



## Updates in Head and Neck Cancer: Updates to Cetuximab Indications and Palifermin for Mucositis Prevention

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Head and neck cancer is the fifth most common type of cancer in the United States. Cetuximab, a monoclonal antibody targeting epithelial growth factor receptor (EGFR), is used in combination with radiation therapy (RT) for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) or as a single agent for the treatment of a patient with recurrent or metastatic SCCHN and failed prior platinum-based therapy.<sup>1</sup> In November 2011 the U.S. Food and Drug Administration (FDA) approved cetuximab with the following new indication: in combination with platinum-based therapy and 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN.

The approval is based on the result of a phase 3, multicenter, randomized trial conducted in European countries in patients with metastatic or locally recurrent SCCHN.<sup>2</sup> Patients were randomized to receive cisplatin 100 mg/m<sup>2</sup> on day 1 (or carboplatin, AUC = 5, day 1) plus 5-FU 1,000 mg/m<sup>2</sup> days 1–4 every 3 weeks with or without cetuximab (*n* = 222 and *n* = 220, respectively). Each treating physician made the

selection of cisplatin or carboplatin. Cetuximab was administered intravenously at a dose of 400 mg/m<sup>2</sup> on week 1, then 250 mg/m<sup>2</sup> every week thereafter. After six cycles, patients with at least stable disease could continue cetuximab and chemotherapy until disease progression or unacceptable toxicities occurred. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS) and objective response rate (ORR).

Among the total 442 patients, most patients had a Karnofsky performance score of 80 or above. Sixty-six percent of patients received cisplatin and 34% of patients received carboplatin as initial therapy. After a median follow-up of 19.1 months and 18.2 months in the experimental and control groups respectively, patients who received cetuximab had a significant improvement of OS compared with patients receiving chemotherapy alone (HR = 0.80; 95% CI, 0.64–0.98; *p* = .034). The median OS in the cetuximab arm was 10.1 months, while the OS in the chemotherapy-alone arm was only 7.4 months. PFS in the cetuximab arm (5.5 months) was also significantly longer than the

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chemotherapy-alone arm (3.3 months;  $p < .0001$ ). The ORR was 35.6% in the cetuximab arm and 19.5% in the chemotherapy arm ( $p < .0001$ ).

The most common side effects in patients receiving cetuximab included nausea, vomiting, anemia, neutropenia, rash, diarrhea, and anorexia. Severe adverse effects associated with cetuximab were infusion-related reactions, hypomagnesemia, hypocalcemia, and hypokalemia. Cardiovascular-related death occurred in 3.2% of patients receiving cetuximab and 1.9% of the patients receiving chemotherapy alone.

In summary, the new clinical trial demonstrated that cetuximab, when combined with platinum-based therapy plus 5-FU, could prolong OS in patients with metastatic and recurrent SCCHN. NCCN guidelines currently list this regimen as the Category 1 recommendation.<sup>3</sup> The approved dose of cetuximab is 400 mg/m<sup>2</sup> intravenously as the initial dose, followed by 250 mg/m<sup>2</sup> weekly in combination with cisplatin/carboplatin plus continuous infusion 5-FU.

Palifermin, a modified human keratinocyte growth factor (KGF), stimulates the growth of basal cells and exerts cytoprotective effects on epithelial cells.<sup>4</sup> It was approved by the FDA for the prevention of mucositis caused by total-body irradiation and high-dose chemotherapy in patients with hematological malignancies. Recently, two phase 3, randomized, placebo-controlled, multicenter trials addressed the role of palifermin to decrease severe oral mucositis (OM) for patients with head and neck cancer.

The first trial was conducted in patients with newly diagnosed stage 3–4 head and neck cancer undergoing definitive chemoradiation.<sup>5</sup> Patients received 70 Gy of fractionated radiation therapy (RT; 2.0 Gy/day x 5 days/week) and cisplatin 100 mg/m<sup>2</sup> IV infusion on days 1, 22, and 43 of RT. Intensity-modulated radiotherapy (IMRT) was not permitted. Patients were randomized to receive either palifermin 180 mcg/kg ( $n = 94$ ) or placebo ( $n = 93$ ) weekly starting 3 days before concurrent chemoradiation and then once weekly until the completion of RT (eight doses total). Medications containing chlorhexidine, hydrogen peroxidase, or diphenhydramine were not allowed, but topical anesthetics such as viscous lidocaine were allowed. The primary endpoint was the incidence of severe OM based on the World Health Organization oral toxicity scale; secondary endpoints included duration of severe OM, time to onset of severe OM, incidence of grade  $\geq 2$  xerostomia at month 4, average mouth and throat soreness (MTS), opioid analgesic use, incidence of chemotherapy delay, and RT breaks for at least 5 days. The study was designed to detect a minimum of 25% incidence of severe OM with  $\geq 90\%$  power and a two-sided 5% type I error.

Patients in both treatment arms were demographically similar; most patients had oropharyngeal cancer (56%) and stage 4 A/B diseases (71%). Patients in the palifermin arm displayed a significantly lower incidence of severe OM (54%) compared with the placebo arm (69%;  $p = .041$ ). The median duration of severe OM in the palifermin arm was 5 days, which was considerably shorter than the 26 days reported for patients in the control arm. Accordingly, the time to develop severe OM was longer in the palifermin arm than that in the control arm (47 versus 35 days). MTS scores in both groups were similar (1.66 for the palifermin group versus 1.86 for the placebo group). Median opioid use was numerically lower for the palifermin group than the

placebo group (283 mg versus 498 mg), although the difference was not statistically significant. After multiplicity adjustment, the  $p$  values for all secondary efficacy endpoints were not statistically significant. The median PFS and OS of patients in both arms were similar after a follow-up period of 25.8 months. The most frequent adverse effects of palifermin were rash, flushing, dysgeusia, nausea, and vomiting; however, no patients withdrew because of toxicity.

The second phase 3, double-blind, placebo-controlled, randomized trial was conducted in postsurgical patients with high-risk stage II–IVB head and neck cancers.<sup>6</sup> Patients received standard RT and cisplatin 100 mg/m<sup>2</sup> on days 1 and 22 (and 43 with incomplete resection). The study design was the same as the first clinical trial (including treatment, efficacy and safety endpoints, and statistical analysis); however, the palifermin dose was decreased from 180 mcg/kg to 120 mcg/kg based on a serious event of respiratory insufficiency after the first 17 patients were enrolled. During the first trial, the primary endpoint of severe OM consistently was seen in 47 of 92 patients (51%) in the palifermin group versus 63 of 94 patients (67%) in the placebo group ( $p = .027$ ). All other secondary endpoints, including duration of severe OM, time to develop severe OM, MTS score, PFS, and OS, were not statistically different after adjustment. Adverse effects that were seen more frequently in the palifermin group included dysphagia, diarrhea, asthenia, headache, abdominal pain, and back pain.

These two randomized trials provided new data regarding the use of palifermin to prevent serious OM in head and neck cancer patients. The results were very similar and met the primary endpoints; however, there were some major limitations. First, the use of IMRT was not permitted in these two trials despite the fact that it has replaced conventional RT as the new standard of care in the United States several years ago. The advantage of IMRT over conventional RT is that it localizes the tumor bed more precisely. Because IMRT decreases the unnecessary exposure significantly, the incidence and severity of OM can be less than conventional RT. Second, both trials used WHO criteria for mucositis toxicity grading, but the National Cancer Institute (NCI) toxicity criteria (Common Terminology Criteria for Adverse Events and Common Toxicity Criteria) are the standard in the United States. Third, none of the secondary endpoints were statistically significant because they were underpowered. Because head and neck cancer is potentially curable, the goal is to help patients undergo chemoradiation without treatment delay. Unfortunately, palifermin did not decrease the incidence of RT breaks or supplemental nutrition or chemotherapy delays in either trial. Finally, the doses of palifermin used in these two trials (180 mcg/kg and 120 mcg/kg, respectively) were much higher than the FDA approved (60 mcg/kg); the true cost-effectiveness ratio needs more data.

In summary, although these two randomized trials demonstrated the efficacy of palifermin to decrease severe OM in patients with head and neck cancer, the limitations of the studies prevent the use of palifermin as the new clinical standard in the United States. More data about the role of palifermin are needed for the prevention of severe OM in locally advanced head and neck cancer. 

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# San Antonio Breast Cancer Symposium 2011: Meeting Highlights

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The 34th Annual San Antonio Breast Cancer Symposium (SABCS), presented in collaboration with the Cancer Therapy & Research Center (CTRC) and the American Association for Cancer Research (AACR), took place December 6–10, 2011. Approximately 8,000 attendees from nearly 90 countries attended.

This year's conference focused on emerging treatments in hard-to-treat populations, including patients with metastatic breast cancer, and new knowledge about prevention and risk. Approximately 40 abstracts were selected for oral presentation during the general sessions.

Below are selected phase 3 randomized trials presented during the general sessions that may be of interest to HOPA members. Details on these studies and all abstracts can be found online at [www.sabcs.org](http://www.sabcs.org).

## Combination Therapy for Metastatic HR+ Breast Cancer

- Abstract S1-1: A phase 3 randomized trial of anastrozole vs. anastrozole and fulvestrant as first-line therapy for postmenopausal women with metastatic breast cancer: SWOG S0226

This phase 3 trial randomized 707 postmenopausal women to either anastrozole (1 mg/day) or anastrozole plus fulvestrant (loading dose) as first-line therapy in hormone receptor positive (HR+) metastatic disease. Patients had no prior therapy (chemotherapy or hormone therapy) for metastatic disease, and patients on the anastrozole-only arm were encouraged to cross over to fulvestrant after progression (there was 41% crossover). The primary endpoint was progression-free survival (PFS), with secondary endpoints of overall survival (OS) and toxicity. PFS for anastrozole alone was 13.5 months versus 15 months for the combination of anastrozole and fulvestrant ( $p = .0070$ ; HR = 0.80; 95% CI, 0.68–0.94). OS was 41.3 months for anastrozole versus 47.7 months for the combination anastrozole plus fulvestrant ( $p = .049$ ; HR = 0.81; 95% CI, 0.65–1.00). Although the results of this study were statistically significant, results from the previously reported FACT trial

with a similar study design (SABCS 2009) were negative; therefore, further study of this combination may be needed.

- Abstract S3-7: Everolimus for postmenopausal women with advanced breast cancer: Updated results of the BOLERO-2 phase III trial

This was a double-blind, randomized, placebo-controlled phase 3 trial evaluating the combination of everolimus (EVE; 10 mg/day) plus exemestane (EXE; 25 mg/day) versus EXE plus placebo in 724 postmenopausal patients with HR+, HER2-negative advanced breast cancer refractory to letrozole or anastrozole (in either the adjuvant or advanced disease setting). The primary endpoint was PFS, with secondary endpoints including OS, quality of life (QoL), and safety. Median follow-up was 12 months. The PFS for EVE + EXE was 7.4 months versus 3.2 months for EXE plus placebo ( $p < 1 \times 10^{-16}$ ; HR = 0.44; 95% CI, 0.36–0.53). OS data are immature. With EVE + EXE versus EXE + placebo (<1%), there were increases in grade 3/4 stomatitis (8%), hyperglycemia (5%), and pneumonitis (3%). Discontinuation rates due to adverse effects were also higher with EVE + EXE (19%) versus EXE + placebo (4%). Combination therapy improved PFS in HR+ advanced breast cancer by 4.2 months, which was statistically significant. Although adverse effects were increased in the combination arm, the time to deterioration in QoL was not significantly affected. The study also appeared online in the December issue of the *New England Journal of Medicine*.

