learner with topic selection and delivery while providing formalized feedback for self-improvement. In addition, the learner provides feedback to improve my facilitation and evaluation skills. These are just a few examples of methods the University of Wisconsin Hospital and Clinics uses to allow their PGY2 residents to improve learner training, facilitate attending pharmacist clinical practice, and achieve a comprehensive PGY2 training experience.

## Reference


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## Scenes from the 2015 HOPA Annual Conference

# Recalls and Safety Alerts from the FDA

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## Recalls

### Mitoxantrone

In December 2014 Hospira, Inc., announced a voluntary recall of 10 lots of mitoxantrone (human and veterinary) for confirmed subpotency and elevated impurity levels. Hospira has not yet received any reports of adverse effects associated with this issue. The impacted lots were distributed to hospitals and veterinary clinics worldwide from February 2013 through November 2014. A root-cause analysis initiated improvements for batches manufactured March 2014 and later. For a full list of recalled products, visit www.fda.gov/Safety/Recalls/ucm427952.htm.

### Sodium Chloride Injection

In January 2015 Hospira, Inc., issued a voluntary nationwide recall of one lot of 0.9% sodium chloride injection, USP, 250 ml (NDC 0409-7983-02) because of particulate matter found in a single unit. Hospira has identified the particulate as a human hair sealed inside the bag at the additive port area. There have been no reports of adverse effects associated with this issue for this lot. This lot was distributed nationwide from September to November 2014. Hospira is conducting a root-cause analysis to determine corrective and preventive actions. For more information, refer to www.fda.gov/Safety/Recalls/ucm430929.htm.

## Safety Alerts

### Lanreotide (Somatuline Depot Injection)

The list of contraindications for lanreotide has been updated to include patient history of hypersensitivity to lanreotide. Postmarketing reports indicate some patients have experienced allergic reactions, including angioedema and anaphylaxis, after receiving lanreotide.

The package insert has been updated to include additional warnings and precautions. In a postmarketing study of 81 patients treated with lanreotide who had baseline heart rates of at least 60 beats per minute (bpm), 23% (19/81) had a heart rate < 60 bpm after lanreotide administration versus 16% (15/94) of patients treated with placebo. Ten patients (12%) had more than one episode of a heart rate < 60 bpm. In both intervention and control groups, 1% in each experienced a heart rate < 50 bpm and had bradycardia reported as an adverse event.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm429783.htm

### Paclitaxel Protein-Bound Particles (Abraxane)

The use of paclitaxel protein-bound particles in patients with hepatic impairment may put them at increased risk of toxicity, particularly myelosuppression requiring close monitoring. Use is not recommended for patients with total bilirubin values > 5 × upper limit of normal (ULN) or aspartate transaminase (AST) > 10 × ULN. Paclitaxel protein-bound also is not recommended for patients with metastatic adenocarcinoma of the pancreas with moderate to severe hepatic impairment (total bilirubin > 1.5 × ULN and AST = 10 × ULN).
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm359951.htm

### Ramucirumab (Cyramza)

Several labeling updates were made for ramucirumab. Additional information was added to warnings and precautions for hemorrhage and hypertension. In one study assessing patients with non-small-cell lung cancer (NSCLC), the incidence of severe bleeding was 2.4% with ramucirumab and docetaxel compared with 2.3% with placebo. This trial excluded patients who were receiving therapeutic anticoagulation or chronic nonsteroidal anti-inflammatory drug (NSAID) therapy or other antiplatelet therapy besides once daily aspirin. Patients with major airway or blood vessel invasion or intratumor cavitation were also excluded. The risk of pulmonary hemorrhage for these patients is unknown because of their exclusion from the study. The incidence of hypertension also was updated to indicate occurrence in 6% of patients who received ramucirumab plus docetaxel compared with 2% of patients who received docetaxel alone.

Information regarding immunogenicity was edited in the context of the study on ramucirumab with docetaxel for NSCLC. No pharmacokinetic interactions were found between ramucirumab and docetaxel. The study included several geriatric patients, allowing outcomes in this group to be assessed in an exploratory subgroup analysis. The hazard ratio for overall survival (OS) for patients < 65 years was 0.74 (95% CI: 0.62, 0.87) and for patients ≥ 65 years 1.10 (95% CI: 0.89, 1.36).

Information regarding ramucirumab use in hepatic impairment was added to clarify the definition of mild hepatic impairment (AST > ULN or total bilirubin > 1.0–1.5 × ULN), for which ramucirumab does not require a dose adjustment.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm429773.htm

### Obinutuzumab (Grazyva)

The warnings and precautions section was updated to include fatal infections reported with use of obinutuzumab. The percent incidence was updated to 33% for grades 3 or 4 neutropenia and 10% for grades 3 or 4 thrombocytopenia when used in combination with chlorambucil.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm404996.htm

### Ruxolitinib (Jakafi)

The ruxolitinib package insert was updated to include information regarding symptom exacerbation to pretreatment levels after discontinuation of ruxolitinib. This may occur over a period of 1 week, and patients may experience one or more of the following: fever, respiratory distress, hypotension, disseminated intravascular coagulation, or multiorgan failure. Periodic skin evaluations should also be conducted for patients taking ruxolitinib because nonmelanoma skin cancers (basal cell, squamous cell, Merkell cell carcinoma) have occurred.

Myelosuppression, thrombocytopenia, anemia, and neutropenia were added to the list of adverse reactions.

Additional information was included in the organ dysfunction section. In patients with polycythemia vera and moderate (creatinine clearance [CrCl] 30–59 ml/min) or severe (CrCl 15–29 ml/min) renal impairment, a dose reduction of ruxolitinib is recommended. Hepatic impairment is another factor that can necessitate dose reductions.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm377314.htm

### Sunitinib (Sutent)

Additional information regarding risk for hypoglycemia was included in the warnings and precautions and patient counseling sections of the sunitinib package insert. Hypoglycemia was seen in 2% of patients with renal cell carcinoma and gastrointestinal stromal tumor who received sunitinib and 10% of patients with primitive neuroectodermal tumor. Not all patients had preexisting abnormalities in glucose control. Glucose values should be regularly assessed during and after discontinuing treatment with sunitinib.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm224050.htm

### Everolimus (Afinitor)

An increased incidence of angioedema has been recorded with concomitant use of everolimus and angiotensin-converting enzyme inhibitors (ACEIs). The incidence of angioedema for patients taking everolimus and an ACEI was 6.8% versus 1.3% for patients taking an ACEI only in a pooled analysis of randomized double-blind oncology clinical trials.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm433415.htm

### Imatinib (Gleevec)

Warnings and precautions about the use of imatinib have been updated. Patients with chronic phase, newly diagnosed Philadelphia chromosome–positive chronic myeloid leukemia (Ph+CML) were given imatinib or nilotinib. In this trial the incidence of severe, grade 3 or 4 fluid retention was seen in 2.5% of patients taking imatinib and in 3.9% of patients taking nilotinib 300 mg twice daily (BID). Similar rates of effusions (pleural or pericardial effusions or ascites) and pulmonary edema occurred: 2.1% (0% grade 3 or 4) in the imatinib arm and 2.2% (0.7% grade 3 or 4) in the nilotinib arm.

The incidence of congestive heart failure and left ventricular dysfunction was assessed in another randomized trial in the same population. Cardiac failure occurred in 1.1% of patients (0.7% grade 3 or 4) in the imatinib arm and 2.2% of patients (0.7% grade 3 or 4) in the nilotinib 300 mg BID arm.

Gastrointestinal (GI) hemorrhage was also evaluated in a randomized trial comparing imatinib and nilotinib as initial treatment for patients with chronic phase Ph+CML; 1.4% of patients receiving imatinib and 2.9% of patients receiving nilotinib 300 mg BID experienced GI hemorrhage (0% grade 3 or 4 and 0.7% grade 3 or 4, respectively). Gastric antral vascular ectasia has been reported through postmarketing experience.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm255333.htm

### Nilotinib (Tasigna)

Changes have been made to the warnings and precautions associated with nilotinib. Additional clinical trial results are available to describe the incidence of cardiac and arterial vascular occlusive events and hemorrhage seen with nilotinib use. The incidence of cardiovascular events seen among patients receiving a median of 60 months of treatment was dose-related, occurring in 9.3% of patients on nilotinib 300 mg BID and 15.2% of patients on nilotinib 400 mg BID. The rates of GI hemorrhage were 2.9% in patients on 300 mg BID (0.7 % grade 3 or 4) and 5.1% in patients on 400 mg BID (1.4% grade 3 or 4). Fluid retention has also been a reported adverse event in clinical trials. Severe, grade 3 or 4 retention occurred in 3.9% of patients receiving nilotinib 300 mg BID and 2.9% of patients receiving 400 mg BID. It is recommended to monitor for signs of severe fluid retention and symptoms of respiratory or cardiac compromise and evaluate and treat patients according to etiology. Additional information on regular monitoring of lipid profiles and glucose (periodically during the first year, at least yearly during chronic therapy) and the use of HMG-CoA reductase inhibitors has been included. Drug-drug interactions should be assessed before initiating lipid lowering therapy.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm218929.htm

### Abiraterone (Zytiga)

The drug interactions section for abiraterone has been updated to include information on CYP2C8 drug-drug interactions in healthy subjects. The area under the curve of pioglitazone, which is a CYP2C8 substrate, was increased by 46% when patients were given pioglitzone and a single dose of 1,000 mg abiraterone. Patients should be monitored closely when given CYP2C8 substrates with narrow therapeutic indexes and abiraterone.
www.fda.gov/Safety/MedWatch/SafetyInformation/ucm314608.htm

### Goserelin Acetate Implant (Zoladex)

Reports of injection-site injury and vascular injury comprising pain, hematoma, hemorrhage, and hemorrhagic shock requiring blood transfusions and surgical intervention have been documented with the use of goserelin acetate implant. Extra care and caution should be utilized in patients with a low body-mass index and patients receiving full-dose anticoagulants.

# Board Update

*Scott Soefje, PharmD MBA BCOP FCCP, HOPA President*

## Annual Meeting Recap

The HOPA annual meeting exceeds expectations every year, and this year was no exception. We topped 1,000 attendees for the first time ever. Holy buckets! As a native Texan and an Austinite, I'm proud that attendees enjoyed a successful annual meeting in our city.

The Programming Committee did another outstanding job. The John G. Kuhn Keynote Lecture was thought-provoking and entertaining. Toby Clark made us consider the footprint we will leave on the profession and the footprint HOPA will leave on health care. The boot camps, concurrent sessions, BCOP sessions, and other educational offerings provided something for everyone.

Every year it gets harder and harder to top the year before. Still, we are already off to a fantastic start for the 2016 Annual Meeting in Atlanta, GA. We have a very special keynote speaker lined up for next year whom I think everyone will be excited about. As teasing as it sounds, you'll just have to wait until we make the formal announcement.

## Strategic Plan

HOPA Past President Mike Vozniak unveiled our new strategic plan at the annual meeting. This plan was developed in early 2015 and will take us through 2020. Like our previous plan, this one comprises four core areas:

- Professional development
- Advocacy
- Research
- Professional resources and tools.

The purpose of the first three areas is to improve our previous work. We are finding ways to expand our professional development offerings, connect with a wider audience through advocacy, and re-focus our research on demonstrating the value of the pharmacist in the hematology/oncology setting.

We added the fourth area, professional resources and tools, because we want HOPA to expand beyond standards. Although standards will remain a large part of this section, we want to explore HOPA's potential to aid hematology/oncology pharmacists in their daily practice. Our goal is to become the go-to place for all things related to hematology/oncology pharmacy.

In May, the board approved the final plan including the prioritization of the objectives under each of the four core areas. You will see the new strategic plan posted on the website shortly.

## BCOP Proposal

HOPA is pleased to announce that the Board of Pharmacy Specialties (BPS) has approved HOPA as a provider of Board Certified Oncology Pharmacist (BCOP) recertification professional development for a 7-year cycle that will begin January 1, 2016. HOPA's program will provide 38 hours per year of opportunities for BCOPs to address and refresh their knowledge on topics essential to practice and earn the required 100 continuing education hours over a 7-year period. The comprehensive approach will address the four domains of oncology pharmacy specialty practice as defined by BPS, and assess participants' knowledge and problem-solving skills pertinent to the application of the scope of material in each of the four domains.

HOPA's proposal is built around four core professional development components:

- Oncology Pharmacy Updates Course
- Live BCOP recertification programming (expansion of our current 6-hour annual conference offerings)
- Self-study modules
- Emerging Issues in Oncology webinar series.

Much more information will be forthcoming in the weeks ahead, including opportunities for members to serve as volunteers on the BCOP Recertification Committee or provide expertise as speakers. Please look for those announcements in the next few days as we will be ramping up quickly to begin programming in January 2016.

The American College of Clinical Pharmacy and American Society of Health-System Pharmacists (a combined program) also were approved to provide BCOP recertification offerings.

## Hill Day

As part of our advocacy agenda in our strategic plan, the board and the Health Policy Committee had our first HOPA Hill Day on April 29. We went to Capitol Hill to meet Representatives and Senators from Connecticut, Florida, Indiana, Kentucky, Minnesota, New York, North Carolina, Ohio, Pennsylvania, Texas, and Washington. In attendance were Mike Vozniak, Jill Rhodes, Heidi Finnes, Ryan Bookout, Lisa Holle, Helen Marshall, Niesha Griffith, David DeRemer, Kellie Weddle, and Jolynn Session,  and I, along with staff from HOPA and the District Policy Group.

We went to promote the role of the hematology/oncology pharmacist and to discuss the value we bring to patients. We also asked for support for H.R. 592/S. 314: Pharmacy and Medically Underserved Areas Enhancement Act. This act would allow pharmacists to bill for clinical services. We also promoted oral chemotherapy access, supporting parity between oral and IV chemo while describing how specialty-tier co-pays hurt patients. Our message seemed well-received, and our advocacy is starting to be noticed in Washington, DC. As a small group, we still have a long road ahead, but we're off to a great start.

Each member of HOPA can make a significant impact in advocacy. Take the time now to contact your senators and local representatives and ask them to support H.R. 592 or S. 314. Every time you reach out to Congress, our voice gets louder and our message gets closer to being heard and accepted.

