



# HOPA News

## The Controversy Remains, a Consensus Is Needed: How to Assess Renal Function for Dosing Carboplatin

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Recently the National Cancer Institute's Cancer Therapy Evaluation Program (NCI/CTEP) authored two action letters to address carboplatin dosing on NCI/CTEP-sponsored protocols and the recent increase in toxicity (the result of which has been an upsurge in oncology practice headlines highlighting the numerous controversies surrounding carboplatin dosing). Although the focus of the recent discussion surrounding carboplatin has been on implementing the isotope-dilution mass spectrometry (IDMS) assay to measure serum creatinine and only using the Cockcroft-Gault equation for calculating creatinine clearance, it is unlikely that these are the only variables contributing to carboplatin-related toxicity.

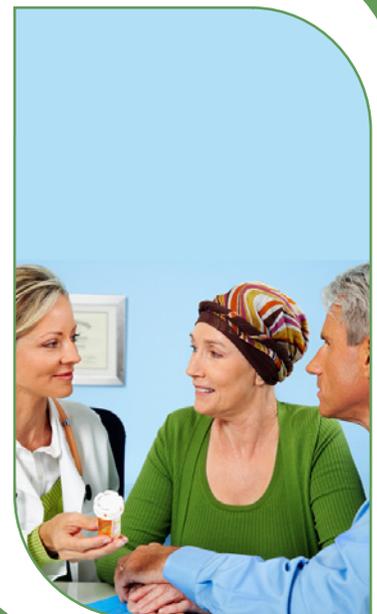
In December 2009 the HOPA Research, Standards, and Education Committees all recognized and agreed that the controversy and variability in carboplatin dosing needed to be addressed. At that time, the HOPA Research Committee had already initiated a survey for carboplatin dosing to determine practice patterns. As such, the decision was made to wait to use the survey results to create evidence-based recommendations that defined the "standard of practice." Initial plans were to correlate patient outcomes from a database of more than 300 patients treated in the Gynecologic Oncology Center at The University of Texas MD Anderson Cancer Center (Research Committee), develop guidelines for dosing carboplatin (Standards Committee), and create educational programming (Education Committee). We were being overly optimistic. As you can see from survey results reported in this issue, the HOPA Carboplatin Dosing survey only confirmed what we already knew: significant variability in clinical practice exists in the assessment of renal function prior to dosing chemotherapy.

In light of the NCI/CTEP action letters, the HOPA Research Committee has proposed to the board that HOPA make a "call to action" to all HOPA members, other pharmacy organizations, and other healthcare professional organizations to work together to achieve consensus regarding how to assess renal function when dosing carboplatin and other medications. Although the concept of consensus may seem simplistic and basic, it might be too ambitious to achieve across all medical specialties. So, at a minimum, I would urge those of us in oncology pharmacy practice to facilitate working with other oncology healthcare professionals (e.g., medical oncologists, nurse practitioners, gynecologic oncologists) to create a standard of practice for the assessment of renal function for dosing medications in oncology patients. The appropriate assessment of renal function for dosing medications extends well beyond carboplatin; there is a need for consistency in dosing all drugs. There exists a narrow therapeutic index in which a slight change in concentration can be associated with a significant increase in toxicity or a decrease in effectiveness. We need consistency in practice.

In the many discussions I have had during the past month about this issue, the best analogue for this situation is assessing anticoagulation using international normalized ratio (INR) values. Regardless of where a patient has had his or her prothrombin time (PT)/INR labs drawn, the INR value is the same (although clinicians' responses to the INR value is likely to vary based on clinical setting, patient factors/conditions, etc.).

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Consequently, when I promote establishing consensus in how we assess renal function for dosing medications, I am not suggesting that the clinical action/response to estimated creatinine clearance (CrCl) will be the same; rather, it will depend on which drug is being administered, clinical indications, and patient factors. Consensus would not replace clinical judgment.

To begin working toward consensus, I think we need to concede that there is no “best” way to estimate renal function that will be as accurate as an actual measured glomerular filtration rate. Each estimation method has its limitations and every clinician will have an argument as to why his or her own approach is best. Undoubtedly, there will be a publication available to support each scenario. Despite this, we need to accept that the decision has already been made. Cockcroft-Gault has been the standard equation used to assess renal function for the development of drug dosing guidelines for the majority of the Food and Drug Administration (FDA)-approved drugs on the market today. The FDA Guidance to Industry previously acknowledged that the method of assessing renal function used during drug development should be the method used in clinical practice; historically, this has overwhelmingly been the Cockcroft-Gault equation.<sup>1</sup> This suggestion for standardization of assessment of renal function for drug dosing is not a new concept. According to Dowling and colleagues, Cockcroft-Gault was used by more than 90% of critical care clinical pharmacists surveyed for drug dosing.<sup>2</sup> Even in the HOPA Carboplatin Dosing survey, more than 86% of respondents were using Cockcroft-Gault to assess renal function.