## Combination Therapy for Metastatic HER2+ Breast Cancer

- Abstract S5-5: A phase 3, randomized, double-blind, placebo-controlled registration trial to evaluate the efficacy and safety of pertuzumab plus trastuzumab plus docetaxel versus placebo plus trastuzumab plus docetaxel in patients with previously untreated HER2+ metastatic breast cancer (CLEOPATRA)

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## Studies of Adjuvant Bisphosphonates in Early-Stage Breast Cancer

- Abstract S1-2: Long-term follow-up in ABCSG-12: Significantly improved overall survival with adjuvant zoledronic acid in premenopausal patients with endocrine-receptor-positive early breast cancer
- Abstract S1-3: Long-term survival outcomes among postmenopausal women with hormone receptor-positive early breast cancer receiving adjuvant letrozole and zoledronic acid: 5-year follow-up to ZO-FAST
- Abstract S2-3: NSABP-B34: A clinical trial comparing adjuvant clodronate versus placebo in early stage breast cancer patients receiving systemic chemotherapy and/or tamoxifen or no therapy-final analysis

- Abstract S2-4: GAIN study: A phase 3 multicenter trial to compare dose dense, dose intense ETC versus EC-TX and ibandronate versus observation in patients with node+ primary breast cancer-1st interim efficacy analysis

## Adjuvant Lapatinib for HER2+ Early-Stage Breast Cancer

- Abstract S4-7: Results of a randomized, double-blind, multicenter, placebo-controlled study of adjuvant lapatinib in women with early stage ERbB2-overexpressing breast cancer (TEACH trial)

## Adjuvant Aromatase Inhibitor Therapy/Quality of Life

- Abstract S6-2: Patient-reported predictors of early treatment discontinuation: NCIC JMA.27/E1Z03 quality of life study of postmenopausal women with primary breast cancer randomized to exemestane or anastrozole 

## Board Update

R. Donald Harvey, PharmD BCPS BCOP FCCP, HOPA President



A new year brings new opportunities, and HOPA continues to explore and expand the role of our members in a variety of practice settings. Certainly, educational offerings for members that provide practical information and tools to help cancer patients is one of our strengths, and I applaud the Program Committee and all others involved in planning for the superb annual conference schedule. From the Boot Camp to special interest groups, novel therapies,

and survivor needs, the topics that will be covered provide a global overview for members at all stages of their careers. This year, in response to requests for a more tailored meeting experience, we will offer clinical, practice, and administration tracks for attendees. If you haven't already done so, please register and make your plans to join us in Orlando, FL.

I take pride in the work of the board, committee, and task force members, as well as our national office staff and the continued growth of our organization. In a time of shrinking personal and professional budgets, the ability of HOPA to be engaged in the national dialogue on cancer and health care is remarkable.

We have contracted with Drinker Biddle & Reath (DBR) and have approved a final advocacy agenda for the organization. With help from DBR, HOPA will focus on legislative actions and organizational exposure in the following areas:

- promoting and improving patient safety by realizing the value and role of hematology/oncology pharmacists in healthcare delivery
- increasing access to oral chemotherapy and developing policy guidelines to outline appropriate oral chemotherapy administration
- addressing the growing oncology drug shortage that is prohibiting patients from accessing or receiving agents for treatment of cancer and cancer-related symptoms.

In addition, we will keep watch on health policy decisions that affect research for cancer treatment, reimbursement, REMS requirements, and patient access to essential pain medications. We are grateful to AMC and the Legislative Affairs Committee for their continued help and input as we put our legislative and policy focus into action.

HOPA has also joined the Commission on Cancer (CoC), a consortium of 50 organizations dedicated to improving survival and quality of life for cancer patients through standard setting, prevention, research, education, and the monitoring of comprehensive quality care. We look forward to more organizational collaboration with the CoC and thank Dr. Rowena Schwartz for representing HOPA.

I expect 2012 to be another year of growth for HOPA and its members. We certainly have challenges and opportunities before us as a profession, and HOPA is here to help address the needs of the profession and our members. 

## Committee Updates

### BCOP Recertification Committee

Ryan Bookout, Chair

Debbie Blamble, Vice Chair

The six 2011 Oncology Pharmacy Specialty Sessions for BCOP Recertification were offered for the final time at the 2011 American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting held in New Orleans on December 6. Thanks again to the 2011 speakers as well as the BCOP Recertification Committee and Review Panel members who worked so hard to make the sessions a success.

During the past fall, the committee and the 2012 speakers were busy developing the 2012 Oncology Pharmacy Specialty Sessions. Currently, the BCOP Review Panel is in the process of field testing the presentations and questions for the recertification credit exam. The 2012 topics will be

- Therapy of T-Cell and Cutaneous Lymphomas: There's More Than Just B Cells—Patrick Kiel, PharmD BCPS BCOP
- Neuroendocrine Tumors: A Focus on Recent Advances in Pharmacotherapy—J. Hoyt Slade III, PharmD BCOP
- Bone Health in the Oncology Population—Chad Barnett, PharmD BCOP
- Treatment Progress for Advanced Non-Small Cell Lung Cancer—Christine Walko, PharmD BCOP
- Trends in Oncology Drug Expenditures and Practical Cost-Management Strategies—James Hoffman, PharmD MS BCPS
- The Emergence of Adolescent and Young Adult Oncology—Kerry Parsons, PharmD BCOP.

The sessions will be offered at the following meetings in 2012: the HOPA Annual Conference in Orlando, FL, March 21–24; the American College of Clinical Pharmacy Annual Meeting in Hollywood, FL, October 21–24; and the ASHP Midyear Clinical Meeting in Las Vegas, NV, December 2–6. We hope everyone has the opportunity to attend the sessions during one of these meetings.

### CPE Accreditation Committee

Carol Balmer, Chair

Jolynn Sessions, Vice Chair

This is a very active time of year for the CPE Review Panel members. They are performing document reviews for the many educational sessions that will be offered at HOPA's 8th Annual Conference in March. Each presentation undergoes a 14-point review of slides, learning objectives, and active learning plan (ALP) to ensure full compliance with Accreditation Council for Pharmacy Education (ACPE) guidelines for accreditation of continuing pharmacy education activities. The review addresses the appropriateness of learning objectives and the ALP, presence or perception of commercial bias, the credibility of literature that is cited, the presentation's focus on evidence-based patient care recommendations, and several other quality points. Two panel members review each presentation. Their comments are compiled and reviewed by both the committee chair and the HOPA education coordinator, then addressed with the faculty presenter if revisions are

needed. This process helps ensure that all learning activities at the annual conference meet the needs of the target audience and are excellent in quality.

The CPE Accreditation Committee addresses policy and procedural issues related to CPE and contributes to required ACPE reports. Members are currently focusing on review and revision of HOPA's CPE-related policies and procedures. This is the first step in preparing for the ACPE reaccreditation self-study that will be submitted in early September. Comprehensive self-assessment studies are required by ACPE at defined intervals to maintain accreditation as a CPE provider.

### Education Committee

Helen Marshall, Chair

Laura Wiggins, Vice Chair

The Education Committee is continuing to develop the 2012 Oncology Boot Camp, which will focus on the use of targeted therapies in hematology/oncology. In other educational offerings, two new programs have been made available on HOPA University (HOPA U): "Individualizing Care for Metastatic Colorectal Cancer" and "Targeting Metastatic Melanoma: Review of Current Guidelines and Practice." The HOPA Education Committee also released a member survey in December regarding the use and effectiveness of HOPA U. The committee will be assessing these results as part of the strategic planning process for HOPA U in the near future. We hope that you were able to participate. In 2012 the committee will begin to discuss other innovative methods for providing education to HOPA members. We hope to see you at the annual conference in Orlando!

### Legislative Committee

Ali McBride, Chair

Tim Tyler, Vice Chair

This past year, the HOPA Legislative Affairs Committee has been working on three topics affecting clinical practice: drug shortages, oral chemotherapy issues, and risk evaluation mitigation strategies (REMS). Drug shortages have been a hot topic during the past few years with a record number of drug shortages—specifically in oncology—being reported in 2011. The HOPA Legislative Committee has been quick to react by participating in the ASHP/Institute for Safe Medication Practices/American Society of Clinical Oncology (ASCO)/American Society of Anesthesiologists (ASA) Drug Shortage Summit, which convened in 2010, and the U.S. Food and Drug Administration (FDA) Drug Shortage Workshop in 2011. The HOPA Drug Shortage survey, written this year by HOPA members James M. Hoffman (St. Jude Children's Research Hospital) and Colleen Westendorf (University of Kentucky), with assistance from participating members of the HOPA Legislative Affairs Committee, attempted to identify drug safety issues, clinical studies, clinical practices, and costs related to drug shortages.

One of the most salient issues affecting our practices is oral chemotherapy. Each year we see an increase in the number of oral oncology agents in the marketplace and the research pipeline. Approximately 25% of all new chemotherapy agents will be developed in oral form.



Unfortunately, patients are not always able to afford their copays, especially when patients have Medicaid and are forced to deal with the high initial cost of these drugs. Several states have adopted or have introduced laws evaluating cost parity when comparable intravenous (IV) formulations are available. In the previous issue of *HOPA News*, Sarah Hudson-DiSalle and Dean Gruber discussed chemotherapy parity legislation that are being considering at the state and federal level to reduce the cost burden on patients and maintain a continuance of care for patients requiring chemotherapy for their disease state. Hudson-DiSalle and Gruber are developing a HOPA survey to identify the issues facing clinical practitioners regarding oral chemotherapy. The survey will be distributed shortly and will help the committee evaluate the salient points affecting our members and which topics to prioritize in our legislative agenda.

The Legislative Affairs Committee has also been working actively on REMS and was one of the first organizations to evaluate clinical practice changes due to REMS. Recently, Phil Johnson, Niesha Griffith, and Lisa Holle were invited to participate in a REMS workshop at ASCO headquarters. Participants included members of FDA, ASCO, Oncology Nursing Society (ONS), American Society of Hematology (ASH), HOPA, patient advocacy groups, industry, and other hematology/oncology healthcare professionals. The purpose of the workshop was to initiate a discussion between hematology/oncology healthcare providers and the FDA regarding hematology/oncology-related REMS programs and REMS-related issues specific to the discipline. We may have seen some abatement of these issues; the FDA withdrew REMS requirements for Promacta and NPlate, so we can all breathe a sigh of relief. However, the HOPA Legislative Affairs Committee will remain vigilant on this important issue because new chemotherapy drugs are in the pipeline.

We are also happy to announce that HOPA has hired a lobbying group—Drinker, Biddle & Reath (DBR)—to help further HOPA’s legislative goals and agenda. We look forward to working with DBR and enhancing HOPA members’ influence on the issues affecting our practice sites and patient care. Look for future updates as we work with DBR to hone our legislative agenda and activities. We will continue to update our members on issues affecting practice and we look forward to comments from HOPA members.