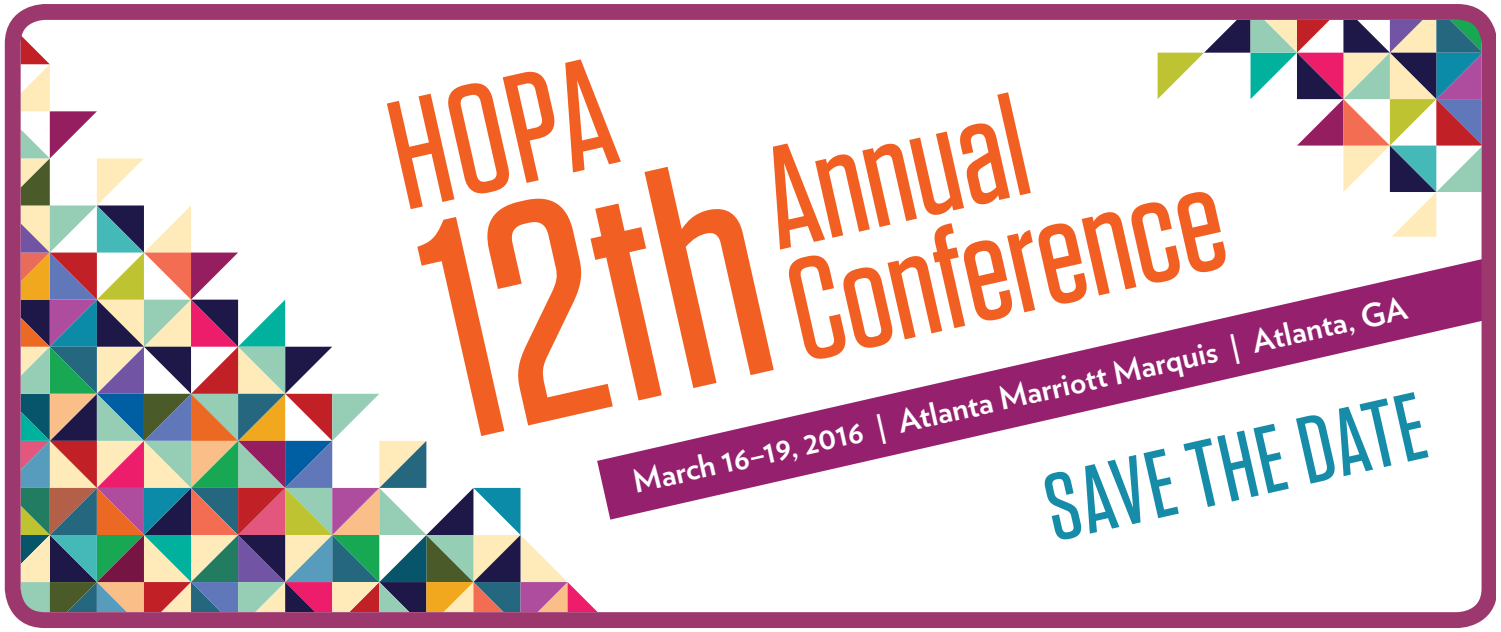
### Fellow Program

The call for nominations/applications for the Fellow of the Hematology Oncology Pharmacy Association (FHOPA) has gone out. We are looking for those individuals who have made a lasting impact on HOPA. This inaugural class will be introduced in Atlanta in March 2016. If you know someone who you think deserves this qualification, please submit a nomination.

### The List

So far I have talked about what we've been doing, and I want to end today with what we have planned. In my opening remarks in Austin, I stated I have a list of items that I have been collecting. Many of the things on my list are areas we are already working on; some are ideas that we should start on but will take more than a year to accomplish; and some are just ideas that we should keep in mind. Like many to-do lists, this one is constantly changing. As I check off "submit BCOP proposal to BPS," I add many additional items that will be required should the proposal be accepted. As we meet with one external organization, we identify two more that may be potential partners with HOPA. And as we promote our healthcare agenda, we ask ourselves how to help our members meet the challenges of being a provider should that bill pass. We will be doing an internal review of the organization, but more on that next time. We are working to expand our influence by partnering with an increasing number of cancer or pharmacy organizations—this will be the topic of the winter update. We will be looking for big ideas, developing new programming, taking a leadership role in oral chemotherapy, and continuing to deliver the quality products you have come to expect from HOPA.

We will continue to provide quality professional development programming, so don't forget about the quarterly webinars, journal club, and the practice management symposium in September. We are becoming a strong voice for cancer care in Washington, and external organizations now seek out our opinions. We are talking with LiveSTRONG, Oncology Nursing Soceity, American Society of Clinical Oncology, and other like-minded organizations. Our call for research proposals has gone out. We are exploring new areas, have a new strategic plan, and are expanding our influence in care for cancer patients. The board, committees, task forces, and work groups are energized to push HOPA to new heights. The coming year will be a busy one for HOPA, but I know we are moving in the right direction.



# Conference Recap

It turns out everything is bigger in Texas, including the HOPA Annual Conference which took place in Austin, TX, in March and brought in record attendance with more than 1,000 registrants! Hematology/oncology pharmacists from across the nation gathered to discuss current research in the screening and treatment of patients with solid tumors and hematologic malignancies, learned about new and emerging therapies for patients, and reviewed recent developments in medical literature regarding medications and dosing. Nearly half of the HOPA membership joined together to share knowledge and expertise over 3.5 days. Meeting attendees took advantage of Austin to discover the great food and arts and entertainment scene the host city offered.

Several preconference events allowed attendees to maximize their time in Austin with extended networking and education events. New this year was a postconference offering from the American Society for Blood and Marrow Transplantation, *Fundamentals of Hematopoietic Cell Transplantation*.

Toby Clark, MSc FASHP FFOP, delivered the John G. Kuhn Keynote Lecture. His address offered thoughts and reflections from his unique vantage point as a pharmacy observer and traveler to more than 500 facilities throughout the world. With nearly 50 years of experience in observing and consulting for hospitals and health systems throughout the world, his keynote address, *What Is Your Footprint?*, was extremely impactful and thought-provoking.


In addition to six specialty sessions and 10 breakout sessions, HOPA was pleased to offer a breadth of general session topics delivered by industry experts throughout conference., including the following:

**Emerging Therapies in CLL**
Jeffrey Bryan, PharmD

**Investigational Agents**
Rowena Schwartz, PharmD BCOP

**New Drug Update: Marketed Agents**
Monique Giordana, PharmD BCOP

**Practice Panel: Survivorship**
Jeff Sivik, PharmD BCOP; Lew Iacovelli, PharmD BCOP CPP; Sarah Scarpace, PharmD MPH BCOP; Kerry Parsons, PharmD BCOP

**Resistance, New Antibiotics, and Continued Fun with Fungus: What the Oncology Pharmacist Needs to Know**
James Lewis II, PharmD FIDSA

**Targeting the Immune System in Cancer**
David Frame, PharmD

HOPA extends a huge thanks to the many other industry professionals who shared their insights throughout conference events!

New this year was an attendee lounge that provided opportunities to "Relax, Network, and Get Charged." The conference also held oncology interest group discussions with conversations on administrative, ambulatory, bone marrow transplantation, new practitioner, and pediatrics topics.

President Michael Vozniak, PharmD BCOP, delivered exciting highlights from the year during his member address: the launch of the HOPA Central online discussion group, the possibility of becoming the primary professional development provider for BCOP Recertification, and the success of the 2nd Annual Oncology Pharmacy Practice Management Program. Dr. Vozniak announced the launch of HOPA's Fellow Program, which will further advance oncology pharmacy as a profession. HOPA also made great progress as an organization through our health policy work. These developments are just a portion of the efforts HOPA has undertaken to continue to serve our mission: to support pharmacy practitioners and promote and advance hematology/

oncology pharmacy to optimize the care of individuals affected by cancer. HOPA was pleased to acknowledge the contributions of board members who worked diligently throughout their time in office and whose terms came to a close:

- Niesha Griffith, Past President
- Daisy Yang, Secretary
- George Carro, At-Large Member
- Michelle Rockey, At-Large Member.

Once again, thank you all for your leadership, service, and commitment to HOPA.

Dr. Vozniak's term as president also came to a close, and he welcomed our new president, Scott Soefje, PharmD MBA BCOP FCCP. Dr. Soefje's career is filled with numerous milestones and contributions to the field of hematology/oncology pharmacy, and we are thrilled to welcome him as the leader of HOPA. As the board members mentioned above completed their leadership service to the organization, HOPA is delighted to welcome several new board members.

**2015–2016 HOPA Board of Directors**

- President, Scott Soefje
- Past President, Michael Vozniak
- President-Elect, Sarah Scarpace
- Secretary, Helen Marshall
- Treasurer, Jolynn Sessions
- At-Large Member, David DeRemer
- At-Large Member, Jill Rhodes
- At-Large Member, Ryan Bookout
- At-Large Member, Heidi Finnes

We thank you in advance for your willingness to continue driving HOPA's success and future direction!

With a strategic plan that will carry HOPA through 2020 and a variety of new developments in the works, we are confident that HOPA will continue to advance the field of hematology/oncology pharmacy and will serve our members to ensure that their investment is a worthy one.

Thank you to all who attended HOPA's 11th Annual Conference. We look forward to HOPA's 12th Annual Conference March 16–19, 2016, in Atlanta, GA, and hope to see you there!

# New Drugs and Drug Updates: Changes in Labeling, Indications, and Dosage Forms (January 1, 2015–February 28, 2015)

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## Busulfex® (Busulfan)

On January 16, the U.S. Food and Drug Administration (FDA) approved changes in the labeling. Additions were made to the Patient Counseling section, and the chemical structure was added to one of the sections in the label.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/020954Orig1s014ltr.pdf

## Zytiga® (Abiraterone Acetate)

On January 23, the FDA approved changes in labeling. New data from a drug-drug interaction trial were added to the sections on drug interactions and pharmacokinetics.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/202379Orig1s015ltr.pdf

## Afinitor® (Everolimus)

On January 23, the FDA approved several changes in labeling. The addition of a warning on the risk for angioedema when used in combination with angiotensin-converting enzyme inhibitors was added to the Warnings and Precautions, Adverse Reactions, Drug Interactions, and Patient Counseling sections. In addition, gingivitis and ovarian cyst were added to the Adverse Reactions section. The Clinical Pharmacology–Mechanism of Action section was modified, and results from a food-effect study were added to the Pharmacokinetics section for the Afinitor Disperz® formulation.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/022334Orig1s029ltr.pdf

## Tasigna® (Nilotinib Hydrochloride Monohydrate)

On January 27, the FDA approved an addition to the labeling. The results from a 60-month follow-up of the CAMN107A2303 (ENESTnd) study, "A phase 3 multicenter, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)" were included in the new version of the labeling.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/022068Orig1s020ltr.pdf

## Imbruvica® (Ibrutinib)

On January 29, the FDA approved the new indication of treatment of Waldenström's macroglobulinemia to the labeling. In addition, the FDA requested a postmarketing study be conducted to evaluate potential dose reductions (with the subsequent addition of additional capsule strengths, if needed) in patients with moderate hepatic impairment, for whom ibrutinib treatment is not currently recommended.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/205552Orig1s002ltr.pdf

## Gleevec® (Imatinib Mesylate)

On January 30, the FDA approved the inclusion of clinical data from a 60-month follow-up of the CAMN107A2023 study, "A phase 3 multicenter, open-label, randomized study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)" to the product labeling.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/021588Orig1s042ltr.pdf

## Elitek® (Rasburicase)

On February 3, the FDA approved a change in the labeling involving the diluent used in the 1.5-mg and 7.5-mg vials.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/103946Orig1s5094ltr.pdf

## Imbrance® (Palbociclib)

On February 3, the FDA granted approval of the new drug, palbociclib. It is approved for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. For more detailed information on this new drug, please see the article "Drug Update: Palbociclib" on page 28 of this newsletter.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207103Orig1s000ltr.pdf

## Zoladex® (Goserelin Acetate)

On February 12, the FDA approved an update to the labeling. The risk of injury at the site of injection (hematoma, hemorrhage, and vascular injury) is now listed in the Dosage and Administration, Warnings and Precautions, and Patient Counseling Information sections of the label.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/019726Orig1s059,020578Orig1s037ltr.pdf

## Lenvima® (Lenvatinib Mesylate)

On February 13, the FDA granted approval of the new drug, lenvatinib. It is approved for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. For more detailed information on this new drug, please see the article "Drug Update: Lenvatinib" on page 20 in this issue of the newsletter.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/206947Orig1s000ltr.pdf

## Revlimid® (Lenalidomide)

On February 17, the FDA approved an expanded indication of use in combination with dexamethasone for the treatment of patients with multiple myeloma.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/021880Orig1s041ltr.pdf

## Farydak® (Panobinostat)

On February 23, the FDA granted approval of the new drug, panobinostat, when used in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. For more detailed information on this new drug, please see the article "Drug Update: Panobinostat," which will be included in the next issue of this newsletter.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/205353Orig1s000ltr.pdf

## Cisplatin

On February 26, the FDA approved revised labeling for this agent. References to the pharmacogenomic implications (increased risk of ototoxicity) of utilizing this agent in patients with a certain variant of the thiopurine S-methyltransferase (TPMT) gene have been removed from all sections of the labeling. A statement has been added stating that genetic factors such as a variant TPMT gene *may* contribute to the ototoxicity of cisplatin, although this association has not been consistent across populations and study designs.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/018057Orig1s083ltr.pdf

## Torisel® (Temsirolimus)

On February 26, the FDA approved a revision to the labeling. Pancreatitis, cholecystitis, and cholelithiasis have been added to the Postmarketing and Other Clinical Experience section of the product labeling.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/022088Orig1s018ltr.pdf

## Casodex® (Bicalutamide)

On February 27, the FDA approved the addition of updated information on photosensitivity in the Adverse Reactions and Patient Counseling Information sections of the product labeling.
www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/020498Orig1s025ltr.pdf

## Blinatumomab (Blincyto®)

**Class:** Bispecific T-cell engaging (BiTE) antibody
**Indication:** Relapsed or refractory Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia
**Dose:** Cycle 1 (weight 45 kg or greater): 9 mcg/day continuous IV infusion on days 1 through 7 and 28 mcg/day continuous IV infusion on days 8 through 28; 4 weeks continuous IV infusion followed by at least 2 weeks of no treatment
**Subsequent cycles (weight 45 kg or greater):** 28 mcg/day continuous IV infusion on days 1 through 28 followed by at least 2 weeks of no treatment; up to two cycles for induction followed by three additional cycles for consolidation (up to a total of five cycles)
**Dose modifications:** Interrupt therapy for the following toxicities: grade 3 cytokine-release syndrome (CRS), grade 3 neurotoxicity, or clinically relevant grade 3 adverse reaction. Therapy should be permanently discontinued for grade 4 CRS or if more than one seizure occurs, and consider permanent discontinuation with other clinically relevant grade 4 adverse reactions.
**Common adverse effects:** Pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation
**Serious adverse effects:** CRS, hypersensitivity reaction, encephalopathy, leukoencephalopathy, headache, neurotoxicity, tremor, pneumonia, serious infectious disease, sepsis, tumor lysis syndrome
**Drug interactions:** Blinatumomab causes a transient release of cytokines that may suppress CYP450 enzymes. No formal drug-drug interactions studies have been conducted but it is important to note that the highest drug-drug interaction risk is during the first 9 days of cycle 1 and the first 2 days of cycle 2 in patients who are receiving concomitant CYP450 substrates with narrow therapeutic indices. Monitor for toxicity or drug concentrations if able and adjust the dose of the concomitant medication as needed.