The challenge that remains is to standardize our use of the Cockcroft Gault assessment tool. The Cockcroft Gault tool is not validated with IDMS serum creatinine. Using it will result in higher creatinine clearance values, which leads to higher doses and, therefore, a higher potential risk of toxicity. There is a need to establish consistency in practice so that the estimated CrCl amount calculated in any major cancer center is the same, reproducible estimate when calculated at any community oncology practice office. Consistency in clinical practice needs to be established and is long overdue. Ultimately, inconsistency in clinical practice contributes to undue risk in oncology patient care and can be easily remedied.

The IDMS assay has helped establish consistency in the measured results for serum creatinine. However, we still need to determine consensus regarding what weight to use for dosing, specifically in obese patients; whether (and how) to convert IDMS to non-IDMS serum creatinine; what lower threshold for SrCr should be used; and what (if any) upper limits of creatinine clearance should be used. After reaching consensus, these factors need to be implemented and universally adapted in a timely fashion into clinical practice to limit the risk of avoidable drug-related toxicity associated with carboplatin as well as all other chemotherapy agents that undergo renal clearance (e.g., cisplatin, pemetrexed, topotecan).

The key point to keep in mind as we move forward, hopefully toward a consensus for this issue, is not about any one person, organization, or agency being “correct” or “winning the debate.” The focus should be identifying what is best for the patient. Consistency in clinical practice is critical for patient safety and effectiveness.

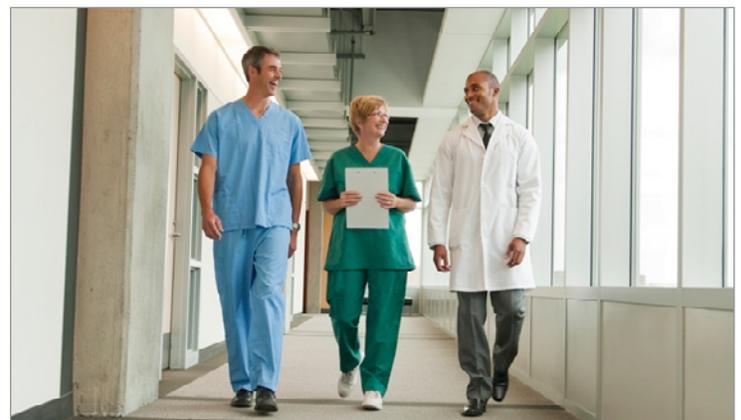
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## HOPA Carboplatin Dosing Survey Summary

Demographics (N = 525)	n	%
<b>Profession (n = 510)</b>		
Pharmacist	421	80.5%
Physician	99	18.9%
Nurse	3	3.0%
Unknown	15	15.0%
<b>Practice site (n = 525)</b>		
Community	25	4.8%
Private practice	47	9.0%
Academic/research	172	32.8%
Hospital setting	256	48.8%
Cancer center	244	46.8%
Inpatient setting	137	26.1%
Outpatient setting	205	39.0%
<b>Time in practice (n = 520)</b>		
<2 years	44	8.5%
2–5 years	90	17.3%
5–10 years	106	20.4%
10–15 years	74	14.2%
>15 years	206	39.6%
<b>Practice devoted to hematology/oncology (n = 521)</b>		
None	19	3.6%
1%–20%	15	2.9%
21%–40%	40	7.7%
41%–60%	46	8.8%
61%–80%	45	8.6%
81%–99%	103	19.8%
100%	253	48.6%

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## HOPA Carboplatin Dosing Survey Summary