## Membership Committee

*Meredith Moorman, Chair*

*Jennifer LaFollette, Vice Chair*

HOPA currently has 1,784 members, an increase of nearly 7% from last January. In the next month, the Membership Committee will send membership recruitment letters to PGY-1 residency directors to share with their residents, and pharmacists who have recently passed the BCOP exam.

There was a great response to the HOPA booth at the ASHP MidYear Clinical Meeting in December. Members of the committee staffed the booth and handed out brochures to prospective new members.

Eighty-eight applicants applied for the travel grant for the 2012 annual conference. After careful evaluation, 40 members were chosen to receive the \$500 grant. A survey will be e-mailed after the conference to all members who applied for the grant. Feedback will help the committee improve the travel grant process next year. Please congratulate the following travel grant recipients:

Melanie Angles	Kenneth Kennedy
Denise Bauer	Jennifer Leonard
Jayde Bednarik	Melissa Mackey
Ryan Bolonesi	Neha Mangini
Valerie Caroselli	Jose R. Murillo Jr.
Courtney Cavalieri	Cham Nguyen
Nicholas Chow	Kimberly Nicholson
Amanda Clary	Nancy Nix
Sean DeFrates	Elyse Panjic
Brian Dinh	Tania Paydawy
Jessica Duda	Erin Saffer
Rebecca Fahrenbruch	Katherine Simondsen
Ferowski Fernandez	April Sondag
Erika Gallagher	Geoffrey Stroud
Lesley Hall	Christan Thomas
Christina Howlett	Laura Tuttle
Cheryl Hyk	Jeryl Villadolid
Elizabeth Irvine	Mildred Vincente
Joseph Kaiser	Sarah Wenger
Young Kang	Candice Wenzell

## Nominations and Awards Committee

*Laura Jung, Chair*

*Jane Pruemer, Vice Chair*

## Board Elections

The Nominations and Awards Committee is pleased to announce the newly elected HOPA Board Members.

Niesha Griffith, MS RPh FASHP, President-Elect (3-year term)  
 David Baribeault, PharmD BCOP, Treasurer (2-year term)  
 Susanne Liewer, PharmD BCOP, At-Large Member (2-year term)  
 Scott Soefje, PharmD BCOP, At-Large Member (2-year term)

These board members will be introduced and officially begin serving their terms on March 24, 2012, during the HOPA Annual Conference. Thank you to all the HOPA members who participated in the election process.

## HOPA Awards

The Nominations and Awards Committee is also pleased to announce the 2012 HOPA Award Recipients.

HOPA Award of Excellence: Susan Goodin, PharmD BCOP FCCP

HOPA New Practitioner Award: Daniel Zlott, PharmD BCOP

HOPA Basic Science and Clinical Research Literature Award: Cindy O'Bryant, PharmD BCOP, for the following article:

*O'Bryant CL, Haluska P, Rosen L, et al. An open-label study to describe pharmacokinetic parameters of erlotinib in patients with advanced solid tumors with adequate and moderately impaired hepatic function. Cancer Chemother Pharmacol. Published online September 2011.*

HOPA Oncology Pharmacy Practice Literature Award: Kristine Crews, PharmD BCPS, for the following article:

*Crews KR, Cross SJ, McCormick JN, et al. Development and implementation of a pharmacist-managed clinical pharmacogenetics service. Am J Health-Syst Pharm. 2011;68:143-150.*

The HOPA Awards will be presented at the Annual HOPA Conference on Wednesday, March 21, at Noon.

## Program Committee

*Jill Rhodes, Chair*

*Larry Buie, Vice Chair*

The Program Committee has been working hard to finalize the details of the HOPA 8th Annual Conference being held in Orlando, FL, March 21–24. The Research Task Force has most recently been reviewing Trainee Research-in-Progress submissions. This year marks a new high for trainee research abstract submission, with a total of 99 being submitted. We are looking forward to seeing you all in Orlando and having a successful meeting! Some highlights of the conference include the return of the preconference boot camp, clinical pearls session, and a practice issue panel on drug shortages. Online registration is now open. Don't miss this exciting opportunity to network with your colleagues and receive cutting-edge oncology updates. Please visit the HOPA website and sign up today. Be sure to register before February 6 for early-bird registration discounts!

## Publications Committee

*Lisa Savage, Chair*

*Brandy Strickland, Vice Chair*

It has been a very busy time for the publications committee and we could not have succeeded with the last edition of the newsletter without the overwhelming number of volunteers who wrote several of the articles. It is a very exciting time for oncology pharmacy. The increasing number of new hematology/oncology drugs approved during the past year is encouraging. The newsletter contains a wealth of information, so for those of you with very busy schedules the HOPA newsletter digest is an ideal resource because it summarizes or highlights the contents of each newsletter.

It is wonderful to see so many people utilizing the HOPA Listserv. As a reminder, please observe the following guidelines when using the Listserv.

- Position and job opportunities are not appropriate postings for the Listserv.
- Any member who would like to survey the HOPA membership, please check the archive first before submitting the question because oftentimes the question has been asked before.
- If there are more than three survey questions, they may require review and approval by the Membership Committee. The purpose of this is to ensure that all parties have equal access to the Listserv and that redundant requests are avoided.

We hope that everyone enjoyed the newsletter this past year, and if you have any ideas, suggestions, or topics for the newsletter, please e-mail us at [info@hoparx.org](mailto:info@hoparx.org).

## Standards Committee

*LeAnne Kennedy, Chair*

*Barry Goldspiel, Vice Chair*

The HOPA Standards Committee is in the process of developing our first guideline—a clinical practice guideline for investigational drug services (IDS). The committee has selected the two lead authors for this project and they have started to determine the timeline, outline, and other authors for this project. We hope to have the guideline completed during the next 12 months. In addition, the board approved a new standard operating procedure for clinical practice guideline Development, which will be used as a blueprint for the IDS guideline process. 



## Brentuximab Vedotin (Adcetris™)

**Class:** Antibody-drug conjugate targeted at CD30 consisting of a CD30-specific chimeric IgG1 antibody cAC10; a microtubule-disrupting agent, monomethylauristatin E (MMAE); and a protease cleavable dipeptide linker (which covalently conjugates MMAE to cAC10)<sup>1</sup>

**Indications:** Treatment of Hodgkin lymphoma after failure of at least two prior chemotherapy regimens (in patients ineligible for transplant) or after stem cell transplant failure; treatment of systemic anaplastic large cell lymphoma after failure of at least one prior chemotherapy regimen<sup>1</sup>

**Dose (for both indications):** 1.8 mg/kg IV (maximum dose: 180 mg) every 3 weeks, continue until disease progression, unacceptable toxicities, or a maximum of 16 cycles.<sup>1</sup> Consult package insert for dose adjustment recommendations for hematologic and nonhematologic toxicities.

**Dosage form:** 50-mg vial

Common adverse effects: Gastrointestinal effects (nausea, emesis, diarrhea), rash, cytopenias, cough, upper respiratory tract infection, fatigue

**Serious adverse effects:** Progressive multifocal leukoencephalopathy (PMN), Stevens-Johnson syndrome, neutropenia/anemia/thrombocytopenia (all grade 3–4), peripheral sensory and motor neuropathies, anaphylaxis (routine premedication not recommended), tumor lysis syndrome (TLS)

**Monitoring:** Complete blood count (CBC) with differential prior to each dose, evaluation for TLS risk

### Drug interactions

CYP3A4 inducers (strong): May decrease the serum concentration of brentuximab vedotin (specifically, concentrations of the active MMAE component)

CYP3A4 inhibitors (strong): May increase the serum concentration of brentuximab vedotin (specifically, concentrations of the active MMAE component)

**Approval date:** August 19, 2011

## Brentuximab Vedotin in the Treatment of CD30-Positive Lymphomas

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Brentuximab vedotin (Adcetris™, Seattle Genetics) was granted accelerated approval by the U.S. Food and Drug Administration (FDA) on August 19, 2011. Specifically, this agent was approved for two indications: (1) for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant or after failure of at least two prior multiagent chemotherapy regimens in patients who are not transplant candidates; and (2) for patients with systemic anaplastic large-cell lymphoma (ALCL) after failure of at least one prior multiagent chemotherapy regimen. Brentuximab is the first new drug approved by the FDA for the treatment of Hodgkin's lymphoma since 1977 and is the first drug ever to receive FDA approval for the treatment of ALCL.<sup>2</sup>

CD30, a member of the tumor necrosis factor family, is expressed on the surface of several types of tumor cells. Specifically, it can be found on the surface of Reed-Sternberg cells in Hodgkin lymphoma and also on the cells found in ALCL; in contrast, CD30 is found on very few normal cells.<sup>3</sup> For the aforementioned reasons, CD30 represents a potentially viable target in the formulation of new selective antitumor agents. Previously developed unconjugated anti-CD30 antibodies showed some activity in vivo against the Reed-Sternberg cells, but clinical results were disappointing. To produce more potent antitumor activity, an antitubulin agent, monomethyl auristatin E, was attached by an enzyme-cleavable dipeptide link to cAC10 (SGN-30), a CD30-specific monoclonal antibody. This conjugated antibody-drug product was first known as SGN-35 and eventually would be named brentuximab vedotin.<sup>2,4</sup>

The mechanism of action of brentuximab is similar in principle to other antitumor drug-antibody conjugates already in use. First, the antibody portion of brentuximab binds the CD30 located on the cell surface. The conjugate is then rapidly internalized and transported to the lysosomes where the dipeptide link binding the antibody to the antitumor agent is cleaved.<sup>5</sup> The antitumor agent (monomethyl auristatin E) binds tubulin, inducing both the disruption of mitosis and the stimulation of apoptosis within the target cell.<sup>2</sup>

The accelerated approval of brentuximab for the Hodgkin lymphoma indication was based on the results of SG035-0003, a single-arm, multicenter phase 2 study designed to evaluate the overall response rate (ORR) of brentuximab as a single agent. Brentuximab was administered to patients during the trial at a dose of 1.8 mg/kg intravenously once every 3 weeks. The median duration of treatment during the study was 27 weeks. The ORR was 75%, with 34% (median duration of response of 20.5 months) and 40% (median duration of response of 3.5 months) reaching complete remission (CR) and partial remission (PR), respectively.<sup>3,5</sup>

The accelerated approval of brentuximab for the systemic ALCL indication was based on the results of SG035-0004, a single-arm, multicenter phase 2 study designed to evaluate the ORR of brentuximab

as a single agent. As in the previous trial, brentuximab was administered to patients during the trial at a dose of 1.8 mg/kg intravenously once every 3 weeks. The ORR was 86% with 57% (median duration of response of 13.2 months) and 29% (median duration of response of 2.1 months) reaching CR and PR, respectively.<sup>3,5</sup>

The most common adverse effects (incidence >20%), noted during both trials, were neutropenia, peripheral neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting.<sup>3,5</sup> Several grade 3–4 toxicities were experienced, including neutropenia (54%–55%; grade 4: 6%–9%), anemia (33%–52%; grade 4: ≤2%), and thrombocytopenia (16%–28%; grade 4: 2%–5%), as well as peripheral neuropathies, both sensory (52%–53%; grade 3: 8%–10%) and motor (7%–16%; grade 3: 3%–4%). Those patients who experienced neuropathies had received approximately 24–27 weeks of therapy. Brentuximab-induced peripheral neuropathy is cumulative; among patients in phase 2 trials who experienced any grade of neuropathy, approximately 50% experienced complete resolution.<sup>7</sup>

MMAE is both a substrate and inhibitor of CYP3A4/5. Both strong inhibitors and strong inducers (including identified herbal preparations) should be used with caution when coadministered with brentuximab. In addition, medications that may display enhanced adverse effects with immunosuppressants (leflunomide, natalizumab, topical tacrolimus) should be avoided, as well as live vaccines.