## Blinatumomab: A Novel, Bispecific T-Cell Engaging (BiTE) Antibody

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Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic malignancy with an age-adjusted incidence rate of 1.7 per 100,000 males and 1.2 per 100,000 females in the United States. In 2015 there will be an estimated 6,250 new cases and 1,450 deaths with a slight predilection toward males.[1] It has a bimodal distribution with the first peak between ages 4 and 10, and the second after age 50.[2] ALL is considered to be primarily a pediatric malignancy, with the median age at diagnosis being 14 years. In adults, ALL comprises 20% of all leukemias diagnosed. Approximately 24% of patients are diagnosed at 45 years or older, and 11% at 65 years or older.[3-5]

The conventional treatment of patients with Philadelphia chromosome (Ph)-negative B-ALL consists of several rounds of chemotherapy requiring 2–3 years to complete. Complete remission (CR) is the initial goal of therapy with rates ranging from 85% to 95% and treatment-related mortality occurring in 5% to 10% of patients. Unfortunately, responses are not maintained long term, with patients experiencing a fairly high rate of relapse. Patients who relapse may undergo allogeneic hematopoietic stem cell transplant (alloHSCT) as a method to improve long-term outcomes, with some patients relapsing after this intense procedure.[2-6] Despite all the advances thus far in diagnosis, classification, and treatment of ALL, improved therapies are needed. The U.S. Food and Drug Administration (FDA) approved blinatumomab (Blincyto®) via an accelerated pathway for the treatment of adult Ph-negative relapsed or refractory B-cell precursor ALL on December 3, 2014.[7] This is a first step in utilizing immunotherapy to improve outcomes in patients with relapsed/refractory B-ALL.

Pediatric experience with blinatumomab is limited; however, pharmacokinetic data from the first phase 1 study of blinatumomab in children indicate similar serum concentrations to those achieved in adults with attainment of steady state concentration within 48 hours of continuous infusion. This trial was a phase 1–2 multicenter study to identify, in the phase 1 portion, the optimal dose of blinatumomab in pediatric patients younger than 18 years old with relapsed/refractory B-cell ALL. In the ongoing phase 1 part of this study, a dose of 15 mcg/m$^2$/day was established as the maximum tolerated dose. Cytokine-release syndrome (CRS) was the dose-limiting toxicity. To reduce the risk of CRS, a dose of 5 mcg/m$^2$/day for 7 days escalating to 15 mcg/m$^2$/day for the remainder of the first cycle (21 days) and all following cycles was determined to be the recommended dosing strategy for future studies. This dose escalation approach has been successful in ameliorating severe CRS to date and is the same strategy employed in adults.[8]

Single-agent activity of blinatumomab in adults with precursor B-ALL was reported in two phase 2 clinical trials with impressive results. One phase 2, open-label, multicenter, single-arm study included 21 adult patients with precursor B-cell ALL in complete hematologic remission (CRh) and were either molecularly refractory or had a molecular relapse. Each patient was treated with blinatumomab 15 mcg/m$^2$/day by continuous infusion daily for 4 weeks followed by a treatment-free period of 2 weeks. Sixteen of 21 patients became minimal residual disease (MRD) negative after one cycle of treatment, resulting in a response rate of 80%. With a median follow-up of 15 months, the 1-year probability of relapse-free survival was 78%.[9]

An international phase 2, multicenter, open-label, single-arm trial of 189 patients with Ph-negative, relapsed or refractory pre-B-ALL was completed to further evaluate the use of blinatumomab. Specific key inclusion criteria encompass adults who were primary refractory after induction or who had relapsed within 12 months of first remission, relapsed within 12 months of receiving alloHSCT, or not responded to or relapsed after first salvage therapy or beyond. Historically, these patients have an estimated median overall survival of 5–9 months. To reduce the incidence of severe CRS, prephase treatment with dexamethasone 10–24 mg/m$^2$/day (for up to 5 days) was administered to patients with bone marrow blasts more than 50%, peripheral blood blasts of 15,000 cells per µL or higher, or elevated lactate dehydrogenase suggesting rapidly progressing disease per investigator opinion. Patients received blinatumomab as continuous intravenous infusion with a portable pump at a target dose of 28 mcg/day in 4-week cycles, followed by 2 treatment-free weeks. During cycle one, dosing was stepwise, as established in the previous phase 2 dose-finding study, with 9 mcg/day for 1 week, then 28 mcg/day for 3 weeks to reduce the risk of CRS. Dexamethasone 20 mg premedication was administered within 1 hour before treatment initiation in each cycle and before the increased dose in cycle one to minimize infusion reactions to blinatumomab. Patients who achieved CR or CRh within the first two cycles could receive up to three additional cycles. Disease was assessed by bone-marrow biopsy at baseline, the end of each cycle, and during follow-up. After two cycles, 81 patients (43%, 95% confidence interval [CI]: 36–50) had achieved the primary endpoint of CR (63 patients, 33%) or CRh (18 patients, 10%). No response effect was noted in the multivariate analysis when controlling for bone marrow blast count and lactate dehydrogenase at baseline in week 1, prephase dexamethasone treatment, or dexamethasone administration before baseline bone marrow biopsy. After a median follow-up time of 8.9 months, 37 (45%) of the 82 patients who had achieved CR or CRh during the core study period were still alive and in remission. The remaining 45 patients had either relapsed (37 patients) or died without documented relapse (seven patients, six of whom died after alloHSCT; one patient without alloHSCT died of infection). One patient relapsed during cycle one of blinatumomab therapy and five patients relapsed during cycle two. The median relapse-free survival was found to be 5.9 months (95% CI: 4.8–8.3) for the 82 patients in CR or CRh, 6.9 months (95% CI: 4.2–10.1) for patients in CR, and 5.0 months (95% CI: 1.4–6.2) for those in CRh, with a median follow-up of 8.9 months (interquartile range 4.6–11.1). Median overall survival was 6.1 months (95% CI: 4.2–7.5) for all 189 patients, with a median follow-up of 9.8 months. Overall, this trial described impressive clinical activity with high MRD response, even in heavily pretreated patients.[10]

In the 2011 study by Topp and colleagues, 81% of patients developed grade 3 or 4 adverse events. The most common grade 3 and 4 adverse event was lymphopenia (33%). The most common adverse events regardless of grade were pyrexia, chills, hypogammaglobulinemia, and hypokalemia. The majority of adverse events were transient. In the first cycle, only one patient had to permanently discontinue treatment because of a grade 3 seizure, which was fully reversible within 1 day after stopping the infusion. Another patient had syncope with convulsion. There were no blinatumomab-related deaths. A median number of three treatment cycles and a total of 59.5 cycles were administered in 20 patients. There was not an increased incidence in adverse events in subsequent cycles.[9]

In 189 patients treated on study, all but one patient (99%) experienced an adverse event of any grade, mostly pyrexia (113 [60%] patients), headache (65 [34%]), febrile neutropenia (53 [28%]), peripheral edema (49 [26%]), nausea (46 [24%]), hypokalemia (45 [24%]), constipation (39 [21%]), and anemia (38 [20%]). Grade 3 and 4 adverse events were reported in 71 (38%) and 56 (30%) patients, respectively. The most frequent grade 3 or 4 adverse events were febrile neutropenia (25%), neutropenia (16%), and anemia (14%). Twenty-three (12%) patients had fatal adverse events, mainly infection. Neurologic events occurred in 98 (52%) patients. These events were mostly grade 1 or 2 in severity (74 [76%] of 98), occurring mostly during cycle one (85 [87%] of 98), and were typically managed with dexamethasone without infusion interruption. Serious central nervous system toxicity occurring in this trial was encephalopathy (3%) and ataxia (2%).[10]

In the clinical trial, three patients (2%) experienced grade 3 CRS. Two of the patients achieved CR or CRh, including one patient who had temporary treatment interruption. The third patient died from disease progression.[10] According to the prescribing information, if a patient presents with grade 3 CRS, blinatumomab should be withheld until resolved, then restarted at 9 mcg/day and escalated to 28 mcg/day after 7 days if the toxicity does not recur. For grade 3 neurotoxicity, treatment should be withheld until grade 1 or less for at least 3 days; restart at 9 mcg/day for 7 days, then increase to 28 mcg/day if toxicity has not recurred. If toxicity occurred at a dose of 9 mcg/day or does not resolve in 7 days or less, permanently discontinue treatment. If treatment interruption is 7 days or less, continue the same cycle to a total of 28 days, including the days before and after the interruption. If treatment interruption is longer than 7 days, start a new cycle. For clinically relevant grade 3 adverse reactions, blinatumomab should be withheld until it is no more than a grade 1 reaction, then resumed at 9 mcg/day and escalated to 28 mcg/day after 7 days if the toxicity does not recur. If it takes longer than 14 days to resolve, blinatumomab should be permanently discontinued. Therapy should also be permanently discontinued for grade 4 CRS, if more than one seizure occurs or for other grade 4 neurologic toxicity, or other clinically relevant grade 4 adverse reactions.[11]

Corticosteroids may control the toxicities associated with CRS; however, their ability to block T-cell activation and diminish clinical benefit is of concern despite the analysis on steroid use in the clinical trial showing no effect. Further studies on the specifics of T-cell proliferation and immune activation that result from treatment with blinatumomab are identifying potentially more targeted management strategies to improve control without decreasing efficacy.[12] In patients who develop CRS, IL-10, IL-6, and INF-Γ are the most highly elevated cytokines. These cytokines also are increased in patients who develop hemophagocytic lymphohistiocytosis (HLH), which also is known as macrophage activation syndrome (MAS). It is hypothesized that

blinatumomab-associated CRS may be induced by HLH/MAS.[13] It is important to note that the degree of elevation may not correlate with the severity of CRS or a patient's response to treatment. CRS management is difficult because some amount of cytokine release is a required component of T-cell activation and therefore efficacy. Corticosteroids are an obvious treatment option for the management of CRS due to their activity in known disorders with activated T cells.[12] To avoid utilizing corticosteroids or minimizing the amount required, tocilizumab, which is an IL-6 receptor antagonist, has been used to treat this toxicity without impairing the T cell–mediated antitumor activity. When utilized in patients, tocilizumab resulted in rapid, dramatic reversal of life-threatening CRS that developed after receiving blinatumomab.[12] It is possible that blinatumomab-induced T-cell proliferation and effector function are maintained after tocilizumab treatment, yet it also is conceivable that blinatumomab activity could be compromised.[13] Improvements in CRS management are needed through more research evaluating the safety and efficacy of potential treatment options as well as their impact on blinatumomab efficacy.

The pharmacodynamic effects of blinatumomab are interesting. Within the first few hours after administration, there is a rapid transient decrease in T cells, followed by an accelerated increase in T cells exceeding baseline values. The initial fall in T cells is attributed to a redistribution phenomenon thought to be caused by an increased adhesion of T cells to the endothelium of the blood vessels, triggered by monovalent binding of blinatumomab to CD3. Following the nadir, T cells expand, likely due to stimulation by subsequent cytokine release. B cells rapidly decrease in less than a day, are below the limit of detection in less than 2 days, and remain undetectable for the duration of the blinatumomab infusion. This latter phenomenon is attributed to B-cell apoptosis. The low dose of blinatumomab needed for response (compared with conventional antibodies) is likely related to the high lytic potential of cytotoxic T cells. These T cells are activated by engagement of only a few CD3 receptor subunits, can rapidly adopt a serial lysis mode, and can proliferate at the site of their activation.[14]

Due to the relatively short half-life (about 2 hours) and mechanism of action, blinatumomab is administered as a continuous IV infusion over a minimum of 4 weeks. The specific BiTE mechanism of action relies on a continued search-and-destroy mode of locating the engaged T cells. When administered in this continuous infusion fashion, drug levels achieved are sustained, predictable, and show dose linearity. A phase 1 trial, designated MT103–104, investigated the safety and benefit/risk profile of continuous infusion administration of blinatumomab over a period of 4 or 8 weeks in non-Hodgkin's lymphoma (NHL) patients. Pharmacokinetic analyses confirmed that continuous infusion led to a sustained presence of blinatumomab in serum at highly predictable drug levels over the entire infusion period and showed dose linearity. Ever since, all future trials with blinatumomab used administration by continuous infusion for a minimum of 4 weeks. The starting dose of study MT103–104 in patients with B-NHL was as low as 0.5 mcg/m$^2$ per day and maximally reached a starting dose of 90 mcg/m$^2$ per day, exceeding the maximum tolerated dose set at the beginning of the trial.[15]

Blinatumomab treatment is complex, requiring glucocorticoids to be given at the start of treatment to mitigate first-dose reactions. Although the infusion is administered over several weeks, it can be managed in the outpatient setting via an implanted port and minipump system. In clinical trials, patients were monitored as inpatients for 3–7 days at the start of each course to observe for infusion reactions. Patients were then discharged to have several infusion changes performed by a home care provider or practitioner or at the respective cancer center. The prescribing information recommends patients initiating therapy be admitted for the first 9 days of the first cycle and the first 2 days of the second cycle.[13] The method of continuous infusion is an accepted method of administration, but the complexity of multiple bag changes and required duration are new challenges with this treatment. The ability to be at home for treatment favorably compares to polychemotherapy given to long-term hospitalized patients. This is a treatment plan that should be thoroughly discussed by the healthcare provider, patient, and caregiver due to the complex administration procedures and treatment risks.