Question	n	Response %
<b>Do you use Calvert formula for dosing carboplatin? (n = 515)</b>		
Yes	511	98.3%
No	9	1.7%
<b>How do you determine GFR for Calvert formula? (n = 489)</b>		
Measured	29	5.9%
Estimated CrCl	460	94.1%
<b>What equation do you use to estimate CrCl? Check all that apply. (n = 515)</b>		
Cockcroft-Gault	460	89.3%
Jelliffe	195	37.9%
MDRD	13	2.5%
Other	18	3.5%
<b>For patients in whom actual body weight is <math>\geq 20\%</math> than ideal body weight, what body weight do you use to estimate CrCl? (n = 441)</b>		
Ideal body weight	41	9.3%
Actual body weight	247	86.0%
Adjusted body weight	153	34.7%
<b>In obese patients, what body weight do you use for estimating CrCl? (n = 456)</b>		
Ideal body weight	53	11.6%
Actual body weight	191	41.9%
Adjusted body weight	212	46.5%
<b>In cachectic patients, what body weight do you use for estimating CrCl? (n = 470)</b>		
Ideal body weight	42	8.9%
Actual body weight	416	88.5%
Adjusted body weight	12	2.6%
<b>Do you use the laboratory reported value for serum creatinine? (n = 513)</b>		
Yes	497	96.9%
No	16	3.1%
<b>Do you used an adjusted/assigned value for serum creatinine when below (less than) your laboratory normal limit? (n = 512)</b>		
Yes	284	55.5%
No	228	44.5%
<b>What adjusted/ assigned value do you use? (n = 225)</b>		
0.7 mg/dL	60	26.7%
0.8 mg/dL	101	44.9%
0.9 mg/dL	9	4.0%
1 mg/dL	55	24.4%
<b>Do you convert IDMS serum creatinine to non-IDMS value prior to calculating creatinine clearance? (n = 495)</b>		
Yes	91	18.4%
No	404	81.6%
<b>Do you have an upper limit (cap) for CrCL when dosing carboplatin?</b>		
Yes	243	47.6%
No	267	52.4%
<b>If so, what is the limit?</b>		
Mean (mL/min)	133 $\pm$ 15 (CV 11.3%)	
Range (mL/min)	100-166	

## Travel Grant Applications Now Being Accepted

HOPA would like to invite members to apply for a travel grant to attend the HOPA 2011 Annual Conference. Forty \$500 travel grants are available this year. We understand funding to attend professional meetings has become more and more scarce and sacrifices are frequently made to travel to educational meetings, so we are pleased to offer this grant opportunity. More information can be found on the HOPA website at [www.hoparx.org](http://www.hoparx.org).



Hematology/Oncology  
Pharmacy Association

## Emerging Role of Gefitinib (Iressa®) in the Treatment of Advanced Non-Small-Cell Lung Cancer

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Non-small-cell lung cancer (NSCLC) continues to be the most common cause of cancer-related death in the United States and worldwide. Current standard cytotoxic chemotherapy is associated with an approximately 20%–35% response rate and median survival times ranging from 8–10 months.<sup>1</sup> Despite advances in the treatment of lung cancer, the benefits of standard chemotherapy have plateaued. The development of agents targeting epidermal growth factor receptors (EGFR) has changed the face of treatment for NSCLC by providing a novel mechanism of action and an attractive side effect profile.

Gefitinib (Iressa®), an oral EGFR tyrosine kinase inhibitor, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced/metastatic NSCLC via fast-track approval in March 2003.<sup>2</sup> This approval was based on data from two phase 2 trials (IDEAL-1, IDEAL-2),<sup>3,4</sup> which found gefitinib to be superior to best supportive care in patients who had failed treatment with a platinum-based and docetaxel chemotherapy. Despite the initial promising results of these trials, a subsequent phase 3 trial (Iressa Survival Evaluation in Lung Cancer or ISEL) failed to show any benefit in overall survival (OS) versus best supportive care.<sup>5</sup> Despite its lack of survival benefit in the overall population, subgroup analysis found a significant improvement in never smokers and Asian patients—two groups known to have a higher incidence of EGFR mutations. In June 2005 the FDA restricted the use of gefitinib to clinical trials and patients deriving benefit from current treatment. Although the results of the ISEL trial failed to demonstrate an OS benefit, several aspects of this trial could have affected results, such as the dosing of gefitinib and high incidence of chemotherapy refractory patients who were enrolled in the trial. Gefitinib continues to be approved in a number of other countries, allowing clinical trials to continue. The results of some of these trials have suggested a potential role for gefitinib in the treatment of advanced NSCLC, particularly those with EGFR mutations.

The Iressa NSCLC trial evaluating response and survival against taxotere (INTEREST) was a multicenter phase 3 study whose primary endpoint was non-inferiority of gefitinib compared to docetaxel in terms of OS.<sup>6</sup> A total of 1,466 pretreated (>1 platinum-based regimen) patients with advanced/metastatic NSCLC were randomized to gefitinib 250 mg orally daily versus docetaxel 75 mg/m<sup>2</sup> intravenously every 3 weeks. At the completion of the trial, researchers reported the non-inferiority of gefitinib compared to docetaxel with a median OS of 7.6 vs. 8 months (hazard ratio = 1.020; 96% CI, 0.905–1.150). Gefitinib was also found to be non-inferior when comparing progression-free survival (PFS; 2.2 vs. 2.7 months,  $p = .47$ ) and objective response rates (9.1% vs. 7.6%;  $p = .33$ ). Surprisingly, the INTEREST trial showed no difference in OS irrespective of EGFR gene copy number, EGFR gene muta-