Full approval of brentuximab for the previously discussed indications is expected following the publication of results of other trials, such as

AETHERA, which are currently in progress. In addition, other clinical trials are studying the role of brentuximab in maintenance therapy as well as its role as a second-line agent.<sup>2,4</sup> The addition of brentuximab to other cytotoxic drugs/regimens is currently being investigated, as are weekly dosing strategies.<sup>6</sup> 

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## Crizotinib (Xalkori®)

**Class:** Anaplastic lymphoma kinase (ALK) inhibitor

**Indication:** Treatment of locally advanced or metastatic non-small cell lung cancer that harbor an ALK mutation

**Dose:** 250 mg PO twice daily

### Dose modifications

- Grade 3 hematologic toxicity: Hold therapy until toxicity improves to grade  $\leq 2$ , then resume at 250 mg twice daily
- Grade 4 hematologic toxicity: Hold therapy until toxicity improves to grade  $\leq 2$ , then resume at 200 mg twice daily
- Any Grade pneumonitis: Discontinue permanently
- Corrected QT (QTc) > 500 ms without serious signs or symptoms of arrhythmia (grade 3): Hold therapy until QTc < 480 ms (grade 1 [450–480 ms]), then resume at 200 mg twice daily; patients with serious signs or symptoms, discontinue permanently
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $\geq 5$  x upper limit of normal (ULN) with grade  $\leq 1$  total bilirubin: Hold therapy until toxicity improves to grade  $\leq 1$ , then resume at 200 mg twice daily
- ALT or AST  $\geq 3.5$  x ULN and total bilirubin  $\geq 1.5$  x ULN: Discontinue permanently

**Common adverse effects:** Vision disorder, nausea, diarrhea, vomiting, edema, constipation

**Serious adverse effects:** Pneumonitis, QTc prolongation, liver function test elevations (AST/ALT, bilirubin)

**Drug interactions:** Strong inducers and inhibitors of CYP3A; concomitant use of QTc-prolonging medications

## Newly Approved Targeted Agent for Non-Small Cell Lung Cancer

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Lung cancer continues to be the leading cause of cancer-related mortality worldwide. Although lung cancer rates decreased in 2011, 157,000 persons reportedly died from the disease, accounting for 27% of all cancer deaths.<sup>1</sup> The two primary types of lung cancer are small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately 85% of all lung cancer cases. NSCLC expresses significantly more molecular targets in

comparison to SCLC and thus lends itself more to molecularly targeted therapy. There are currently four U.S. Food and Drug Administration (FDA)-approved targeted therapies for NSCLC: bevacizumab for advanced or recurrent nonsquamous carcinoma, cetuximab for advanced or recurrent disease, erlotinib for positive epidermal growth factor receptor (EGFR) mutations,<sup>2</sup> and crizotinib, which is the newest targeted agent that received FDA approval within the past year. Crizotinib is for patients with locally advanced or metastatic NSCLC that harbor an anaplastic lymphoma kinase (ALK) mutation.

In NSCLC, the EML4-ALK fusion oncogene is the most commonly reported ALK mutation.<sup>3</sup> The EML4-ALK fusion is due to the inversion of chromosome 2 from the echinoderm microtubule-associated protein-like 4 (EML4) region with the ALK region, inv(2)(p21p23). The EML-ALK fusion mediates ligand-independent dimerization of the kinase, causing continuous downstream signaling of the PI3K-AKT, STAT3, and Ras-Raf-ERK pathways, which drive cell survival and proliferation.

Approximately 2%–7% (or 10,000) of patients with NSCLC in the United States are estimated to have NSCLC with ALK mutations.<sup>2</sup> Similar to the clinical phenotype of patients that harbor an EGFR mutation, ALK mutation is associated with clinicopathologic features that include the diagnosis of NSCLC at a younger age, no or minimal smoking history ( $\leq 10$  pack years), adenocarcinoma, and are mutually exclusive with EGFR or KRAS mutations.<sup>2,3</sup>

In patients with ALK-rearranged NSCLC, crizotinib inhibits the phosphorylation of ALK, preventing cellular proliferation and inducing apoptosis.<sup>3</sup> In the two-stage phase 1 trial, 82 patients with ALK-rearranged advanced NSCLC received crizotinib 250 mg twice daily until tumor progression to evaluate response to therapy and safety.<sup>4</sup> The patients included in the study were on average 51 years of age, had at least one prior therapy (93%), had adenocarcinoma histology (96%), and had no-to-minimal smoking history (94%). The overall response rate (ORR; complete and partial response) was reported to be 57%, in addition to a 33% disease stabilization rate, producing a 90% disease control rate overall. The estimated progression-free survival (PFS) at 6 months was 72% with a median follow-up of 6.4 months. The most common grade 1 side effects were nausea, diarrhea, visual disturbances, and liver function test (LFT) abnormalities. Grade  $\geq 3$  toxicity was primarily limited to LFT elevations. The authors concluded that crizotinib provided promising disease control rates in ALK-rearranged NSCLC patients with minimal toxicities.

At the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting, preliminary results from the phase 2 trial, PROFILE 1005, for patients with advanced and metastatic ALK-rearranged NSCLC who progressed after  $\geq 1$  chemotherapy regimen were presented.<sup>5</sup> Baseline characteristics were similar to the previous phase 1 trial in which patients were younger (average 52 years of age), had adenocarcinoma histology (94%), and were never smokers (68%). Patients received crizotinib 250 mg twice daily for a median of 9 weeks. Of the 76 patients evaluated for tumor response, 63 patients (83%) had target lesion shrinkage based on RECIST (Response Evaluation Criteria in

Solid Tumors) criteria; 41 patients had  $\geq 30\%$  decrease in tumor size. The most common grade 1 and 2 adverse events were nausea, vomiting, diarrhea, and vision disorder. The most common grade 3 and 4 adverse events were LFT elevations, dyspnea, and neutropenia. Two of the nine deaths were determined to be treatment related as a result of pneumonitis. Based on the initial results, the authors concluded that crizotinib provided antitumor activity with minimal side effects in patients who received previous NSCLC treatments.

The most common adverse reactions ( $\geq 25\%$ ) were vision disorders, nausea, diarrhea, vomiting, constipation, and edema.<sup>6</sup> Vision disorders included visual impairment, photopsia, photophobia, blurry vision, and diplopia. The most common grade 3 or 4 adverse reactions were LFT elevations (4%) with alanine aminotransferase (ALT) elevation being reported more than aspartate aminotransferase (AST). Severe life-threatening treatment-related pneumonitis occurred within 2 months of initiating crizotinib, leading to permanent discontinuation of therapy in 1.6% of the patients.

Dose modifications are recommended for patients who experience hematologic toxicities, LFT elevations, and QTc prolongation. Patients who develop grade 4 hematologic toxicities should hold therapy until counts recover to a grade  $\leq 2$  and reduce the dose of crizotinib to 200 mg twice daily. For ALT or AST elevations ( $>5\times$  ULN), patients should hold therapy until the values resolve ( $<1.5\times$  ULN) and reduce the dose to 200 mg twice daily. However, if patients have an elevated bilirubin ( $>1.5\times$  ULN) in combination with an ALT or AST elevation, treatment is permanently discontinued. For patients with QTc prolongation ( $>500$  ms), the dose is reduced to 200 mg twice daily, unless patients experience symptoms of serious arrhythmia, at which time treatment would be permanently discontinued. LFTs should be tested monthly while patients are on crizotinib. In addition, periodic electrocardiogram and electrolyte monitoring are recommended for patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities, or for those taking QTc-prolonging medications.

Crizotinib is predominantly metabolized in the liver and is an inhibitor of CYP3A4.<sup>6</sup> CYP3A inhibitors such as ritonavir, ketoconazole, clarithromycin, and St. John's Wort will increase systemic levels of crizotinib. CYP3A inducers such as rifampin, phenytoin, and phenobarbital will decrease the systemic levels of crizotinib. Dose reductions may be required for coadministered medications that are CYP3A4 substrates.

Crizotinib is available as 200- and 250-mg oral capsules.<sup>6</sup> The initial dose is 250 mg twice daily. It should be taken whole without regard to meals. Patients should avoid foods that contain a high quantity of furanocoumarin compounds, such as grapefruit juice, while on the medication. Patients should be counseled on the symptoms of arrhythmias (QTc prolongation), pneumonitis, vision changes, and gastrointestinal and peripheral edema adverse effects. Crizotinib is only available through certain specialty pharmacies. More information regarding obtaining the medication and the patient assistance program can be found on the Xalkori® website ([www.xalkori.com](http://www.xalkori.com)).

Currently, there are ongoing phase 3 trials comparing crizotinib to standard-of-care chemotherapy regimens. In the phase 3 randomized open-label trial (PROFILE 1007), there is an estimated enrollment of 318 patients comparing crizotinib to second-line therapy (either docetaxel or pemetrexed) for patients with ALK-rearranged advanced NSCLC (clinicaltrials.gov, identifier NCT00932893). In another phase 3 randomized open-label trial (PROFILE 1014), an estimated 334 patients with newly diagnosed ALK-rearranged NSCLC have enrolled (clinicaltrials.gov, identifier NCT01154140). Patients treated with crizotinib will be compared to those treated with pemetrexed and either cisplatin or carboplatin. PROFILE 1007 and PROFILE 1014 are estimated to be completed by September 2012 and December 2013, respectively.

Despite the initial results of phase 1 and 2 trials, there have been increasing reports of resistance to crizotinib within the first year of initiating treatment.<sup>7</sup> Some of the secondary mutations after initiating crizotinib involve L1196M, C1156Y, and F1174L.<sup>8</sup> There are newer generation ALK inhibitors being developed such as X-276/396 against L1196M mutations, and CH5424802 against L1196M, C1156Y, and F1174L mutations. In addition, there may be potential benefits in the utilization of combination treatments with crizotinib and EGFR inhibitors to prevent the activation of the EGFR signaling pathway to bypass ALK inhibition. There is a phase 1 trial evaluating erlotinib with or without crizotinib in patients with advanced NSCLC (clinicaltrials.gov identifier NCT00965731). In another phase 1 trial, crizotinib combined with PAN-HER inhibitor (PF-00299804) is being evaluated for the efficacy and safety in patients with erlotinib-resistant advanced NSCLC.

In addition to inhibiting ALK, crizotinib is also a tyrosine kinase inhibitor (TKI) of c-Met and its receptor, hepatocyte growth factor (HGF).<sup>9</sup> C-Met/HGF activation has been implicated in causing disease progression in advanced cancers due to its various roles in tumor invasion and metastasis.<sup>3,9</sup> Therefore, crizotinib is being studied in patients with ALK or c-Met mutations in various cancers such as anaplastic large-cell lymphoma, relapsed/refractory solid tumors, and brain and central nervous system tumors.<sup>3,4,9</sup>

Based on current results, National Comprehensive Cancer Network recommends crizotinib as a first-line therapy for patients who have ALK-rearranged NSCLC.<sup>2</sup> Crizotinib is the first FDA-approved small-molecule ALK inhibitor. Crizotinib has shown to improve response rates with minimal toxicities in phase 1 and 2 trials. Long-term benefits will need to be further evaluated from the current phase 3 trials.