The Institute for Safe Medication Practices released a notice in February 2015 regarding issues with the complex mixing instructions of blinatumomab due to a need for 24- versus 48-hour bags and the possible inability to safely prepare different doses. In addition to making different bags, an IV solution stabilizer is used to coat the prefilled IV bag prior to addition of reconstituted blinatumomab to prevent adhesion to the bag and tubing.[11] Errors in compounding instructions have been noted by electronic health record users with printed dispense labels not accounting for overfill, and difficulty created by the inability to purchase the stabilizer independently. Several places are only preparing 24-hour infusions to prevent confusion with different bags that require an additional stabilizer. There also is the potential that the stabilizer will be inadvertently used for mixing the product, whereas the intent of the stabilizer is to prevent adhesion to the bag and tubing prior to adding blinatumomab.

Blinatumomab has a risk evaluation and mitigation strategy (REMS) program associated with it. The goal of the REMS program is to mitigate the risk of CRS, which may be life-threatening or fatal; the risk of neurological toxicities, which may be severe, life-threatening, or fatal, and the risk of preparation and administration errors associated with use of blinatumomab. Amgen will send a REMS Letter for Healthcare Providers, REMS Letter for Hospital and Home Healthcare Pharmacists, and REMS Letter for Professional Societies within 30 days of the REMS approval date and every 6 months for a total of 18 months.[11]

The excitement over this treatment breakthrough has been somewhat tempered by concerns over cost. The recently FDA-approved immunotherapy agents typically cost more than $100,000 and this is nothing new to that group.[16] It is predicted that blinatumomab will cost approximately $89,000 per cycle with patients in clinical trials receiving a median of 2 to 3 cycles.[17] In addition to the medication cost, it is important to consider the complex administration and coordination costs required for 28 days of continuous infusion with several infusion exchanges due to the medication's short stability. In comparison, the median cost for an alloHSCT for ALL within the first 100 days is approximately $102,574 and $128,800 in the first year.[18]

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## Lanreotide (Somatuline® Depot)

**Class:** Somatostatin analog, endocrine-metabolic agent
**Indication:** Unresectable gastroenteropancreatic neuroendocrine tumors that are well-differentiated or moderately differentiated and locally advanced or metastatic
**Dose:** 120 mg deep subcutaneous injection every 4 weeks
**Dose modifications:** No dose adjustments are necessary for patients with mild or moderate renal impairment. There are insufficient data to recommend a dose for patients with severe renal impairment. No recommendations are provided, and there are insufficient data to recommend a dose for patients with hepatic impairment who are being treated for gastroenteropancreatic neuroendocrine tumors. No dose adjustment is necessary for geriatric patients.
**Common adverse effects:** Bradycardia, hypertension, injection-site reaction, abdominal pain, diarrhea, nausea, vomiting, musculoskeletal pain, dizziness, headache, and anemia
**Serious adverse effects:** Bradyarrhythmia, diabetes mellitus, hyperglycemia, hypoglycemia, hypothyroidism, cholelithiasis, pancreatitis, anaphylaxis, depression, antibody development, and pancreatitis
**Drug interactions:** Lanreotide may enhance the hypoglycemic effect of blood glucose lowering agents, and dose adjustments may be required. When lanreotide is given with bradycardia-inducing medications, the reduction of heart rate may be increased. It may decrease the relative bioavailability of cyclosporine. Lanreotide may increase the serum concentration of bromocriptine and may also delay bromocriptine absorption and time to maximum plasma concentration. It also can increase the plasma concentrations of quinidine and terfenadine.
**Monitoring parameters:** Progression-free survival may be indicative of efficacy in gastroenteropancreatic neuroendocrine tumors. Blood glucose levels should be measured at the initiation of treatment and following dose adjustments. In thyroid stimulating hormone (TSH)-secreting adenomas, plasma TSH, free T4, free T3, and lanreotide levels should be monitored periodically. Thyroid function should be monitored when clinically indicated. Heart rate and gall bladder ultrasonography should be noted prior to initiation and periodically during therapy.

## Lanreotide (Somatuline® Depot) Now Approved for Metastatic Gastroenteropancreatic Neuroendocrine Tumors

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Neuroendocrine tumors are a form of cancer that can arise from neuroendocrine cells found throughout the body. However, more than 50% of these neoplasms originate in the gastrointestinal system or pancreas, with the majority of patients presenting with distant metastases at diagnosis.[1] Overall, these are considered a rare form of cancer with an annual incidence of five cases per 100,000 people in the United States.[2] Patients presenting with advanced pancreatic neuroendocrine tumors usually have unresectable disease, and depending on the stability of disease, tumor burden, and presence of symptoms, providers may recommend observation or several different treatment options. For advanced neuroendocrine tumors, few pharmacologic treatments have been approved on the basis of their efficacy in inhibiting tumor growth.[1] Current National Comprehensive Cancer Network (NCCN) guidelines state that systemic therapy options include somatostatin analogs (octreotide or lanreotide), biologically targeted agents (everolimus or sunitinib), or cytotoxic chemotherapy.[3]

Evidence suggests that somatostatin analogs are effective in treating symptoms associated with hormone hypersecretion and have a favorable safety profile, although data supporting their use for antiproliferation are limited. The CLARINET trial was the first large, randomized, double-blind trial to evaluate the use of lanreotide, a somatostatin analog, for patients with enteropancreatic neuroendocrine tumors.[1]

Lanreotide (Somatuline Depot) received U.S. Food and Drug Administration approval on December 16, 2014, based on improved progression-free survival (PFS) in patients with unresectable, well or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).[4] The approval was granted because of the results of the CLARINET trial, a 96-week, multicenter, international, randomized, double-blind, parallel-group, placebo-controlled study. In this phase 3 trial, Caplin and colleagues assessed the safety and efficacy of lanreotide compared with placebo in 204 patients. Patients 18 years and older with sporadic neuroendocrine tumors that were well differentiated or moderately differentiated and measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) were eligible for study. The tumors were required to have a centrally assessed proliferation index of less than 10%; be located in the pancreas, midgut, hindgut, or of unknown origin; and be nonfunctioning (except for gastrinomas that had been adequately controlled by means of proton pump inhibitors). Exclusion criteria included patients who (a) received treatment with interferon, chemoembolization, or chemotherapy within 6 months before entering the study; (b) received a radionuclide at any time; (c) had major surgery related to the neuroendocrine tumor within 3 months before entering the study; (d) had multiple endocrine neoplasia; (e) had previous cancer; and (f) had baseline abnormalities or medical conditions that could interfere with the study or threaten a patient's safety.[1]

Eligible patients were randomized in a 1:1 ratio to receive either an extended-release aqueous-gel formulation of lanreotide (120 mg) or placebo (sodium chloride) via a deep subcutaneous injection every 28 days. Patients were withdrawn from the study for the following reasons: evidence of tumor progression according to RECIST criteria by central review of an imaging scan from a study visit or from

unscheduled imaging prompted by biologic or clinical signs of disease progression, investigator's judgment, patient's request, or an adverse event that could compromise the patient's safety. Patients were allowed to crossover from the placebo group to the lanreotide group following disease progression. The primary endpoint was PFS, and secondary endpoints included the proportion of patients who were alive without disease progression at 48 and 96 weeks, the time to tumor progression, overall survival (OS), quality of life, level of chromogranin A, pharmacokinetic data, and safety. Baseline characteristics were generally well matched in the study groups. Of the 204 patients randomized, approximately half were male, the median age was 63 years, and 16% in each arm had received prior treatment.[1]

The study was conducted between June 2006 and April 2013. Fifty-eight patients in the placebo group had centrally assessed disease-progression events compared with 30 patients in the lanreotide group. PFS was significantly improved in the lanreotide group compared with the placebo group in the primary analysis (median PFS not reached versus 18.0 months, $p < .001$; hazard ratio for progression or death 0.47; 95% confidence interval [CI]: 0.30–0.73). At 24 months the estimated rates of PFS were 65.1% in the lanreotide group and 33.0% (95% CI: 23.0–43.3) in the placebo group.[1]

The number of patients alive without disease progression was significantly greater in the lanreotide group at both 48 weeks (66% versus 49%; $p < .05$) and 96 weeks (52% versus 25%; $p < .001$). In addition, the time to tumor progression was statistically significantly improved, with a median time of not reached in the lanreotide group versus a median time of 18 months in the placebo group ($p < .001$). OS was not significantly different between the study groups, although this was complicated by crossover of patients from placebo to lanreotide treatment. Quality of life also was not significantly different between the two groups. The odds ratio of patients experiencing > 50% reduction in the level of chromogranin A from baseline significantly favored lanreotide over placebo (42% versus 5%; $p < .001$). Pharmacokinetic data showed that serum lanreotide levels reached steady-state concentrations after 24 weeks (six injections) and were maintained thereafter.[1]

Comparable amounts of patients in the two groups experienced adverse events; 88% in the lanreotide group and 90% in the placebo group. The most common adverse reactions among both treatment arms were diarrhea (26% versus 9%), abdominal pain (14% versus 2%), and cholelithiasis (10% versus 3%). Most of the adverse events in both arms were either mild or moderate in intensity (17% and approximately 44%, respectively). However, serious adverse events occurred in both of the treatment arms (26% in the lanreotide group and 31% in the placebo group), but only 3% of these in the lanreotide group and 1% in the placebo group were determined to be related to study treatment. Fifty percent of the patients in the lanreotide group experienced adverse events related to the study drug versus 28% in the placebo group. Other adverse events that were study drug–related included hyperglycemia (5%) and cholelithiasis (10%). A total of six patients withdrew from the study because of adverse events, with only one considered by the investigator to be related to the use of lanreotide.[1]

For patients being treated for gastroenteropancreatic neuroendocrine tumors (GEP-NETs) with mild or moderate renal impairment, no dose adjustment is recommended. Information and data are lacking to recommend a different or specific dose for patients with severe renal impairment or hepatic impairment of any severity in this patient population.[5]

Following an injection of lanreotide, a drug depot is formed leading to passive diffusion of precipitated medication into surrounding tissues, followed by absorption into the bloodstream. Lanreotide is composed of a slow-release (microsphere) formulation and is released in two phases. Initially it is released in a relatively large amount from the surface of the microspheres to facilitate a rapid increase in plasma levels, followed by slower liberation via enzymatic breakdown of the copolymer.[5]

Lanreotide may enhance the glucose-lowering effect of hypoglycemic agents; therefore, close monitoring is recommended. Similar to somatostatin, lanreotide inhibits the release of insulin and glucagon. Blood glucose levels should be monitored at treatment initiation or dose modification. Antidiabetic treatment should be initiated or altered based on blood glucose results. Lanreotide may decrease the relative bioavailability of cyclosporine, requiring close monitoring of serum cyclosporine concentrations when patients concurrently receive a somatostatin analog. Cyclosporine dose adjustments may be required to maintain therapeutic levels. The administration of lanreotide with bradycardia-inducing medications (e.g., beta blockers) may compound the reduction of heart rate seen with lanreotide, potentially requiring dose adjustments of concomitant medications. Lanreotide may decrease the metabolic clearance of compounds that are known to be metabolized by cytochrome P450 enzymes. Because it cannot be excluded that lanreotide may have this effect, medications mainly metabolized by CYP3A4 with a low therapeutic index (e.g., quinidine, terfenadine) should be used with caution when administered with lanreotide. Dose reductions of medications metabolized by the liver may be necessary because these other drugs may be metabolized more slowly in the presence of lanreotide.[5-7]

Patients should be advised to report symptoms of cholethiliasis, such as middle-upper abdominal pain, nausea and vomiting, fever, and jaundice. Other adverse events to report include weakness, syncope, fatigue, or other symptoms of clinically significant bradycardia. Diabetic patients also report fluctuating or worsening glycemic control. Additional notable side effects include diarrhea, nausea, injection-site reactions, musculoskeletal pain, vomiting, and headaches.[5-7]

For the treatment of GEP-NETs, the recommended dose of lanreotide is 120 mg administered by deep subcutaneous injection every 4 weeks. Lanreotide is supplied in strengths of 60 mg/0.2 ml, 90 mg/0.3 ml, and 120 mg/0.5 ml in a single, sterile, prefilled, ready-to-use, polypropylene syringe fitted with an automatic needle guard and a 20-mm needle covered by a low-density polyethylene sheath. Lanreotide must be stored in a refrigerator at 2 °C to 8 °C (36 °F to 46 °F) and protected from light in its original package. It should be removed from the refrigerator and taken out of the box 30 minutes prior to injection to allow it to

warm to room temperature. The pouch containing the syringe must be kept sealed until immediately prior to injection.[5]

Octreotide and lanreotide, both somatostatin analogs, possess antiproliferative effects on neuroendocrine tumors. Based on the results of the CLARINET trial, lanreotide is supported by the NCCN treatment guidelines as a systemic treatment option for unresectable and metastatic neuroendocrine tumors of the gastrointestinal tract and unresectable and metastatic pancreatic neuroendocrine tumors.[1,3]

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## Lenvatinib (Lenvima™)

**Class:** Tyrosine kinase inhibitor; vascular endothelial growth factor (VEGF) inhibitor
**Indication:** Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer
**Dose:** 24 mg orally once daily; administered with or without food
**Dose modifications:** Interrupt therapy for the following toxicities: grade 3 hypertension; grade 3 cardiac dysfunction or hemorrhage; grade 3 or 4 renal failure, impairment, or hepatotoxicity; proteinuria of ≥ 2 grams/24 hours; grade 3 or 4 QT interval prolongation, or reversible posterior leukoencephalopathy syndrome (RPLS). Therapy should be permanently discontinued for life-threatening hypertension, arterial thrombotic event, hepatic failure, nephrotic syndrome, gastrointestinal perforation or life-threatening fistula, or severe or persistent neurologic symptoms.
**Common adverse effects:** Hypertension, peripheral edema, fatigue, headache, increased thyroid stimulating hormone level, weight loss, hemorrhage, gastrointestinal (GI) effects, proteinuria, arthralgia, myalgia
**Serious adverse effects:** Increased risk of hypertension, GI perforation or fistula, GI toxicity, hemorrhage, hepatotoxicity, hypocalcemia, palmar-plantar erythrodysesthesia, renal toxicity, RPLS, thromboembolic events
**Drug interactions:** Avoid combining with agents known to prolong the QT interval, ivabradine, and mifepristone.

## Lenvatinib for Radioiodine-Refractory Differentiated Thyroid Cancer

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The 5-year survival rate for newly diagnosed thyroid cancer is 97.8%.[1] This is because of the availability of effective therapy in the form of radioactive iodine, along with the fact that 68% and 26% of patients are diagnosed with localized and regional disease, respectively. In contrast to the remarkable overall survival rate, patients with radioiodine-refractory differentiated thyroid cancer have a 10-year survival rate of 10%. Treatment options had been limited until the recent development of targeted therapies. Molecular pathways, including but not limited to VEGF, BRAF, NRAS, and HRAS have been explored as potential targets for treatment of iodine-refractory thyroid cancer. Prior to the approval of lenvatinib, sorafenib was the only oral tyrosine kinase inhibitor with a U.S. Food and Drug Administration (FDA)-approved indication for thyroid cancer.