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## Deferiprone (Ferriprox®)

**Class:** Iron chelating agent

**Indication:** Transfusional iron overload secondary to thalassemia syndromes after previous failure of other iron chelation therapy

**Dose**

Adults: 25 mg/kg to 33 mg/kg orally three times per day of total body weight

Pediatrics: Safety and efficacy not established

**Dosage form:** 500-mg tablets

**Common adverse effects:** Chromaturia, nausea, vomiting, abdominal pain, arthralgia, neutropenia, and increased alanine transaminase (ALT)

**Serious adverse effects:** Agranulocytosis

**Monitoring**

- Serum ferritin concentration; every 2–3 months to assess body iron stores for efficacy
- Absolute neutrophil count (ANC); before starting therapy, then weekly during therapy
- Serum ALT levels; monthly during therapy
- Plasma zinc concentrations; during therapy

**Drug interactions:** Polyvalent cations contained in minerals and antacids (e.g., iron, aluminum, zinc) should be avoided for 4 hours prior to or after ingestion of deferiprone

**Approval date:** October 14, 2011

## Treating Iron Overload with Deferiprone in Patients with Thalassemia After Failure or Intolerance of Other Iron Chelation Therapy

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The treatment of thalassemia is primarily dependent on red blood cell transfusion. This lifesaving therapy also brings about complications including iron overload, which causes significant morbidity and mortality in this patient population.<sup>1</sup> Deposition of iron occurs most frequently in the heart, liver, and endocrine glands, resulting in tissue and organ dysfunction and, ultimately, death.<sup>2,3</sup> Ferritin levels greater than 1,000 mg/mL typically evoke symptoms, while levels below 2,500 mg/mL are

correlated with decreased risk for cardiac disease and improved survival.<sup>2,4</sup> The treatment of iron overload requires its own unique therapy, namely, iron chelating agents (e.g., deferoxamine [Desferal<sup>®</sup>], deferasirox [Exjade<sup>®</sup>], and, more recently, deferiprone [Ferriprox<sup>®</sup>]). Although there is much debate about when to initiate therapy based on ferritin levels, the overall use of iron chelation therapy has doubled life expectancy in patients with iron overload secondary to thalassemia major.<sup>2</sup>

The oldest chelating agent, deferoxamine, has been in use for more than 40 years.<sup>3-6</sup> Categorized as a hexadentate chelator, it can bind one deferoxamine molecule to each iron atom. Deferoxamine reduces ferritin levels in the serum and liver, reduces endocrine complications and acute and long-term cardiac complications, and improves overall survival in thalassemia patients.<sup>7-9</sup> Although intramuscular (IM) and intravenous (IV) administration is possible with this product, 8- to 24-hour continuous subcutaneous (SC) infusions are preferred secondary to its limited half-life.<sup>3-5</sup> Adherence to SC infusion administration can be a major issue, and noncompliance with deferoxamine has been linked to early mortality.<sup>5</sup> Adverse events related to hearing loss, vision, growth, and bone changes are closely related to overchelation and can be minimized with dose reductions adjacent to a reduction in ferritin levels. Vitamin C has been used as an adjunct with deferoxamine to aid with iron excretion in doses  $\leq 200$  mg/day in adults.<sup>10</sup> Vitamin C doses greater than 500 mg/day can potentiate iron levels in cardiac tissues to toxic levels and should be avoided. Vitamin C should not be used in patients with heart failure who are also taking deferoxamine. Deferoxamine is renally excreted and should not be used in patients with severe renal dysfunction or anuria.<sup>6</sup>

The approval of deferasirox in 2005, the first orally available iron chelating agent in the United States, gave hope for improvements in adherence over deferoxamine.<sup>11</sup> Deferasirox is a tridentate chelator (1:2), which requires two deferasirox molecules to bind one iron atom.<sup>3-5</sup> A longer half-life (8–16 hours) promotes once-daily dosing. The ESCALATOR and EPIC trials have demonstrated reductions in both hepatic and serum ferritin levels.<sup>12,13</sup> Other trials have shown deferasirox to prevent but not reverse cardiac dysfunction, and more long-term data are needed to demonstrate effects on overall survival.<sup>14</sup> Although deferasirox appears to have solved problems with adherence, it comes with major side effects including, renal and hepatic failure and gastrointestinal hemorrhage.<sup>11</sup> Deferasirox contraindications are listed in **Table 1**. Deferasirox is only available through a closed distribution system as part of Exjade Patient Assistance and Support Services (EPASS<sup>™</sup>), a risk evaluation mitigation strategy (REMS) program. Both patients and prescribers are required to enroll in EPASS<sup>™</sup>. Distribution of deferasirox is only available from the three specialty pharmacies (BioScrip, Accredo Health Group, and US Bioservices).

The newest FDA-approved agent in the United States, deferiprone, is an oral agent that has been available in more than 50 countries for more than 10 years.<sup>3-5,15</sup> Deferiprone is an oral bidentate chelator (1:3) with a half-life of 2–3 hours, requiring three-times-per-day dosing. It is approved for transfusional iron overload secondary to thalassemia syndromes after previous failure of other iron chelation therapy. Safety for deferiprone has not been established for patients with other

chronic anemias. The recommended dosing for deferiprone ranges from 25 mg/kg to 33 mg/kg orally three times per day and doses should be rounded to the nearest 250 mg (half-tablet).

**Table 1: Comparison of Iron Chelating Agents<sup>1-6,11,15</sup>**

	Deferiprone (Ferriprox <sup>®</sup> )	Deferasirox (Exjade <sup>®</sup> )	Deferoxamine (Desferal <sup>®</sup> )
Stoichiometry (chelator:iron)	1:3 (bidentate)	1:2 (tridentate)	1:1 (hexadentate)
Dose	75–99 mg/kg/day in three divided doses	Initial dose: 20 mg/kg/day on empty stomach  Increase 5–10 mg/kg monthly based on serum ferritin  Max dose: 40 mg/kg/day	<i>Preferred route</i> SC: 1,000–2,000 mg (20–40 mg/kg/day) over 8–24 hours for 5–7 days  IM: 500–1,000 mg/day  IV: 1,000–2,000 (20–40 mg/kg/day); max rate 15mg/kg/hr
Route	Oral	Oral	Continuous SC, IM, IV
Dosage form	500-mg scored tablets	125-mg, 250-mg, 500-mg tablets to be dissolved into a suspension by patient	500-mg and 2,000-mg vial
Dose adjustments	None listed	Child-Pugh B: Reduce starting dose by 50% Child-Pugh C: Avoid use	Severe renal impairment: Avoid use
Half-life (plasma)	2–3 hours	8–16 hours	20–30 minutes
Excretion	Urine	Stool	Urine and stool
Major adverse effects	Agranulocytosis	Hepatic failure, renal failure, fatal gastrointestinal bleeding, hypersensitivity reactions, cytopenias	Flushing, hypotension, increased risk of infection, hearing loss, visual changes, growth retardation, bone changes
Contraindications	None	CrCl < 40 mL/min, or SCr > 2X ULN, poor performance status with high risk MDS or advanced malignancies, platelets < 50 x 10 <sup>9</sup> /L	Severe renal disease, anuria
REMS Program	No	Yes	No

*Note. MDS = myelodysplastic syndrome; ULN = upper limit of normal.*

Because of initial concerns of hepatotoxicity (namely hepatic fibrosis, which has not been seen in subsequent trials) deferiprone has been slow to arrive on the market.<sup>4</sup> Although its approval in the United States is based on reductions in serum ferritin levels, there are data showing greater efficacy in patients with more severe iron overload.<sup>16-18</sup> Another trial demonstrated long-term efficacy with deferiprone in some patients for up to 3 years.<sup>19</sup> Data regarding cardiac benefits, including combination therapy with deferoxamine, are the newest trend in iron chelation. These trials are not only demonstrating an improvement in serum ferritin level but an advantage with deferiprone in cardiac iron elimination as well. It should be noted that these trials use

doses, some of which are in combination, which vary from the current FDA-approved schedule.<sup>9,18,20-22</sup>

Common side effects of deferiprone are gastrointestinal: nausea, abdominal pain, and vomiting. Other effects include chromaturia, neutropenia, and arthralgia.<sup>15</sup> Deferiprone can cause agranulocytosis (1.7%), and fatal cases of agranulocytosis have also been reported. The mechanism of agranulocytosis from deferiprone is not well understood. Neutropenia can foreshadow the development of agranulocytosis; this requires monitoring absolute neutrophil count prior to initiation of therapy and weekly thereafter. Therapy requires cessation if patients develop an infection or become neutropenic. Patients should be encouraged to report any signs or symptoms of infection to their healthcare provider. Serum ferritin levels should be monitored every 2–3 months. If the serum ferritin falls below 500 mcg/L consistently, deferiprone therapy should be interrupted until levels constitute reinitiating therapy.<sup>15</sup>

The primary route of elimination of deferiprone is through hepatic metabolism of the 3-O-glucuronide. Glucuronidation of deferiprone is primarily responsible via UDP glucuronosyltransferase (UGT) 1A6. Patients with concurrent use of UGT 1A6 inhibitors such as silymarin (milk thistle) should be monitored closely to determine if reductions in deferiprone are necessary, although no formal evaluations have been conducted.<sup>15</sup>

The treatment of iron overload is critical to improve the outcomes of patients with thalassemia. Deferiprone is a newly approved agent to help fill the gap for patients who are not able to undergo iron chelation therapy with other first-line therapies. The major advantages of deferiprone include a better tolerated side effect profile, improved adherence with oral administration, and fewer restrictions to therapy based on renal and hepatic function. Combination therapy with deferiprone and deferoxamine is an exciting new area of research and is currently under investigation. 

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## Denosumab (Prolia®)

**Class:** Human IgG2 monoclonal antibody with affinity and specificity for human receptor activator of nuclear factor kappa-B ligand (RANKL)

**Expanded indications:** Increase bone mass in patients at high risk for fracture receiving androgen deprivation therapy (ADT) for non-metastatic prostate cancer or adjuvant aromatase inhibitors (AI) for breast cancer

**Dosage form and strength:** 60-mg single-use prefilled syringe or vial in a 1-mL solution, injection for subcutaneous use

**Dose and administration:** 60 mg every 6 months in combination with calcium 1,000 mg daily and  $\geq 400$  IU vitamin D daily

**Common adverse effects:** Arthralgias, back pain, extremity pain, and musculoskeletal pain

**Serious adverse effects:** Hypocalcemia, serious infections including skin infections, dermatologic reactions, and osteonecrosis of the jaw

**Monitoring:** Serum calcium and mineral levels (magnesium and phosphorus) are recommended

**Drug interactions:** No drug-drug interaction studies have been conducted.

**Approval date:** September 16, 2011

## Denosumab and Expanded Indications for Cancer Treatment–Induced Bone Loss (CTIBL) Due to Hormone Ablation in Prostate and Breast

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Prostate cancer is the most common malignancy among men; it was estimated to account for 29% of new cases in 2011.<sup>1,2</sup> Androgen deprivation therapy (ADT) is the most effective systemic treatment for prostate cancer; several adverse effects of ADT are osteoporosis and a greater incidence of clinical fractures.<sup>3</sup> In prospective trials ADT has been shown to cause accelerated bone turnover and decreased bone mineral density (BMD), a surrogate for fracture risk.<sup>4</sup> A study by Shahinian and colleagues analyzed the Surveillance, Epidemiology, and End Results (SEER) Medicare database of more than 50,000 men with prostate cancer. Patients who were treated with ADT and were alive 5 years after diagnosis had a higher incidence of fractures compared to

those not receiving ADT (19.4% versus 12.6%;  $p < .001$ ). A statistically significant relationship was found between the number of doses of gonadotropin-releasing hormone analogs received during the 12 months after diagnosis and subsequent risk of fracture, demonstrating that elevated fracture risk is correlated to treatment duration.<sup>5</sup>

Breast cancer is the most common malignancy among women; it was estimated to account for 30% of new cancer cases in women in 2011.<sup>1,6</sup> Aromatase inhibitors (AI) play a diverse role in the treatment of breast cancer for postmenopausal women with locally advanced or metastatic disease, disease progression following tamoxifen therapy, or adjuvant treatment of early hormone-receptor-positive disease.<sup>6</sup> A class effect of AIs is decreased BMD due to its mechanism of action, ultimately decreasing circulating estrogen levels and allowing for unmitigated bone resorption and bone loss. Clinically relevant long-term consequences that have been demonstrated in studies include an increased risk for development of osteoporosis and fractures.<sup>7</sup>

Denosumab is a human IgG2 monoclonal antibody that binds to human RANKL, a transmembrane, or soluble, protein essential for the formation, function, and survival of osteoclasts. It prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.<sup>8</sup>

Denosumab's initial U.S. Food and Drug Administration (FDA) approval on June 2, 2010, was for treatment of postmenopausal women with osteoporosis at high risk for fracture.<sup>8</sup> On November 19, 2010, it received FDA approval and was marketed by Amgen under Xgeva® for prevention of skeletal-related events in patients with bone metastases. Dosing for this indication is 120 mg as a subcutaneous injection every 4 weeks compared to its earlier FDA-approved dose of 60 mg as a subcutaneous injection every 6 months.<sup>9</sup> On September 16, 2011, the FDA approved two new indications for denosumab (Prolia®): as treatment to increase bone mass in (1) women at high risk for fracture receiving adjuvant (AI) therapy for breast cancer, and (2) men at high risk for fracture receiving (ADT) for nonmetastatic prostate cancer. In patients with prostate cancer, denosumab also reduces the incidence of vertebral fractures. These new indications make denosumab the first and only therapy for cancer treatment–induced bone loss (CTIBL) in patients undergoing hormone ablation therapy.

Approval for the extended indication for CTIBL was based on the results of Trial 20040138 and Trial 20040135. These were two phase 3 multinational, randomized, double-blind, placebo-controlled trials in 1,468 men receiving ADT for nonmetastatic prostate cancer and 252 postmenopausal women receiving adjuvant AI therapy for nonmetastatic breast cancer. Trial 20040138 was a 3-year study that included men older than 70 years of age or men younger than 70 with either a baseline BMD T-score at the lumbar spine, total hip, or femoral neck of  $< -1.0$  or history of osteoporotic fracture. Trial 20040135 was a 2-year study that included women with BMD T-scores between  $-1.0$

and -2.5 at the lumbar spine, total hip, or femoral neck, and had not experienced fracture after age 25.<sup>10,11</sup> The primary endpoints for Trial 20040138 and Trial 20040135 were percent change in lumbar spine BMD from baseline to month 24, and baseline to month 12, respectively. A secondary endpoint in Trial 20040138 was the incidence of new vertebral fractures through month 36.<sup>10,11</sup> Patients were randomized to receive subcutaneous injections of either placebo or denosumab 60 mg once every 6 months, for a total of six doses in Trial 20040138 and four total doses in Trial 20040135. In both trials, all patients were instructed to take at least calcium 1,000 mg and vitamin D 400 IU orally daily.<sup>10,11</sup> Randomization for Trial 20040138 was stratified by age (<70 years versus ≥70 years) and duration of ADT at trial entry (≤6 months versus >6 months). Eighty-three percent of men were ≥70 years of age and 76% received ADT for more than 6 months at trial entry.<sup>10</sup> Randomization for Trial 20040135 was stratified by duration of adjuvant AI therapy at trial entry (≤6 months versus >6 months). Sixty-three percent received adjuvant AI therapy for more than 6 months at trial entry.<sup>11</sup>

Denosumab resulted in a statistically significant change in lumbar spine BMD from baseline in both studies. In prostate cancer, BMD was increased at 24 months by 6.7% in the denosumab group compared to the placebo group (5.6% versus -1.0%;  $p < .001$ ). In addition, denosumab significantly reduced the incidence of new vertebral fractures at 36 months (1.5% versus 3.9%;  $p = .0125$ ).<sup>10</sup> With breast cancer, BMD was increased at 12 months by 5.5% in the denosumab group compared to the placebo group (4.8% versus -0.7%;  $p < .0001$ ).<sup>11</sup> The most common adverse effects (≥10%) were arthralgias and back pain. Pain in the extremities (9.9%) and musculoskeletal pain (6%) were also reported. The most common adverse reactions leading to discontinuation were back pain and constipation.<sup>8</sup> A greater incidence of cataracts was observed in men with nonmetastatic prostate cancer receiving denosumab compared to placebo (4.7% versus 1.2%).<sup>10</sup>

Denosumab may exacerbate hypocalcemia, thus preexisting hypocalcemia must be corrected prior to initiating therapy. Clinical monitoring of calcium, phosphorus, and magnesium are recommended for patients who are predisposed to hypocalcemia and disturbances of mineral metabolism, such as history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, and severe renal impairment. Patients with severe renal impairment (CrCL < 30 mL/min) or receiving dialysis should be counseled about the symptoms of hypocalcemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation. Other serious adverse effects such as serious infections, severe dermatologic reactions (e.g., dermatitis, eczema, rashes), and osteonecrosis of the jaw have also been reported. Denosumab was approved with a Risk Evaluation and Mitigation Strategy (REMS) program; a Dear Healthcare Professional Letter and Medication Guide are provided to inform healthcare providers about potential adverse effects. No drug-drug interaction studies have been conducted with denosumab.<sup>8</sup>

The dose for treatment of CTIBL in nonmetastatic breast and prostate cancer patients undergoing hormone ablation therapy is 60 mg as a subcutaneous injection every 6 months in the upper arm, upper thigh, or abdomen. Denosumab should be administered by a

healthcare professional. Patients should also be instructed to take calcium 1,000 mg and vitamin D at least 400 mg IU orally daily. No dose adjustment is necessary in patients with renal impairment. However, because of increased risk of hypocalcemia in patients with severe renal impairment (CrCL < 30 mL/min) or receiving dialysis, consider the benefit-risk profile when administering to this patient population. No clinical studies have been conducted to evaluate the effect of hepatic impairment on its pharmacokinetics. Denosumab (Prolia<sup>®</sup>) is available as a single-use prefilled syringe containing 60 mg in a 1-mL solution and a single-use vial containing 60 mg in a 1-mL solution.<sup>8</sup>

Currently, trials are underway that will further evaluate the efficacy and safety of denosumab for existing and new indications. The long-term safety and efficacy for the treatment of osteoporosis will be evaluated in a multinational, multicenter, open-label, single-arm extension study of the patients who completed the 3-year pivotal study; anticipated follow-up is 7 years (clinicaltrials.gov identifier, NCT00523341). The ADAMO trial is a phase 3 randomized, double-blind, placebo-controlled study that will examine denosumab's efficacy and safety in males with low BMD (clinicaltrials.gov, identifier NCT00980174). The D-CARE trial is a phase 3 multicenter, randomized, double-blind, placebo-controlled study of denosumab as adjuvant treatment for women with early-stage breast cancer at high risk of recurrence. Primary outcome will be bone metastasis-free survival. Dosing for this study will be 120 mg subcutaneously once monthly for 6 months, then 120 mg subcutaneously every 3 months for the next 4½ years (clinicaltrials.gov identifier NCT01077154). In addition, there is a phase 2 multicenter, single-arm, proof-of-concept study for the treatment of hypercalcemia of malignancy in patients with elevated serum calcium despite recent treatment with IV bisphosphonates. Primary outcome will be proportion of patients with a response, defined as corrected serum calcium ≤11.5 mg/dL within 10 days after the first dose of denosumab. Dosing for this study will be 120 mg subcutaneously every 4 weeks with a loading dose of 120 mg subcutaneously on study days 8 and 15 (clinicaltrials.gov, identifier NCT00896454).

The use of AI and ADT for breast and prostate cancer and the accelerated bone loss associated with these treatments represents a challenge in this patient population. Twice yearly administration of denosumab demonstrated significant increases in BMD from baseline when compared to placebo in men and women at high risk for fracture from ADT and AI therapy, respectively. The new FDA-approved indications make denosumab the first and only therapy for CTIBL in patients undergoing hormone ablation therapy. 

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## Rays of Hope Yoga Fundraiser

Saturday, March 24, 6:30-7:30 am at the HOPA 8th Annual Conference

Yoga Fundraiser includes one 1-hour session, a T-shirt, and light refreshments (donation \$40).

Stretch Your Wallet Not Your Body Donation: \$25

Not attending conference? Contact HOPA member services at 877.467.2719 to donate.



Proceeds from the event will benefit the Give Hope Foundation, a nonprofit organization that provides support to children and families in Central Florida who are battling childhood cancer and have a unique combination of medical, emotional, and financial needs.

Make your donation while registering for conference at [Conference Web Central](http://ConferenceWebCentral.com) and reserve your spot.

Rays of Hope



## Ruxolitinib (Jakafi™)

**Class:** Janus kinase (JAK1 and 2) inhibitor

**Indications:** FDA approved for the treatment of intermediate or high-risk myelofibrosis, including primary, postpolycythemia vera and postessential thrombocythemia myelofibrosis

**Dose:** Dosing is based on the patient's platelet count and renal or hepatic function.

- Normal renal, hepatic function and platelet count  $>200 \times 10^9/L$ : start at 20 mg orally twice daily
- Platelet count 100–200  $\times 10^9/L$ : start at 15 mg orally twice daily
- Do not use if platelets less than 100  $\times 10^9/L$

Doses should not be increased during the first 4 weeks of therapy and no more frequently than every 2 weeks.

**Dosage form:** Oral tablet: 5 mg, 10 mg, 15 mg, 20 mg, 25 mg

**Common adverse effects:** Hematologic (e.g., thrombocytopenia, anemia, neutropenia), bruising, increase in serum cholesterol, hepatic enzyme elevations, dizziness, and headache

**Serious adverse effects:** Grade 3–4 thrombocytopenia (13%) and anemia (45%)

**Monitoring:** Complete blood count performed every 2–4 weeks after starting ruxolitinib and dosing adjusted based on platelet counts. Doses should not be increased during the first 4 weeks of therapy and no more frequently than every 2 weeks.