Lenvatinib (Lenvima™, Eisai) is an oral, multitargeted tyrosine kinase inhibitor of VEGF receptors 1, 2, and 3, along with fibroblast growth factor receptors (FGFR) 1–4, platelet-derived growth factor receptor A (PDGFR), RET, and KIT signaling pathways. The approval of lenvatinib came 2 months ahead of schedule after a priority review by the FDA. The approval was based on results of the SELECT trial, a phase 3, randomized, double-blind, multicenter study.[2] Patients in this study were randomized 2:1 to receive lenvatinib at a daily dose of 24 mg or placebo. The primary end point was progression-free survival, and secondary end points were response rate and overall survival. Median progression-free survival was 18.3 months in the lenvatinib arm and 3.6 months in the placebo arm (hazard ratio [HR] = 0.14–0.31).

The most common adverse events of any grade included hypertension (69%), diarrhea (59%), fatigue or asthenia (59%), decreased appetite (50%), decreased weight (46%), nausea (41%), stomatitis (36%), palmar-plantar erythrodysesthesia (32%), proteinuria (31%), vomiting (28%), headache (28%), dysphonia (24%), arthralgia (18%), dysgeusia (17%), rash (16%), constipation (15%), myalgia (15%), dry mouth (14%), abdominal pain (12%), peripheral edema (11%), alopecia (11%), and dyspepsia (10%). Serious adverse effects included cardiac failure, arterial thromboembolic events, hepatotoxicity, renal failure and impairment, gastrointestinal perforation or fistula formation, QT prolongation, hypocalcemia, reversible leukoencephalopathy syndrome, hemorrhage, fetal toxicity, and impairing suppression of the production of thyroid-stimulating hormone.

Lenvatinib has been shown to cause fetal harm when administered to pregnant rats and rabbits. Animal studies demonstrated dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal skeletal anomalies. Females with reproductive potential should be advised to use effective contraception during treatment and for at least 2 weeks following completion of therapy.

Lenvatinib requires no dose adjustments when administered with CYP3A and p-glycoprotein inhibitors or inducers. Care should be taken when administering lenvatinib with other known QT-prolonging agents. Daily dose is given as two 10-mg capsules and one 4-mg capsule, with or without food. Treatment continues until disease progression or development of unacceptable toxicity. Missed doses can be made up unless the next dose is due within 12 hours. No data are currently available regarding extemporaneous preparations. The success of lenvatinib provides a new option for patients with progressive iodine-refractory differentiated thyroid cancer.

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## Netupitant and Palonosetron (Akynzeo®)

**Class:** Substance P/neurokinin 1 receptor antagonist, selective 5-$HT_3$ receptor antagonist
**Indication:** Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy
**Dose:** One capsule (containing netupitant 300 mg and palonosetron 0.5 mg) by mouth approximately 1 hour prior to initiation of chemotherapy on day 1. This medication is used in combination with a corticosteroid such as dexamethasone.
**Dose modifications:** No dosage adjustment is necessary in mild to moderate renal or hepatic impairment. Avoid use in severe renal impairment or end-stage renal disease. Avoid use in severe hepatic impairment (Child-Pugh score greater than 9).
**Common adverse effects:** Headache, asthenia, fatigue, indigestion, constipation, erythema
**Serious adverse effects:** Serotonin syndrome
**Drug interactions:** Netupitant is extensively metabolized via CYP3A4; palonosetron is metabolized by CYP2D6, CYP3A, and CYP1A2. Avoid use with strong inducers and inhibitors of these isozymes.

# A Fixed Combination of Netupitant and Palonosetron for Chemotherapy-Induced Nausea and Vomiting

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Chemotherapy-induced nausea and vomiting (CINV) involves various molecular pathways. Neurotransmitters involved in the activation of serotonin and neurokinin-1 (NK-1) receptors often are targets of therapeutic interventions. 5-$HT_3$ receptors are found on the terminals of the vagus nerve and centrally in the chemoreceptor trigger zone of the area postrema. Stimulation and release of serotonin from the enterochromaffin cells of the small intestine produce CINV. This leads to the activation of vagal afferent nerves and activation of the vomiting reflex. Acute emesis is dependent on the activation of serotonin and 5-$HT_3$ receptors. Activation of tachykinin family NK-1, found in the central and peripheral nervous systems, has been largely associated with delayed nausea and vomiting.

Highly and moderately emetogenic chemotherapy is known to cause delayed nausea and vomiting in many patients, despite effective treatments. Current guidelines recommend a combination of a 5-$HT_3$ receptor antagonist, dexamethasone, and an NK-1 receptor antagonist as prophylaxis when highly emetogenic chemotherapy is administered. This often is achieved with the use of aprepitant- or fosaprepitant-containing regimens.[1] The novel agent Akynzeo® may prove to be an alternative when used with a corticosteroid. This agent combines netupitant and palonosetron (NEPA). Netupitant (NETU) is a new selective NK-1 receptor antagonist and palonosetron (PALO) is a second-generation 5-$HT_3$ receptor antagonist with a higher affinity for the 5-$HT_3$ receptor when compared with first-generation antagonists.[2] The three trials that led to the recent U.S. Food and Drug Administration (FDA) approval of NEPA are discussed below.

Hesketh and colleagues conducted a phase 2, multicenter, randomized, double-blind, double-dummy, parallel group study at 29 sites. A total of 694 chemotherapy-naïve, solid-tumor patients received chemotherapy that included cisplatin ≥ 50 mg. The study was randomized to five arms: NETU 100 mg, 200 mg, or 300 mg with 0.5 mg of PALO, 0.5 mg PALO alone, and an exploratory arm using aprepitant (125 mg PO day 1, followed by 80 mg PO daily on days 2 and 3) plus ondansetron 32 mg intravenous (IV) given on day 1. A combination of 3 days of oral aprepitant and IV ondansetron 32 mg also was used in the exploratory arm; however, the trial was not designed to directly compare NEPA with the aprepitant-containing regimen. All therapy was given on day 1 and all patients also received oral dexamethasone (DEX) on days 1 through 4. Patients were excluded from the trial if they received a bone marrow or stem cell transplant, moderately or highly emetogenic chemotherapy from days 2 to 5 following chemotherapy, or moderately or highly emetogenic radiotherapy either within 1 week before day 1 or from days 2 to 5. In addition, subjects were excluded if they experienced nausea 24 hours before day 1, had serious cardiovascular disease, or if they had taken CYP3A4 inhibitors or substrates within 1 week or CYP3A4 inducers within 4 weeks of day 1. Patients were not permitted to receive antiemetics or systemic corticosteroids within 24 or 72 hours of day 1, respectively. The primary endpoint of the study was complete response (CR), defined as no emesis or need for rescue medication in a 0 to 120 hour phase. All three NEPA groups had significantly higher CRs compared with PALO alone. The primary endpoint was met in 76.5% of patients in the PALO group. The groups given NEPA with 100 mg, 200 mg, and 300 mg of NETU had 87.4%, 87.6%, and 89.6% CR rates, respectively. CR was reached in 86.6% of the aprepitant and IV ondansetron group.[3] The most common side effects included hiccups and headache, neither of which were dose related.

As a result of the efficacy and safety demonstrated by the 300 mg NEPA combination, Aapro and colleagues conducted a phase 3, multicenter, randomized, double-blind, double-dummy, parallel group study of 1,455 chemotherapy-naïve patients with solid tumors. The primary endpoint was to demonstrate the superiority of NEPA over PALO in preventing CINV in patients receiving doxorubicin or epirubicin in combination with cyclophosphamide (AC)-based moderately emetogenic

chemotherapy (MEC). Patients were to receive one dose of either NEPA (NETU 300 mg/PALO 0.50 mg) plus 12 mg DEX or PALO 0.50 mg plus 20 mg DEX on day 1 only. Patients were excluded if they were scheduled to receive highly emetogenic chemotherapy (HEC). Otherwise, the exclusion criteria used were identical to the criteria used in the study by Hesketh and colleagues. The primary endpoint was met during the delayed phase with a CR rate of 76.9% versus 69.5% ($p$ = .001). CR rates were significantly higher for NEPA compared with PALO during the acute and overall phases as well. The majority of patients in the study were female, and 98% had breast cancer. CR was met in 76.9% of patients in the NEPA group versus 69.5% in the PALO group ($p$ = .001).[4] Side effects were comparable in both arms, with headache and constipation most frequently reported.

Gralla and colleagues conducted a phase 3, multinational, multicenter, randomized, double-blind, double-dummy, parallel group study with a cohort of 413 chemotherapy-naïve patients with malignant tumors. Patients were randomized to a single dose of NEPA and DEX or 3 days of aprepitant in combination with PALO and DEX. NEPA and aprepitant/PALO combinations were administered prior to each multiple cycle of HEC and MEC. The DEX dose and schedule for delayed nausea/vomiting was comparable in both groups. Patients were excluded if they were scheduled to receive AC, had a history or predisposition to cardiac conduction abnormalities, Torsades de pointes, or severe cardiovascular disease. Otherwise, exclusion criteria were similar to Hesketh and colleagues'. The primary endpoint of this study was safety, and it was designed to compare treatment-emergent adverse events (TEAEs). It was not designed to compare the regimens in terms of efficacy and thus, numerical, not statistical differences in efficacy, were reported. In this trial, 76% of patients received MEC and 24% received HEC. The authors reported numerically similar rates of TEAEs between the groups. CR, which was defined as no emesis or need for rescue medication in a 0–120 hour phase after cycle one, was achieved in 81% of patients in the NEPA group and 76% of patients in the group taking aprepitant in combination with PALO.[5]

The rates of serious adverse events in the studies mentioned above were rare. According to the prescribing information, adverse events that occur at a rate of 3% or more are headache, asthenia, dyspepsia, fatigue, constipation, and erythema. Coadministration of NETU 600 mg and PALO 1.5 mg had little impact on the QTc interval in pharmacodynamic studies.[2]

NEPA is supplied as a hard gelatin capsule and requires storage at room temperature. It should be administered at approximately 1 hour prior to the start of chemotherapy. NETU is extensively metabolized through CYP3A4. However, it is also a moderate inhibitor of CYP3A4, so there is potential for increased plasma concentration of CYP3A4 substrates. This interaction may last up to 4 days. Caution is advised if NEPA is used with CYP3A4 substrates. Using NEPA with a patient who requires the chronic use of CYP3A4 inducers should be avoided because this may result in decreased concentration of NETU. NEPA concentration may be increased by inhibitors of CYP3A4; however, recommendations for dose adjustments have not been made.[6]

NEPA does not require adjustment for mild to moderate renal or hepatic disease. It has not been studied in patients with severe hepatic impairment as defined by a Child-Pugh score greater than 9. Because of this, use in such patients should be avoided. NEPA also should be avoided in severe renal impairment or patients with end-stage renal disease because NETU has not been studied in this patient population.[2]

NEPA is classified as pregnancy category C. It is not known whether NEPA is present in human milk. PALO is known to cause tumors in rats. The potential risks and benefits of therapy should be carefully considered. Safety and effectiveness in pediatric patients have not been established. One should use caution when administering Akynzeo® to elderly patients because they may have decreased hepatic, renal, or cardiac function. The elderly also are more likely to be on multiple medications, increasing the likelihood of drug interactions with NEPA therapy.[2]

NEPA provides an additional option for the treatment of CINV. The FDA approved NEPA in October 2014 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including but not limited to, HEC.[7] NEPA, when used in combination with a glucocorticoid, is an alternative to aprepitant- and fosaprepitant-containing regimens for patients receiving HEC, such as those containing cisplatin or a combination of an anthracycline plus cyclophosphamide.

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## Nivolumab (Opdivo®)

**Class:** Human-programmed cell death receptor-1 (PD-1) inhibitor
**Indications:** Unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor; metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy
**Dose:** 3 mg/kg intravenous infusion over 60 minutes every 2 weeks and continued until disease progression or unacceptable toxicity
**Dose modifications:** Dose may need to be withheld or permanently discontinued in the event of moderate or severe (grade 2 or above) immune-mediated hepatitis, colitis, pneumonitis, renal toxicity, or thyroid disorder and any common terminology criteria for adverse events grade 3 or 4 reaction.
**Common adverse effects:** Fatigue, rash, pruritus, nausea, constipation, decreased appetite, hyperkalemia, hyponatremia, and cough
**Serious adverse effects:** Immune-mediated hepatitis, colitis, nephritis, pneumonitis, thyroid dysfunction, adrenal insufficiency, neuropathy, pancreatitis, uveitis, and increased ALT, AST, alkaline phosphatase, total bilirubin, and serum creatinine
**Drug interactions:** No known clinically significant drug interactions

## Nivolumab: A Novel Immune Checkpoint Inhibitor

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The therapeutic landscape of cancer immunotherapy is rapidly changing with the development of antibodies targeting immunologic regulators, or checkpoints, including the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein-1 (PD-1) pathway.[1,2] In phase 3 trials, the anti-CTLA-4 antibody ipilimumab (Yervoy®) significantly improved overall survival (OS) in previously treated and untreated patients with unresectable and metastatic melanoma.[2,3,4] Ipilimumab also improved long-term survival in advanced melanoma with estimated survival rates of 20.8% at 3 years and the longest reported survival reaching 10 years. The success of ipilimumab has generated considerable interest for targeting other immunologic checkpoints including human-programmed cell death receptor-1 (PD-1).[4]

PD-1 is an immunomodulatory receptor expressed on T cells, B cells, monocytes, natural killer cells, and many tumor-infiltrating lymphocytes and serves as a negative regulator of T-cell activity when engaged by its two known programmed death ligands, PD-L1 and PD-L2. A variety of cancers including melanoma, hepatocellular carcinoma, glioblastoma, lung, kidney, breast, ovarian, pancreatic, and esophageal cancer, as well as hematologic malignancies, have increased expression of PD-L1, which may be associated with a poor prognosis.[1]

Nivolumab (Opdivo®) is a fully humanized IgG4 anti-PD-1 monoclonal antibody that selectively binds to PD-1, blocking its interaction with PD-L1 and PD-L2 and disrupting the negative signal that regulates T-cell activation and proliferation.[5]

The U.S. Food and Drug Administration (FDA) granted accelerated approval of nivolumab in December 2014 for the treatment of patients with unresectable or metastatic melanoma after the use of ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. In March 2015, the FDA granted approval of nivolumab for the treatment of metastatic, squamous, non-small cell lung cancer (NSCLC) following progression on or after platinum-based chemotherapy.