**Drug interactions:** Ruxolitinib is a CYP3A4 substrate.

- For concomitant therapy with strong CYP3A4 inhibitors: ruxolitinib dose reduced to 10 mg twice daily
- For concomitant CYP3A4 inducers: no dose adjustments are recommended at this time

**Approval date:** November 16, 2011

## Ruxolitinib for Treatment of Intermediate or High-Risk Myelofibrosis

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Myelofibrosis is a myeloproliferative disorder. It can be the primary diagnosis or secondary due to other diseases or medications. Patients are typically middle age to elderly at the time of diagnosis. Patients commonly present with fatigue, symptoms caused by an enlarged

spleen (i.e., fullness), weight loss, or night sweats. Some patients are asymptomatic and may be diagnosed after an incidental finding of hepato- or splenomegaly or an abnormality during a routine CBC.<sup>1</sup>

Ruxolitinib is a Janus kinase (JAK 1 and 2) inhibitor that is U.S. Food and Drug Administration (FDA) approved for the treatment of intermediate or high-risk myelofibrosis, including primary, postpolycythemia vera, and postessential thrombocythemia myelofibrosis. Ruxolitinib is the first medication specifically approved by the FDA for myelofibrosis.<sup>2</sup>

Two phase 3 studies have been conducted to determine the efficacy of ruxolitinib and are available in abstract form. Both studies were conducted in patients with primary, postpolycythemia, or postessential thrombocythemia myelofibrosis. In both studies patients had palpable splenomegaly at least 5 cm below the costal margin and an International Working Group Consensus Criteria risk category of intermediate or high.

The first phase 3 trial (Comfort-I trial<sup>3</sup>) was a double-blind, randomized, placebo-controlled study of 309 patients who were refractory or not eligible for currently available therapies. The median age was 68 (range 40–91 years), median hemoglobin was 10.5 g/dL, median platelet count was 251  $\times 10^9/L$ , median palpable spleen length was 16 cm below the costal margin, and median spleen volume as measured by magnetic resonance imaging (MRI) or computed tomography (CT) was 2,595  $\text{cm}^3$ . The primary endpoint of the study was the proportion of patients achieving  $>35\%$  reduction in spleen volume at week 24. Secondary endpoints were duration of response and proportion of patients with  $>50\%$  reduction in total symptom score (TSS) at week 24 (as measured by Myelofibrosis Symptom Assessment Form [MFSAF v 2.0]). A significantly higher proportion of patients in the treatment group had a  $>35\%$  reduction in spleen volume at 24 weeks. In the treatment group, 41.9% of patients achieved the primary endpoint of  $>35\%$  reduction in spleen volume at week 24 compared to 0.7% in the placebo group ( $p < .0001$ ). The secondary endpoint of  $>50\%$  reduction in TSS at week 24 was achieved by 45.9% in the treatment group and only 5.3% in the placebo group ( $p < .0001$ ). The TSS score assesses symptoms of abdominal discomfort, pain under left ribs, early satiety, night sweats, itching, and bone or muscle pain. The proportion of patients with  $>50\%$  reduction in individual symptom score at week 24 was much higher in the treatment group (35%–60%) than the placebo group (10%–15%).

The second phase 3 trial (Comfort-II trial<sup>4</sup>) as an open-label, randomized study of 219 patients who received ruxolitinib or best available therapy. Median age was 66 years (range 35–85 years), median hemoglobin was 10.4 g/dL, median platelet count was 236  $\times 10^9/L$ , median palpable spleen length was 15 cm below the costal margin, and median spleen volume by MRI or CT was 2,381  $\text{cm}^3$ . The primary efficacy endpoint was proportion of patients achieving  $>35\%$  reduction in spleen volume at week 48. The secondary endpoint was the proportion of patients achieving  $>35\%$  reduction in spleen volume at week 24. In the treatment group, 28.5% of patients had a  $>35\%$  reduction in

spleen volume at week 48 compared to 0% in the best available therapy group ( $p < .0001$ ). Median duration of response was 11 months.

Patients may experience difficulty in discontinuing therapy.<sup>5</sup> Patients who were part of the original phase 1 and 2 studies were evaluated in a recent publication from the Mayo Clinic. Ninety-two percent of the 51 patients evaluated had discontinued treatment. The majority of the patients discontinued treatment because of a loss of therapeutic effect, and some patients had to discontinue treatment because of adverse events. Patients were found to have an acute relapse of disease symptoms, splenomegaly, cytopenias, and, in severe cases, shock-like symptoms including hemodynamic instability. These symptoms developed rapidly for some patients (within 24 hours). Adverse events upon discontinuation were so severe in five of the patients (11%) that they had to be managed in an acute care setting. If a patient needs to discontinue the medication, they should be tapered by 5 mg twice daily each week under the close monitoring and guidance of the healthcare team. Even with a tapering schedule, some of the patients still experienced adverse events. Patients should be counseled on this risk prior to starting therapy.

Dosing is complicated and based on the patient's platelet count and renal and/or hepatic function (Table 1). Patients with normal renal and hepatic function and a platelet count  $>200 \times 10^9/L$  should be started on 20 mg twice daily. If the patient has a platelet count  $100-200 \times 10^9/L$ , they should be started on 15 mg twice daily. Ruxolitinib should not be used in patients with a platelet count  $<100 \times 10^9/L$ .

**Table 1. Starting Dose of Ruxolitinib (Normal Renal and Hepatic Function)**

Platelet Count	Starting Dose
$>200 \times 10^9/L$	20 mg twice daily
$100-200 \times 10^9/L$	15 mg twice daily
$<100 \times 10^9/L$	Avoid use

Patients with moderate (CrCl 30–59 mL/min) to severe renal impairment (CrCl 15–29 mL/min) and a platelet count of  $100-150 \times 10^9/L$  should reduce their dose to 10 mg twice daily. Dosing for patients with end-stage renal disease (ESRD; CrCl  $<15$  mL/min) on dialysis and a platelet count  $100-199 \times 10^9/L$  is 15 mg or platelet count  $>200 \times 10^9/L$  is 20 mg. Doses should be given on dialysis days after dialysis sessions. Patients with ESRD not on dialysis should not receive ruxolitinib. Patients who have any hepatic impairment and a platelet count  $100-150 \times 10^9/L$  should have their dose reduced to 10 mg twice daily.

The following dosing guidelines should be followed to adjust the patient's dose if they experience a decline in platelets (Table 2).

**Table 2. Dosing for Thrombocytopenia**

Current Jakafi Dose	25 mg twice daily	20 mg twice daily	15 mg twice daily	10 mg twice daily	5 mg twice daily
Platelet Count	New Dose				
$100-125 \times 10^9/L$	20 mg twice daily	15 mg twice daily	No change	No change	No change
$75-99 \times 10^9/L$	10 mg twice daily	10 mg twice daily	10 mg twice daily	No change	No change
$50-74 \times 10^9/L$	5 mg twice daily	No change			
$<50 \times 10^9/L$	Hold	Hold	Hold	Hold	Hold

Following the dose reductions above when a patient begins to experience thrombocytopenia can help avoid treatment interruptions. If the patient experiences a platelet count below  $50 \times 10^9/L$ , the dose should be held until platelets recover to acceptable levels. Dosing should be restarted at 5 mg twice daily below the dose prior to the dosing interruption. New dosing for the patient should not exceed the following levels after a restart (Table 3):

**Table 3. Maximum Restarting Doses After Interruption**

Platelet Count	Maximum Dose After Restarting
$>125 \times 10^9/L$	20 mg twice daily
$100-124 \times 10^9/L$	15 mg twice daily
$75-99 \times 10^9/L$	10 mg twice daily x2 weeks, then may increase to 15 mg twice daily if platelet count is stable
$50-74 \times 10^9/L$	5 mg twice daily x2 weeks, then may increase to 10 mg twice daily if platelet count is stable
$<50 \times 10^9/L$	Hold

Patients should have a CBC performed every 2–4 weeks after starting ruxolitinib, and dosing should be adjusted based on platelet counts. Doses should not be increased during the first 4 weeks of therapy and no more frequently than every 2 weeks.

Hematologic side effects are the most common events with the administration of ruxolitinib and are dose related.<sup>6</sup> Thrombocytopenia occurred in almost 70% (all grades) of patients and anemia in more than 96% (all grades) of patients. These adverse effects could be quite severe with almost 13% of patients experiencing grade 3–4 thrombocytopenia and more than 45% experiencing grade 3–4 anemia. Neutropenia also occurred but was much lower at approximately 20% (all grades). Other common side effects ( $>10\%$ ) included bruising, an increase in serum cholesterol, hepatic enzyme elevations, dizziness, and headache.

Pharmacokinetic/pharmacodynamic studies in healthy volunteers show that ruxolitinib is a CYP3A4 substrate.<sup>7</sup> For patients receiving concomitant therapy with a strong CYP3A4 inhibitor (i.e., azole antifungals, clarithromycin, antiretrovirals) the AUC of ruxolitinib could be

increased more than 90%. Patients taking strong inhibitors should have their ruxolitinib dose reduced to 10 mg twice daily and then monitored closely for further dosing adjustments. For patients taking concomitant CYP3A4 inducers there was a decrease in the AUC of ruxolitinib, but the pharmacodynamic effect was felt to not be clinically significant. Patients on concomitant inducers should be monitored carefully, but no dose adjustments are recommended with the concurrent use of CYP3A4 inducers at this time.

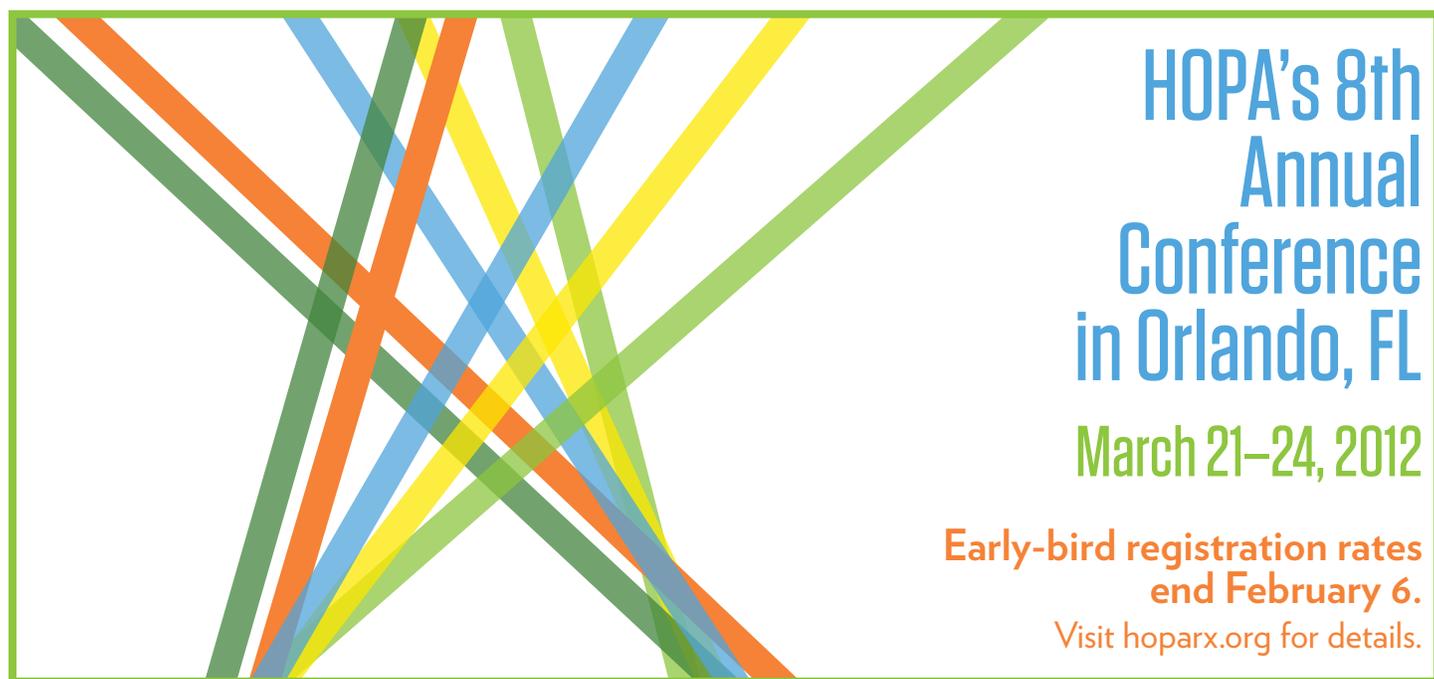
Ruxolitinib is only available through specific specialty pharmacies. IncyteCARES facilitates access to the medication.<sup>8</sup> The patient and the provider will need to complete and sign the enrollment form. The provider's office should send the form to the CARES program. They will verify patient benefits and send the prescription to the pharmacy that will provide the lowest out-of-pocket cost for the patient. The medication is shipped directly to the patient.

The dispensing pharmacy should provide the FDA-approved patient information sheet every time the patient receives their Jakafi™ prescription. Patients should be educated about the need to monitor their blood counts throughout their treatment. Ruxolitinib can be taken with or without food, and patients should be instructed not to drink grapefruit juice while on ruxolitinib. Patients should be advised to speak with their physician before starting or stopping any medications or supplements and to let their healthcare team know if they have any signs of bleeding, bruising, or infection. It is important that patients understand the risk of discontinuing therapy without the guidance of their physician.

This medication gives symptomatic relief to patients who had few options prior to the approval of ruxolitinib. It will be interesting to see further data on the duration of response and whether there is an impact on overall survival. 

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# American Society of Hematology: 2011 Meeting Summary

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The 53rd Annual American Society of Hematology (ASH) Annual Meeting and Exposition took place in San Diego, CA, December 10–13, 2011. The clinical data presented highlighted 2011's top developments in hematology, which are certain to have practical implications in the years to come. Below are summaries a few key abstracts for pharmacists practicing in the field of hematology/oncology.

During the plenary session, results from a trial comparing the use of filgrastim-mobilized peripheral blood stem cells (PBSCs) with bone marrow for unrelated donor transplants were presented. The use of PBSCs is very common in allogeneic transplant; previous data have indicated use of PBSCs in matched sibling donor transplant results in improved engraftment, relapse rates, and survival. However, in this phase 3, randomized, multicenter trial, PBSCs failed to provide any advantage in relapse rates or survival for unrelated donor transplant. Two-year overall survival (OS) among 273 patients randomized to receive PBSCs from an unrelated donor was 51% versus 46% of 278 patients randomized to bone-marrow transplants ( $p = .25$ ). In addition, rates of chronic extensive graft versus host disease (GVHD) were significantly higher in the PBSC arm (46% versus 31%). Acute GVHD rates were similar between the two arms. PBSCs did perform better than bone marrow in time to engraftment (faster by 5–7 days), and had lower rates of graft failure (2.7% versus 9.1%). Future studies will be necessary to determine the best methods to balance the risks and benefits between the two approaches in unrelated donor transplant.

Additional clinical data presented during the plenary session included information about gemtuzumab ozogamicin (Mylotarg), which was withdrawn from the U.S. market in 2010. Gemtuzumab ozogamicin may enjoy renewed interest after a French trial showed it may increase survival in de novo acute myeloid leukemia. Patients ( $n = 280$ ) ages 50–70 years were randomized to receive induction therapy with daunorubicin 60 mg/m<sup>2</sup> days 1–3 and cytarabine 200 mg/m<sup>2</sup> days 1–7 with or without gemtuzumab ozogamicin using a fractionated dosing scheme of 3 mg/m<sup>2</sup> on days 1, 4, and 7. Patients achieving a complete response (CR) went on to receive two consolidation courses with daunorubicin 60 mg/m<sup>2</sup> on day 1 and cytarabine 2 grams/m<sup>2</sup> every 12 hours on days 1–4 with or without gemtuzumab ozogamicin 3 mg/m<sup>2</sup> on day 1, according to randomization arm. Complete response + partial complete response (CR+CRp) rates were similar between the groups: 80% in the gemtuzumab group versus 75% in the control group ( $p = .31$ ). However, event free survival (EFS) and OS were significantly improved in the gemtuzumab group versus controls, with a 2-year EFS of 41.4% versus 15.6% ( $p = .0018$ ), and median survival of 25.4 months versus 15.3 months ( $p = .037$ ), respectively. The rate of fatal adverse events was not significantly different between the two arms; however, prolonged thrombocytopenia requiring transfusion was more frequently observed in the gemtuzumab arm. Three cases of veno-occlusive disease, two of which were fatal, also occurred in the gemtuzumab arm.

A novel targeted and currently unnamed agent generated excitement in the areas of chronic lymphocytic leukemia (CLL) and mantle cell

lymphoma. PCI-32765 is an oral irreversible inhibitor of Bruton's tyrosine kinase, a central mediator of B-cell receptor signaling and normal B-cell development. In a follow-up of a phase 1b/2 trial in patients with CLL previously presented at the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting, PCI-32765 was highly active and well tolerated. The trial enrolled 61 patients with relapsed/refractory CLL/small lymphocytic lymphoma using two dosing cohorts: 420 mg ( $n = 27$ ) and 840 mg ( $n = 34$ ). With 10.2 months of follow-up in the 420 mg cohort, objective response rate (ORR) was 70% by International Workshop on CLL criteria (an increase from 48% at 6.2 months follow-up reported at ASCO 2011). ORR in the 840-mg cohort was 44% at 6.5 months median follow-up. An additional 19% and 35% of patients in the cohorts, respectively, had reduction in lymphadenopathy with residual lymphocytosis. Interestingly, responses were independent of molecular risk features. The drug was well tolerated, with only two patients discontinuing therapy due to adverse events and six patients requiring dose reduction.

In addition to the CLL data, early results from a phase 2 trial of PCI-32765 at a dose of 560 mg daily in relapsed/refractory mantle cell lymphoma were also encouraging. Thirty-nine patients initiated treatment in this study, with 24 (12 bortezomib-naïve, 12 bortezomib-exposed) evaluable for efficacy. The ORR was 67% (16/24), with ORR of 58% (7/12) in the bortezomib-naïve cohort and 75% (9/12) in the bortezomib-exposed cohort. Treatment was well tolerated with 35 of 39 patients remaining on PCI-32765; reasons for discontinuation included progressive disease ( $n = 3$ ) and investigator decision ( $n = 1$ ). Longer follow-up will be needed to determine duration of response and PFS.

Obinutuzumab (GA101), which is another new drug, is a humanized type II monoclonal antibody targeting the CD-20 receptor. It showed a higher response rate in relapsed indolent lymphoma patients in a head-to-head trial with rituximab. One hundred forty-nine patients with follicular lymphoma who had a previous response to rituximab were randomized to receive 4 weekly infusions of either obinutuzumab 1,000 mg ( $n = 74$ ) or rituximab 375 mg/m<sup>2</sup> ( $n = 75$ ). Patients who responded to treatment without evidence of progression following induction therapy received ongoing treatment with obinutuzumab or rituximab at the same dose every 2 months for up to 2 years. After independent radiology review, the ORR for follicular lymphoma patients was 43.2% in the obinutuzumab group versus 28% for rituximab. The complete response/complete response unconfirmed (CR/CRu) rate in the obinutuzumab arm was 10.8% compared to 6.7% for rituximab. Obinutuzumab was well tolerated, but a higher number of low grade infusion reactions were noted.

In Hodgkin's lymphoma, 12-year overall survival data from the HD6 trial were presented and simultaneously published in the *New England Journal of Medicine* (Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med*. 2011. DOI: 10.1056/NEJMoa1111961.) This trial examined the long-term survival implications of chemotherapy

alone versus radiation-based therapy in limited stage Hodgkin's lymphoma patients. Initiated in 1994, the trial randomized 405 patients with stage 1A or 2A Hodgkin's lymphoma to receive either ABVD alone ( $n = 196$ ) for 4–6 cycles or treatment that included subtotal nodal irradiation therapy, up to 35 Gy in 20 daily fractions ( $n = 203$ ). Patients in the radiation therapy group who had a favorable risk profile received subtotal nodal radiation therapy alone, while patients with an unfavorable risk profile received two cycles of ABVD followed by subtotal nodal radiation therapy. Earlier published reports from this trial had indicated lower rates of disease relapse in the radiation arm, with no difference in OS. However, long-term survival data presented at ASH showed chemotherapy alone was associated with higher rates of OS when compared with the radiation arm (94% versus 87% of patients were still alive at 12 years; hazard ratio, 0.50; 95% CI, 0.25–0.99;  $p = .04$ ). The lower rate of survival in the radiation arm primarily was the result of deaths from causes other than Hodgkin's lymphoma, mostly second cancers and cardiac events. The results of this trial emphasize the point that better short-term disease control does not always result in patients living longer. It is important to note that since this trial's initiation in 1994, the use of subtotal nodal irradiation is no longer standard, having been supplanted by lower dose-involved field radiation.

From the nonmalignant hematology perspective, results from the RE-COVER II trial confirmed the noninferiority of dabigatran to warfarin in the treatment of acute venous thromboembolism (VTE). This double-blind, double-dummy trial randomized 1,279 patients to dabigatran 150 mg twice daily, and 1,289 patients to warfarin dosed to maintain an international normalized ratio of 2–3. Treatment was continued for 6 months, and all patients received 5–11 days of initial VTE treatment with low-molecular-weight or unfractionated heparin. In the dabigatran group, 30 (2.4%) had recurrent VTE compared with 28 (2.2%) in the warfarin group, which met the prespecified noninferiority margin ( $p < .0001$ ). Bleeding events were also not statistically different, with major bleeding occurring in 15 patients treated with dabigatran and 22 patients treated with warfarin (hazard ratio 0.69; 95% CI, 0.36–1.32). Currently, dabigatran is approved in the United States only for the prevention of stroke in patients with nonvalvular atrial fibrillation.

The wealth of data presented at the 2011 ASH Annual Meeting and Exposition will certainly enrich our knowledge base in hematology and prompts new questions about our practice. Will PBSCs continue to be used more frequently than bone marrow for unrelated donor transplant? Is there perhaps a way to mitigate the increased risk of chronic GVHD with PBSCs? Is the obinutuzumab data compelling enough to consider it a “better” anti-CD20 antibody than rituximab? Will gemtuzumab ozogamicin return to the market? We'll look to answer these questions and more in the years to come. 