Nivolumab received its FDA-labeled indication for the treatment of unresectable or metastatic melanoma based on a planned interim analysis of phase 3 data from CheckMate 037[6] presented at the 2014 European Society for Medical Oncology Conference. In this multicenter, open-label study, patients with advanced melanoma were randomized to receive either nivolumab 3 mg/kg every 2 weeks ($n$ = 268) or the investigator's choice of chemotherapy (ICC; $n$ = 102; dacarbazine 1,000 mg/m$^2$ every 3 weeks or carboplatin AUC 6 + paclitaxel 175 mg/m$^2$ every 3 weeks) until disease progression or unacceptable toxicity. Included patients were required to have experienced disease progression on or following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Exclusion criteria included autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastases, or a history of grade 4 ipilimumab-related adverse reactions (except endocrinopathies) or grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks. Coprimary endpoints included objective response rate (ORR) and OS. The planned interim analysis of ORR was performed after 120 patients receiving nivolumab and 47 patients receiving ICC had received at least 6 months of follow-up. Confirmed ORR in patients receiving nivolumab and ICC were 32% (95% confidence interval [CI]: 24, 41) and 11% (95% CI: 3.5, 23), respectively. Median time to response was 2.1 months (range: 1.6, 7.4) and 3.5 months (range: 2.1, 6.1) with nivolumab and ICC treatment, respectively. Median duration of response was not reached in the nivolumab group (1.4+, 10+ months) with 36 of 38 (95%) patients still in response at the time of analysis. Median duration of response for ICC was 3.6 months (range: 1.3+, 3.5) with 4 of 5 (80%) patients still in response at the time of analysis. Grade 3-4 drug-related adverse events were observed in 9% and 31% of patients treated with nivolumab and ICC, respectively. Therapy

was discontinued due to drug-induced adverse events in 2.2% and 7.8% of patients receiving nivolumab and ICC, respectively. The most common adverse events were rash (21%), hyponatremia (25%), and increased alkaline phosphatase (22%). Other adverse reactions included pruritus (19%), hyperkalemia (15%), increased ALT (16%), increased AST (28%), increased serum creatinine (13%), cough (17%), and upper respiratory infection (11%).

Currently, in the treatment of advanced melanoma, nivolumab is only FDA indicated for treatment after progression on or following ipilimumab +/- a BRAF inhibitor. However, the most recent National Comprehensive Cancer Network (NCCN) *Clinical Practice Guidelines in Oncology (NCCN Guidelines®)* (Version 2.2015)[7] state that there is consensus among the NCCN panel that nivolumab should be included as an option for first-line treatment of advanced or metastatic melanoma. Indeed, safety and efficacy have been demonstrated in a large phase 3 study[5] evaluating nivolumab therapy in previously untreated, unresectable, stage 3 or 4 melanoma without a BRAF V600 mutation. In this multicenter, double-blind, double-dummy study, patients were randomized to receive either nivolumab 3 mg/kg every 2 weeks + dacarbazine-matched placebo every 3 weeks or dacarbazine 1,000 mg/m$^2$ every 3 weeks + nivolumab-matched placebo every 2 weeks. Key exclusion criteria included BRAF V600 mutation positivity, active brain metastases, uveal melanoma, or a history of serious autoimmune disease. The primary endpoint was OS. At 1 year, the OS was 72.9% (95% confidence interval [CI]: 65.5, 78.9) for patients in the nivolumab group ($n$ = 210) and 42.1% (95% CI: 33, 50.9) in the dacarbazine group ($n$ = 208) with a resulting 0.42 hazard ratio (HR) of death (99.79%; 95% CI: 0.25, 0.73; $p < 0.001$). Median progression-free survival was also significantly improved with nivolumab therapy (5.1 versus 2.2 months; HR = 0.43; 95% CI: 0.34, 0.56; $p < 0.001$). ORR was 40% (95% CI: 33.3, 47) in the nivolumab group versus 13.9% (95% CI: 9.5, 19.4) in the dacarbazine group (odds ratio: 4.06; $p < 0.001$). Median duration of response was not reached in the nivolumab group but was 6 months in the dacarbazine group (95% CI: 3 to not reached). Grade 3–4 drug-related adverse events were observed in 11.7% and 17.6% of patients treated with nivolumab and dacarbazine, respectively. The most common adverse events associated with nivolumab therapy were fatigue (19.9%), pruritus (17%), and nausea (16.5%).

Nivolumab received its FDA-labeled indication for the treatment of metastatic squamous NSCLC after data were released from two clinical trials. The first was a multinational, phase 2, single-arm trial (CheckMate 063)[8] that included patients with squamous NSCLC who had progressed after treatment with a platinum doublet-based regimen and at least one additional systemic treatment. All patients ($n$ = 117) in this trial received nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Key exclusion criteria included untreated brain metastases, autoimmune disease, disorders requiring systemic immunosuppressive drugs, previous treatment with an antibody or drug specifically targeting T-cell costimulation or checkpoint pathways, positive test for HIV, hepatitis B, hepatitis C, symptomatic interstitial lung disease, or prior treatment for NSCLC within the 2 weeks prior to randomization. The primary endpoint ORR was found in 17 of 117 patients (14.5%; 95% CI: 8.7, 22.2). Median time to response was 3.3 months (IQR: 2.2, 4.8), and median duration of response was not reached (95% CI: 8.31, not reached). At the time of analysis (at least 10 months for all patients), 13 of 17 (77%) responders had ongoing responses. The most common adverse events of any grade were fatigue (33%), decreased appetite (19%), nausea (15%), and rash (11%). None of these adverse events occurred at a frequency greater than 5% with a severity of grade 3 or 4.

CheckMate 017[9] was a multinational, phase 3, randomized (1:1), open-label study comparing treatment with nivolumab 3 mg/kg every 2 weeks to docetaxel 75 mg/m$^2$ every 3 weeks in patients with metastatic squamous NSCLC. Patients in this trial were required to have received prior therapy with one platinum-based regimen. Key exclusion criteria were similar to CheckMate 063. The primary endpoint was OS. A total of 135 patients were randomized to the nivolumab arm and 137 were randomized to the docetaxel arm. Median OS was significantly improved with nivolumab therapy when compared to the docetaxel arm (9.2 versus 6 months; HR = 0.59; 95% CI: 0.44, 0.79; $p$ = .00025). Adverse event data have not been released for this trial. Based on its mechanism of action and data from animal studies, nivolumab is expected to cause fetal harm if administered during pregnancy. Women of reproductive age should use highly effective contraception during therapy and for at least 5 months following the last dose of nivolumab.[9]

Pharmacokinetic studies have demonstrated no clinically significant differences in the clearance of nivolumab when given to patients with renal or hepatic impairment. No dose adjustments are recommended in patients with baseline renal or hepatic dysfunction; although, nivolumab has not been studied in patients with moderate (total bilirubin > 1.5–3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment. Nivolumab should be withheld for any common terminology criteria for adverse events (CTCAE) grade 3 or 4 adverse reactions and permanently discontinued if grade 3 or 4 adverse events persist after holding dose beyond 12 weeks without resolution. The use of systemic corticosteroids may be indicated for the management of grade 2 or higher immune-mediated adverse reactions.[9]

Nivolumab is supplied as an intravenous solution in 100-mg and 40-mg single-use vials. The recommended dose of nivolumab is 3 mg/kg administered as an IV infusion over 60 minutes through a sterile, nonpyrogenic, 0.22-micron in-line filter every 2 weeks and continued until disease progression or unacceptable toxicity. Because checkpoint blockade does not only enhance tumor-specific immune responses, unique adverse effects can occur through other nonspecific immunologic activation.[2] Patients should be closely monitored and counseled about the possibility of immune-mediated adverse effects including pneumonitis, colitis, hepatitis, nephritis, thyroid dysfunction, and rash.[9]

For the treatment of metastatic melanoma and metastatic squamous NSCLC, nivolumab has demonstrated durable responses with statistically significant improvements in overall survival. Nivolumab is well

tolerated but has the potential for rare, clinically significant immune-mediated adverse reactions. At this time, there are several other PD-1 and PD-L1 antibodies in the drug development pipeline. Nivolumab is currently being studied in a variety of solid tumors and hematologic malignancies as both monotherapy and in combination with other agents including ipilimumab.

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## Olaparib (Lynparza™)

**Class:** Poly (ADP-ribose) polymerase (PARP) inhibitor
**Indication:** Monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by a U.S. Food and Drug Adminsitration–approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy
**Dose:** 400 mg orally twice daily, continued until disease progression or unacceptable toxicity
**Dosage form:** 50-mg capsules
**Dose modifications:** Dose adjustments should be made to mitigate adverse reactions to 200 mg orally twice daily and may be further reduced to 100 mg orally twice daily if needed. If CYP3A inhibitors cannot be avoided, consider reducing olaparib to 150 mg orally twice daily for strong inhibitors, and 200 mg orally twice daily for moderate inhibitors.
**Common adverse effects:** Anemia, fatigue, nausea, vomiting, diarrhea, dysgeusia, dyspepsia, decreased appetite, abdominal pain/discomfort, headache, nasopharyngitis/pharyngitis/upper respiratory infection, cough, arthralgia/musculoskeletal pain, myalgia, back pain, and dermatitis/rash
**Serious adverse effects:** Myelodysplastic syndrome/acute myeloid leukemia occurred in ≥ 2% of patients exposed to olaparib, pneumonitis.
**Drug interactions:** Olaparib primarily is metabolized by CYP3A. Avoid concomitant use of strong and moderate CYP3A inhibitors and inducers, decrease the dose or be aware of potential for decreased efficacy if inhibitors or inducers cannot be avoided, respectively.

## Olaparib (Lynparza™) in the Treatment of Advanced Ovarian Cancer

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Olaparib (Lynparza™, AstraZeneca) is the first poly (ADP-ribose) PARP inhibitor approved by the U.S. Food and Drug Administration (FDA). The FDA approved olaparib via accelerated approval on December 19, 2014, for the treatment of ovarian cancer in women with known or suspected BRCA mutations who have received at least three prior lines of chemotherapy.[1,2] BRACAnalysis CDx is a genetic test that was approved with olaparib. This diagnostic test detects BRCA gene mutations, which are estimated to be associated with 10% to 15% of all ovarian cancer cases.

PARP enzymes are involved in DNA transcription, cell cycle regulation, and DNA repair.[1] PARP dissociates from DNA once repairs are complete due to the high negative charge of PAR polymers and extensive autoPARylation. [3] Inhibiting PARP leads to an accumulation of recombinogenic substrates, which increases the cytotoxicity of PARP inhibitors in tumors cells with BRCA mutations. Olaparib has shown to both inhibit PARP enzymatic activity as well as increase the number of PARP-DNA complexes in vitro.[1] The dual mechanisms result in cellular homeostasis disruption and subsequent cell death. PARP inhibitors vary in potency due to varying degrees of PARP catalytic inhibition as well as ability to form PARP-DNA complexes.

Olaparib was studied as monotherapy at a dose of 400 mg orally twice daily in patients who had advanced cancer and BRCA 1/2 mutation.[4] This study included patients with ovarian, breast, pancreatic, or prostate cancer. The primary endpoint was tumor response rate in all patients. Secondary endpoints were objective response rate (ORR), progression-free survival (PFS), and duration of response. Safety and tolerability also were assessed. Two hundred and ninety-eight patients received at least one dose of study drug, and 193 had ovarian cancer. Ovarian cancer patients were at least 18 years of age, had an Eastern Cooperative Oncology Group performance status of 0–2, and were platinum resistant or unable to receive additional platinum therapy. Ovarian cancer patients had received an average of 4.3 prior regimens. Seventy-seven percent of ovarian cancer patients had a BRCA1 mutation, 23% had a BRCA2 mutation, and one patient had both BRCA1 and BRCA2 mutations.

The primary endpoint of tumor response rate was 26.2% for all 298 patients.[4] The tumor response rate in the ovarian cancer cohort was 31.1% (95% confidence interval [CI]: 24.6–38.1). Stable disease that persisted for at least 8 weeks was experienced by 40.4% of ovarian cancer patients ($n$ = 78, 95% CI: 33.4–47.7). The median duration of response for ovarian cancer patients was 225 days. The objective response, in all patients with baseline measureable disease, was 29.3% (95% CI: 23.9–35.2). PFS and OS for patients with ovarian cancer were 7 months and 16.6 months, respectively.

Fifty-four percent of all patients experienced adverse events (AEs) of at least grade 3; 30.9% were considered causally related to olaparib.[4] The most common AEs for ovarian cancer patients of greater than grade 3 were anemia (18.7%), abdominal pain (7.3%), and fatigue (6.2%). Thirty percent of ovarian cancer patients experienced serious AEs; 10.4% that were causally related to olaparib. Nine deaths were reported as results of AEs: sepsis ($n$ = 2), leukemia ($n$ = 2), chronic obstructive pulmonary disease ($n$ = 1), pulmonary embolism ($n$ = 1), myelodysplastic syndrome (MDS; $n$ = 1), wound dehiscence ($n$ = 1), and cerebrovascular accident ($n$ = 1). One case of sepsis and MDS each were considered causally related to olaparib by investigators. AEs led to discontinuation of olaparib in 3.7% of patients.[4] Dose modifications (interruptions and/or reductions) occurred as a result of AEs for 40.3% of patients; 9.7% with anemia, 7% with vomiting, and 5% with fatigue.

Olaparib comes as a 50-mg capsule.[1] The recommended dose is 400 mg orally twice daily until disease progression or unacceptable toxicity. AEs can be managed by dose interruptions or dose reductions. Initial dose reduction to 200 mg orally twice daily is recommended, but a

final dose reduction to 100 mg orally twice daily is acceptable, if necessary. Olaparib primarily is metabolized by CYP3A, and it is recommended to avoid concomitant use of strong and moderate CYP3A inhibitors. If inhibitors cannot be avoided, dose reductions of olaparib are recommended to 150 mg orally twice daily or 200 mg orally twice daily for strong or moderate CYP3A inhibitors, respectively. Avoid use of strong CYP3A inducers concomitantly with olaparib. If they cannot be avoided, be aware of decreased efficacy of olaparib. Olaparib was not studied in patients with baseline hepatic impairment (serum bilirubin > 1.5 x ULN) because these patients were excluded from the clinical trials; therefore, there are no data on the effect of hepatic impairment on olaparib exposure.[1] Patients with mild renal impairment (CrCl = 50–80 mL/min) compared to those with normal renal function (CrCl > 80 mL/min) showed a 1.5-fold increase in mean exposure to olaparib. No dose adjustments for patients with CrCl of 50–80 mL/min are necessary, but they should be monitored closely for signs of toxicity. There are no data for olaparib use in patients with moderate to severe renal impairment (CrCl < 50 mL/min) and those on dialysis.

Warnings and precautions related to serious AEs exist including MDS/acute myeloid leukemia (AML), pneumonitis, and embryo-fetal toxicity.[1] Six patients out of 298 (2%) who were enrolled in the olaparib monotherapy study developed confirmed MDS/AML. Less than 1% (22 of 2,618) of all patients treated with olaparib reported developing MDS/AML with durations of therapy ranging from less than 6 months to greater than 2 years. All patients with MDS/AML had received prior platinum chemotherapy and/or other DNA damaging chemotherapy. Due to the risk of developing secondary MDS or therapy-related AML, complete blood count testing at baseline and monthly during olaparib therapy is recommended. Pneumonitis was reported in less than 1% of all patients who were treated with olaparib. Olaparib is pregnancy category D based on animal studies.[1] It is recommended that women of reproductive potential avoid pregnancy during therapy and for 1 month after therapy is complete. It is unknown if olaparib is excreted in breast milk.

PARP inhibition is a novel strategy for cancer treatment. The approval of olaparib as the first in class is promising for further development and approval of additional PARP inhibitors. Olaparib has shown acceptable response rates for ovarian cancer patients with BRCA mutations. The safety profile is manageable with anemia, nausea, vomiting, and fatigue being the most common AEs reported. As post-marketing surveillance occurs, additional information about the safety and efficacy of olaparib will be available.

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## Palbociclib (Ibrance®)

**Class:** Signal transduction inhibitor; cyclin-dependent kinase 4 and 6 inhibitor[1,2]
**Indication:** Initial endocrine-based treatment in postmenopausal women with ER-positive, HER2-negative metastatic breast cancer in combination with letrozole[2]
**Dose:** 125 mg orally once daily (with food) for 21 consecutive days, then 7 days off. Cycle is to be repeated every 28 days until disease progresses or if intolerable toxicity would occur. Palbociclib is used in combination with letrozole 2.5 mg orally once daily throughout each 28-day palbociclib cycle.[2]
**Dose modifications:**[2] Dose modifications are made in the following increments: first modification to 100 mg and second modification to 75 mg. Hold palbociclib for grade 3 hematologic toxicity, for grade 3 neutropenia (ANC < 500–1,000/mm$^3$) with a fever > 38.5 °C and/or infection, for grade 4 hematologic toxicity, for > grade 3 hepatotoxicity (AST or ALT > 5 x ULN or total bilirubin > 3 x ULN), and for > grade 3 nephrotoxicity (SCr > 3 x baseline or > 4 mg/dL or requiring dialysis). Resume palbociclib treatment at the appropriate lowered dose when adverse events have improved to ≤ grade 2. Discontinue treatment when patients cannot tolerate the 75-mg dose.
**Common adverse effects:**[2] Lymphopenia, neutropenia, leukopenia, fatigue, anemia, upper respiratory infections, stomatitis, nausea, alopecia, diarrhea, thrombocytopenia, anorexia, vomiting, peripheral neuropathy, asthenia, and epistaxis
**Serious adverse effects:** Pulmonary embolism and thromboembolism[1]
**Drug interactions:**[2] Palbociclib is a major substrate and weak inhibitor of CYP3A4. Consider a dose reduction to 75 mg when coadministration with strong CYP3A4 inhibitors cannot be avoided. Try to avoid coadministration of moderate or strong CYP3A4 inducers.

# Palbociclib (Ibrance®) Adding a Cyclin-Dependent Kinase Inhibitor to Achieve Cell Cycle Arrest

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Different complex proteins control the cell through the various phases of growth, replication, and division. Within cancer cells, some of these regulatory proteins are potential targets of treatment to stop the dividing cell within different stages of growth. One such target includes the cyclin-dependent kinases (CDK). The CDK work with proteins called cyclins to regulate checkpoints within the cell cycle.[3]

One such transition in the cell cycle under the control of CDK activity is the G1-S phase. The regulators of this transition are CDK4 and Cyclin D1 (CCND1). These two combine to form a complex that leads to downstream signaling for progression through the G1 phase into the S phase, where DNA synthesis occurs. There are four possible mechanisms of CDK4-CCND1 regulation that are abnormal and potential causes of cancer growth: amplification/overexpression of CCND1, amplification of CDK4, a mutation that activates CDK4, or loss of p16, which inhibits CDK4.[3]

Palbociclib is a second-generation CDK4/6 inhibitor that binds selectively to the AT-binding site of the CDK4-CCND1 complex, thereby preventing the retinoblastoma (Rb) protein mediated phosphorylation and inducing G1 cell cycle arrest. This antiproliferative effect of CKD4/6 inhibition has the potential to benefit a number of cancer cell lines, including hematologic and solid tumors, as long as the downstream target of Rb remains intact.[3] Palbociclib has demonstrated in vitro preferential selection toward ER-positive luminal breast tissue.[4]

Palbociclib received U.S. Food and Drug Administration accelerated approval 2 based on the results of the PALMOA-1/TRIO-18 trial.[6] The open-label, phase 2 study randomized 165 breast cancer patients to receive either palbociclib plus letrozole ($n$ = 84) or letrozole alone ($n$ = 81). Palbociclib was given as a 125-mg dose for 3 weeks on, 1 week off on a 28-day cycle, while letrozole was given as 2.5 mg daily continuously for both treatment arms.[5,6] Eligible patients were postmenopausal women with ER-positive and HER2-negative disease who had not received any systemic treatment for their advanced disease. Patients initially were enrolled into two cohorts to determine whether CCND1 amplification (cohort 2) would be a predictor of patient response. The primary endpoint was investigator-assessed progression-free survival (PFS) in the intention-to-treat population. However, an interim analysis determined clinically meaningful activity of palbociclib plus letrozole combination compared to the letrozole only group ($p$ = .006). At this point, accrual into cohort 2 was stopped because CCND1 amplification appeared to have no impact on response to treatment. The final analysis of the primary endpoint was completed on both cohorts combined.[6] Forty-one of the 84 patients enrolled in the palbociclib plus letrozole group achieved a PFS event, while 59 of 84 in the letrozole only group achieved a similar event. The median PFS was 20.2 months in the combination group compared with 12.2 months in the letrozole only group (one-sided $p$ = .0004). Within each cohort, the PFS analysis favored the combination therapy. In cohort 1, the palbociclib/letrozole combination group had PFS of 26.2 months while the letrozole group had a PFS of 5.7 months (one-sided $p$ < .0001). In cohort 2, the combination group had PFS of 18.1 vs. 11.1 months with letrozole alone (one-sided $p$ = .0046).[6] Of note, the median overall survival was 37.5 months (95% confidence interval [CI])

in the palbociclib plus letrozole group and 33.3 months in the letrozole alone group (hazard ratio [HR] = 0.813; 95% CI: 0.492–1.345; two-sided $p$ = .42). One of the limitations to this study was the fact that the primary endpoint analysis was not conducted at a centralized location. A phase 3 study with a similar population already is underway to confirm the results of PALOMA-1. In addition, palbociclib is being studied with other antihormonal drugs in breast cancer patients.

The most common adverse effects seen in the trial included neutropenia (75%), leukopenia (43%), and fatigue (41%).[2,6] Despite the higher incidence of neutropenia and leukopenia in the palbociclib/letrozole treatment group, there were no cases of febrile neutropenia reported,[6] but patients should be closely monitored for this adverse event.[2] Other adverse events seen in the treatment group include anemia (35%), upper respiratory infection (31%), stomatitis (25%), nausea (25%), alopecia (22%), diarrhea (21%), thrombocytopenia (17%), decreased appetite (16%), vomiting (15%), peripheral neuropathy (13%), asthenia (13%), and epistaxis (11%).[2] Pulmonary embolism (PE) did occur at a higher rate in the palbociclib/letrozole group (5%) compared to the letrozole only group with no known cases. Patients should be monitored for signs and symptoms of PE and treated appropriately.[2]

Dose modifications for palbociclib are made in a step-wise fashion, with the first reduction to 100 mg and the second reduction to 75 mg on treatment days.[2] If patients do not tolerate palbociclib at the 75-mg dose, discontinuing therapy is recommended over further dose reduction. No dose reductions are recommended for grade 1 or 2 hematologic or nonhematologic adverse reactions. If patients should experience grade 3 hematologic adverse reactions, no dose adjustment is required, but withholding treatment is recommended until recovery to ≤ grade 2. If there is grade 3 ANC (500 to 1,000/mm$^3$) and fever (≥ 38.5 °C) or infection, then withhold palbociclib until counts recover to ≤ grade 2 to begin the subsequent cycle at the next lower dose. Withhold palbociclib for any grade 4 hematologic adverse reaction and resume at the next lower dose when counts have recovered to ≤ grade 2. For nonhematologic adverse events ≥ grade 3 that persist despite medical treatment, withhold palbociclib and resume at the next lower dose when symptoms resolve to ≤ grade 2 if it is not considered a safety risk to the patient.[2]

Palbociclib is a time-dependent inhibitor of the CYP3A enzyme, which also is the primary enzyme for metabolism. Concurrent use with strong CYP3A inhibitors has shown increased exposure to palbociclib in healthy subjects. Dose modification of palbociclib to 75 mg daily on treatment days may be warranted if concurrent therapy with strong inhibitors of CYP3A cannot be avoided. Concurrent use of strong CYP3A inducers have been shown to decrease palbociclib exposure in healthy subjects, suggesting concurrent use should be avoided. This may also be an issue with moderate inducers, therefore, avoiding these agents should be considered. Other drugs that are metabolized by CYP3A may see an increase in plasma concentrations. If concurrent use is necessary, consider dose reducing these medications to avoid excess exposure to the patient.[2]

Palbociclib is supplied as 75-mg, 100-mg, and 125-mg capsules, which is consistent with the recommended dose modifications. Exposure to food on administration demonstrated less intersubject variability in palbociclib exposure.[2] Instruct patients to take their dose with a meal at about the same time every day. Capsules should be swallowed whole and inspected for damage prior to taking them. If a dose is missed, that dose should be skipped and the patient should resume treatment the next day. Patients should also avoid grapefruit and grapefruit products because it may increase the exposure to palbociclib.[2] Palbociclib is a very expensive agent and currently available through specialty pharmacies.

Women of childbearing age should use effective birth control throughout treatment and at least 2 weeks after discontinuation of palbociclib. It is unknown whether palbociclib is excreted into breast milk. Patients should discuss with their provider whether they should breast feed and take palbociclib at the same time.[2]

Targeting cell cycle arrest using CDK inhibitors may be beneficial in more than just breast cancer patients. Currently, clinical trials are enrolling for other cancers, including mantle cell lymphoma, non-small cell lung cancer, multiple myeloma, central nervous system tumors, and various others. Some trials are studying single agent therapy, while various combination therapies are being considered as well. In addition, further investigation to validate the current information regarding palbociclib with letrozole in similar patient populations is also underway. These results will hopefully further confirm the use of this combination.

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## Ramucirumab (Cyramza®)

**Class:** Vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist
**Indication:** Approved for use in combination with docetaxel for patients with metastatic non-small cell lung cancer who have progressed on or after platinum-based chemotherapy. If a patient has an EGFR- or ALK-positive tumor, progression on approved targeted therapy is required prior to receiving ramucirumab.
**Dose:** Administer ramucirumab 10 mg/kg IV on day 1 every 21 days prior to docetaxel. Continue until disease progression or unacceptable toxicity occur.
**Dose modifications:** No dose adjustments necessary for patients with renal impairment or in those with mild hepatic impairment (total bilirubin within ULN and AST > ULN or total bilirubin > 1.0–1.5 x ULN and any AST) based on population pharmacokinetic analyses. No recommendations are provided for dose adjustment in moderate to severe hepatic impairment. Clinical deterioration has been reported in patients with Child-Pugh B or C liver dysfunction receiving ramucirumab. Dose reductions or treatment interruptions may be warranted in the setting of infusion-related reactions, severe hypertension, or proteinuria (urine protein levels ≥ 2 g/24 hours). Therapy should be held prior to surgery and may be resumed once surgical wound is fully healed. Therapy should be permanently discontinued in the setting of nephrotic syndrome, arterial thrombosis, gastrointestinal perforation, grade 3 or 4 bleeding, or reversible posterior leukoencephalopathy syndrome (RPLS).
**Common adverse effects:** Neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation
**Serious adverse effects:** Febrile neutropenia, pneumonia, and neutropenia
**Drug interactions:** Ramucirumab may enhance the adverse/toxic effects of belimumab and this combination should be avoided. It may also increase the risk for osteonecrosis of the jaw if used concurrently with bisphosphonate derivatives.
**Monitoring parameters:** Blood pressure should be monitored every 2 weeks or more frequently if indicated. Other monitoring parameters include liver function tests, urine protein, signs and symptoms of arterial thrombotic events, hemorrhage, gastrointestinal perforation, wound healing impairment, and RPLS.

# Ramucirumab: Now Approved in Combination with Docetaxel for Metastatic Non-Small Cell Lung Cancer

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Lung cancer is the leading cause of cancer-related death in the United States despite the steadily decreasing incidence over the past decade. There will be an estimated 221,200 new cases of lung and bronchial cancer diagnosed in 2015; 115,610 men and 105,590 women. It is estimated that 158,040 deaths will occur in 2015 from the disease. Approximately one-fifth (21%) of patients diagnosed with non-small cell lung cancer (NSCLC) are alive 5 years after diagnosis.[1] The average age at diagnosis is 70 years, with a range of 65–74 years.[2] NSCLC makes up more than 85% of diagnosed lung cancers.[3] The majority of cases are diagnosed in the advanced stage, making successful treatment more challenging.[2,3] Platinum-based doublet therapy is recommended as first-line therapy for patients with advanced or metastatic disease. Overall response rates (ORR) with these doublet regimens are approximately 25%–35% with time to progression ranging from 4 to 6 months. Based on these poor response rates, improved second-line therapies are needed.[3]

Ramucirumab received expanded approval by the U.S. Food and Drug Administration (FDA) for metastatic NSCLC based on the results of the REVEL trial (I4T-MC-JVBA).[4] This was an international, randomized, placebo-controlled, double-blind phase 3 trial in patients with stage 4 NSCLC who had progressed during or after first-line, platinum-based chemotherapy with or without maintenance treatment. Patients were randomized in a 1:1 ratio to treatment with docetaxel 75 mg/m$^2$ plus ramucirumab 10 mg/kg or docetaxel 75 mg/m$^2$ plus placebo. Medications were administered on day 1 every 21 days and continued until disease progression, unacceptable toxicity, noncompliance, or patient's withdrawal of consent.[5,6]

Patients were recruited between December 3, 2010, and January 24, 2013. The study screened 1,825 patients and randomized 1,253 adults from academic medical centers and community clinics in 26 countries on 6 continents. Patients were eligible if they had stage 4 NSCLC with squamous or nonsquamous histology that had progressed during or after a single platinum-based therapy, with or without bevacizumab or maintenance therapy. Patients who were included had recurrent disease that was treated with adjuvant or neoadjuvant therapy or chemoradiation for locally advanced disease if

- their disease had progressed up to 6 months after completion of adjuvant or neoadjuvant platinum-based therapy
- their disease had progressed more than 6 months after therapy and during or after one subsequent platinum-based chemotherapy regimen.

Patients also had to have an ECOG performance status of 0 or 1. Patients were excluded if their only previous therapy was EGFR tyrosine kinase inhibitor monotherapy. Additional exclusion criteria encompassed major blood vessel involvement, intratumor cavitation, poorly controlled hypertension, gastrointestinal perforation or fistulae, arterial thromboembolic event within 6 months prior to randomization, gross hemoptysis within 2 months, or grade ≥ 3 gastrointestinal bleeding within 3 months.[6]

Periodic reviews of data and safety were conducted by an independent data monitoring committee. On May 11, 2012, the committee recommended that patients enrolled from East Asia receive dose-reduced docetaxel (60 mg/m$^2$) because of the incidence rates of neutropenia and febrile neutropenia. Docetaxel dose reductions followed the package insert recommendations. Patients were allowed to receive colony-stimulating and erythropoietin growth factors at the investigator's discretion. Up to two dose reductions were allowed for ramucirumab if treatment-related adverse events occurred. Patients who discontinued therapy for treatment-related adverse events with either agent were able to continue monotherapy.[6]

Baseline characteristics were similar between the two arms. Data were cut off on December 20, 2013, for publication. At this time, 884 patients had died; 429 (68%) patients in the ramucirumab arm, 456 (73%) patients in the placebo arm. The median overall survival (OS) was 10.5 months in the study arm (interquartile range [IQR] 5.1–21.2) and 9.1 months in the control arm (IQR 4.2–18.0); (hazard ratio [HR] = 0.86; 95% confidence interval [CI]: 0.75–0.98; $p$ = .023). The number of patients continuing on treatment after study discontinuation was well balanced between arms with 320 patients (51%) in the ramucirumab continuing and 343 patients (55%) in the control group. Median progresion-free survival (PFS) was 4.5 months (IQR 2.3–8.3; 11.1% censoring) versus 3.0 months (IQR 1.4–6.9; 6.7% censoring) for the study arm compared to the control arm, respectively (HR = 0.76; 95% CI: 0.68–0.86; $p$ < .001). Investigator-assessed ORR was seen in 144 patients (23%) in the ramucirumab arm and 85 (14%) patients in the placebo arm (OR = 1.89; 95% CI: 1.41–2.54; $p$ < 0.0001). Disease control rate was also determined to be superior in the ramucirumab arm with 402 patients (64%) versus 329 patients (53%) in the control arm experiencing benefit (1.60, 1.28–2.01; $p$ < .0001). The median treatment duration was longer in the ramucirumab arm; 15 weeks (IQR 6.1–26.6) versus 12 weeks (IQR 6.0–21.0). A relative dose intensity of 94.6% was determined for the ramucirumab arm with a median of 4.5 infusions administered (IQR 2.0–8.0). For the placebo arm, patients received a median of 4.0 infusions (IQR 2.0–7.0).[6]

For the safety analysis, 627 patients were assessed in the combination arm and 618 patients in the placebo arm. Adverse events resulting in at least one dose adjustment occurred in 33% of the patients in the ramucirumab arm ($n$ = 204) and 23% of patients in the placebo arm ($n$ = 139). A dose adjustment included reduction, delay, or omission of any study drug during a cycle. The most common causes for ramucirumab dose adjustments compared with placebo include neutropenia (12% versus 9%), fatigue (9% versus 6%), and febrile neutropenia (7% versus 5%).

The most common adverse events leading to discontinuation of ramucirumab were infusion-related reactions (0.5%) and epistaxis (0.3%).[6,7]

Adverse events of grade ≥ 3 occurring in at least 10% of patients in the ramucirumab arm included neutropenia (49%), febrile neutropenia (16%), and leukopenia (14%). The use of granulocyte colony stimulating factors and granulocyte macrophage colony stimulating factors was not different between groups; 42% versus 37%, study arm versus placebo arm, respectively. Febrile neutropenia requiring admission occurred in 13% of patients in the ramucirumab arm and 8% of patients in the control arm. The incidence of sepsis did not differ between groups with three deaths occurring in each arm. The incidence of anemia requiring a transfusion occurred more often in the control arm (12%) compared to the study arm (10%). Patients in the ramucirumab group had more bleeding or hemorrhage events of any grade 29% versus 15%, although rates of grade ≥ 3 were similar (2% in each arm). The overall incidence of pulmonary hemorrhage was greater in patients with squamous cell histology compared to nonsquamous cell histology (10% versus 7%; 1% ≥ grade 3 in both groups). The overall incidence of serious adverse events was similar in both groups.[6-7]

Upon study entry, 77% of patients in the study arm and 79% of patients in the control arm provided data on quality of life using the Lung Cancer Symptom Scale and the EuroQoL Five Dimensions questionnaire. At 30-day follow-up, 47% of patients in the study arm and 49% in the control arm provided data. Utilizing the global quality of life assessment, the time to deterioration did not differ between treatment groups (HR = 1.00; 95% CI: 0.84–1.19; $p$ = .99).[6]

Ramucirumab in combination with docetaxel as a treatment option was added to the NCCN NSCLC guidelines as a category 2A recommendation for treatment of metastatic disease with progression on or after platinum-based chemotherapy.[3] Patients with targeted therapies for specific mutations, EGFR or ALK, should have failed FDA-approved treatment prior to receiving ramucirumab.[3,7] Ramucirumab has a 1.4 month OS benefit and is an important treatment option for second-line therapy on advanced NSCLC.[6]

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## Ruxolitinib (Jakafi®)

**Class:** Janus-associated kinase inhibitor
**Indication:** Polycythemia vera (in those with inadequate response to or intolerance to hydroxyurea)
**Dose:** 10 mg twice daily with dose titrated based on subsequent safety and efficacy evaluations; 5 mg twice daily recommended for patients taking strong CYP3A4 inhibitors and for those patients with moderate-to-severe renal impairment or hepatic impairment
**Dose modifications:** Dose reductions should be considered for hemoglobin and platelet count decreases:

- Hemoglobin 10 to less than 12 g/dL *and* platelet count 75 to less than 100 x $10^9$/L: Dose reductions should be considered with the goal of avoiding dose interruptions for anemia and thrombocytopenia.
- Hemoglobin 8 to less than 10 g/dL *or* platelet count 50 to less than 75 x $10^9$/L: Reduce dose by 5 mg twice daily. For patients on 5 mg twice daily, decrease the dose to 5 mg once daily.
- Hemoglobin less than 8 g/dL *or* platelet count less than 50 x $10^9$/L: Interrupt dosing. After recovery of the hematologic parameter(s) to acceptable levels, dosing may be restarted.

**Common adverse effects:** Thrombocytopenia, anemia, bruising, dizziness, and headache
**Serious adverse effects:** Thrombocytopenia, anemia, and neutropenia; risk of infection; symptom exacerbation following interruption or discontinuation of treatment; nonmelanoma skin cancer
**Drug interactions:** Major substrate of CYP3A4; drug levels and effects may be increased by CYP3A4 inhibitors and decreased by CYP3A4 inducers. Avoid use with fluconazole doses greater than 200 mg.
**Monitoring parameters:** Complete blood count at baseline and every 2–4 weeks until dose is stabilized, then as clinically indicated; renal function; hepatic function; heart rate; blood pressure; and signs and symptoms of infection. Consider obtaining an EKG at baseline and periodically throughout therapy.

## Ruxolitinib for Polycythemia Vera

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Polycythemia vera (PV) is a clonal stem cell disorder with trilineage myeloid involvement characterized by hematopoietic cell hyperplasia and clonal erythrocytosis.[1-3] Other disease features, which may or may not be present, include splenomegaly, leukocytosis, thrombocytosis, thrombohemorrhagic complications, and potential evolution into acute leukemia or myelofibrosis.[1,2] In addition, patients may have symptom burden related to pruritus, fatigue, and night sweats.[4] PV is classified as a myeloproliferative neoplasm, one of five categories of myeloid malignancies according to the World Health Organization, along with essential thrombocythemia and primary myelofibrosis.[2] Most patients with PV harbor a janus kinase 2 (JAK2) mutation; however, the disease-causing mutation for PV has yet to be identified.[2]

Patients with PV are stratified according to their risk for thrombotic complications, which has led to the development of risk-adapted therapy. Risk factors that may increase a patient's potential for thrombosis include advanced age, history of thrombosis, and leukocytosis.[2] None of the current agents used to treat PV have been shown to alter the course of the disease; therefore, the current goals of therapy are to prevent thrombotic events while avoiding harm to the patient and disease transformation.[4] Current recommendations are to treat high-risk patients with low-dose aspirin, phlebotomy, and cytoreductive therapy, most commonly hydroxyurea.[2] Cytoreductive therapy also may be indicated for patients with persistent or progressive hematologic abnormalities, splenomegaly, high symptom burden, or those who cannot undergo phlebotomy.[4] Recommendations have been to utilize interferon alpha or busulfan in the case of intolerance or resistance to hydroxyurea, although many patients continue to receive hydroxyurea at the highest dose that is tolerated.[2]

Ruxolitinib is a JAK 1 and 2 inhibitor that has previously been approved by the U.S. Food and Drug Administration (FDA) for treatment of myelofibrosis.[5] This agent initially was shown to have clinical benefit in patients with PV in a phase 2 study and was approved by the FDA on December 4, 2014, for the treatment of PV based on results from the phase 3 RESPONSE trial.[5,6] RESPONSE was an international, randomized, open-label, multicenter study that randomized 223 patients to receive either ruxolitinib at a starting dose of 10 mg twice daily ($n$ = 110) or single-agent therapy as determined by the treating physician (standard therapy, $n$ = 112).[4] Despite previous intolerance or inadequate response, the majority of patients in the standard therapy arm received hydroxyurea (58.9%). Other patients in the standard therapy arm were treated with interferon (11.6%), anagrelide (7.1%), immunomodulators (4.5%), pipobroman (1.8%), or no medication (15.2%).[4]

The primary endpoint for RESPONSE was the proportion of patients who had both hematocrit control and a reduction of 35% or more in spleen volume from baseline at week 32. Secondary endpoints included assessment of patients who met the primary endpoint at week 32 to determine if that response was maintained at week 48, proportion of patients who had a complete hematologic remission (hematocrit control, platelet count ≥ 400 x$10^9$/L, and a white cell count ≤ 10 x $10^9$/L) at week 32, duration of response, symptom reduction, and safety. Patients were allowed to cross over to the ruxolitinib arm at week 32 if the primary endpoint was not met or in the case of disease progression.[4]

The primary endpoint was achieved in significantly more patients in the ruxolitinib arm compared with the standard-therapy arm (20.9% versus 0.9%, $p < .001$) with at least one component of the primary endpoint being met in 77.3% of patients receiving ruxolitinib.[4] The probability that a primary response to ruxolitinib would be maintained for 1 year from the time of initial response was 94%. In addition, at week 32, 49% of patients in the ruxolitinib arm versus 5% of patients in the standard-therapy arm reported at least a 50% reduction in their total symptoms score as assessed by the 14-item MPN-SAF tool.[4]

Patients in both arms reported few grade 3–4 nonhematologic adverse events. Of note, grade 1–2 herpes zoster infections occurred in seven patients in the ruxolitinib arm compared with no patients in the standard-therapy arm.[4] In addition, low-grade elevations in cholesterol, triglyceride, alanine aminotransferase, and aspartate aminotransferase levels were observed with ruxolitinib therapy. Hematologic abnormalities observed with ruxolitinib therapy included low-grade anemia and thrombocytopenia. Thromboembolic events occurred in one patient in the ruxolitinib arm and six patients in the standard-therapy arm through week 32. Myelofibrosis developed in three patients assigned to ruxolinitib compared with one patient in the standard-therapy arm. Two additional patients assigned to standard therapy were diagnosed with myelofibrosis after crossover to ruxolitinib. Discontinuation due to adverse events was observed in 4% of patients treated with ruxolitinib.[4]

The recommended starting dose of ruxolitinib for PV is 10 mg twice daily, although patients taking strong CYP3A4 inhibitors, patients with moderate-to-severe renal impairment, or with hepatic impairment should be initiated at 5 mg twice daily.[7] Doses are subsequently titrated based on safety and efficacy evaluations. Ruxolitinib currently is available as 5-mg, 10-mg, 15-mg, 20-mg, and 25-mg oral tablets and a suspension for nasogastric administration may be prepared with the tablets as well.[7] It is classified as a hazardous agent and requires appropriate precautions for handling and disposal.[7] Tablets should be administered orally with or without food. Ruxolitinib is classified as pregnancy category C because reduced fetal weights were observed in animal reproduction studies. Use during pregnancy should only be considered if potential treatment outweighs the risks of therapy.[7]

Ruxolitinib demonstrated efficacy in controlling hematocrit, reducing spleen size, and improving symptoms in a high-risk PV patient population who were either intolerant or refractory to hydroxyurea.[4] Ruxolitinib also was well tolerated and most patients continued to receive this therapy at time of data analysis. Alternative treatments in this setting that are both well tolerated and efficacious are limited. Therefore, the promising data from RESPONSE indicate that ruxolitinib is a valid therapeutic option for PV patients after hydroxyurea. The RESPONSE trial, while not enrolling more subjects, is still ongoing and additional results may be reported in the future.

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