tion status, or KRAS mutation, biomarkers previously reported to predict response to anti-EGFR tyrosine kinase inhibitors.<sup>7</sup> Despite a lack of survival benefit, patients whose tumors harbored EGFR mutations had longer PFS and higher objective response rates if they received gefitinib.<sup>8</sup> Patients of Asian origin, female sex, and adenocarcinoma histology were associated with longer OS, but this was true in both the gefitinib and docetaxel treatment groups. The toxicity profiles for both agents were as expected. Rash and diarrhea occurred more frequently with gefitinib; whereas hematologic toxicities, asthenic disorders, fluid retention, and alopecia occurred more often with docetaxel. Patients receiving gefitinib reported improvement in quality of life using the FACT-L and FACT-L TOI, but no difference was found when comparing lung cancer symptoms per the FACT-L LCS. The authors concluded that gefitinib was non-inferior compared to docetaxel in previously treated advanced NSCLC while having the added benefit of reduced toxicity and improved quality of life.

In the Iressa Pan-Asian Study (IPASS) phase 3 trial, researchers investigated the potential role of first-line gefitinib versus a standard platinum-based doublet in a clinically selected population.<sup>9</sup> Patients were enrolled if they had untreated advanced pulmonary adenocarcinoma and were never smokers (<100 cigarettes in their lifetime) or former light smokers (stopped smoking at least 15 years prior and <10 pack years). The primary endpoint evaluated was PFS. A total of 1,217 patients from East Asia were randomized to gefitinib 250 mg orally daily or carboplatin AUC of 5 or 6 with paclitaxel 200 mg/m<sup>2</sup> given intravenously every 3 weeks. This study met its primary objective by demonstrating the superiority of gefitinib over standard chemotherapy when comparing PFS (hazard ratio = 0.74; 95% CI, 0.65–0.85;  $p < .001$ ). The median PFS was similar between the gefitinib and chemotherapy groups (5.7 vs. 5.8 months); however, this coincided with crossing of Kaplan Meier curves at 6 months. The 12-month PFS rates were higher with gefitinib treatment versus chemotherapy (24.9% vs. 6.7%) as were the objective response rates (43% vs. 32%;  $p < .001$ ). Four hundred thirty-seven available patients samples were analyzed for EGFR mutations in an attempt to further explore the role of EGFR mutations as predictors for efficacy. Of the 437 patient samples, 261 (59.7%) were positive for a mutation. In patients with EGFR mutations, PFS was found to be significantly longer among those receiving gefitinib (hazard ratio = 0.48; 95% CI, 0.36–0.64;  $p < .001$ ), but shorter for those without EGFR mutations (hazard ratio = 2.85; 95% CI, 2.05–3.98;  $p < .001$ ). Objective response rates for those with EGFR mutations were 71.2% with gefitinib versus 47.3% with carboplatin plus paclitaxel ( $p < .001$ ), but only 1.1% vs. 23.5% in the EGFR mutation negative subgroup, respectively ( $p = .001$ ).

The mature OS rates, recently presented at the 35th Annual Meeting of the European Society for Medical Oncology (ESMO), found that there was no difference in median OS between gefitinib and standard chemotherapy in the overall population (18.8 vs. 17.4 months).<sup>10</sup> Patients with EGFR mutations had longer median survival rates regardless of whether gefitinib or chemotherapy was given (21.6 months and 21.9 months) compared to those without EGFR mutations (11.2 months and 12.7 months). Serious adverse events occurred less frequently with gefitinib treatment compared to carboplatin and paclitaxel.<sup>8</sup> The most common adverse effects associated with gefitinib included acne-like rash and diarrhea; neurotoxicity, neutropenia, and alopecia occurred more frequently with chemotherapy. Patients in the gefitinib group also reported an improve-

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ment in quality-of-life scores, which supports the findings of the INTEREST trial. Researchers concluded that gefitinib is superior to carboplatin-paclitaxel as initial treatment for Asian nonsmokers or former light smokers with advanced adenocarcinoma of the lungs, in particular in those with EGFR mutations.

In the NEJ002 study, researchers investigated the effect on PFS in patients with previously untreated metastatic NSCLC in the first-line setting.<sup>11</sup> This phase 3 trial recruited 230 Japanese patients whose tumors were positive for EGFR mutations and randomized them to receive gefitinib 250 mg orally daily or carboplatin (AUC = 6) plus paclitaxel 200 mg/m<sup>2</sup> intravenously every 3 weeks. Patients were stratified according to sex, stage of cancer, and institution. During a planned interim analysis after enrollment of the 200th patient, PFS was found to be twice as long as in patients receiving gefitinib (10.4 months vs. 5.5 months, hazard ratio = 0.36; 95% CI, 0.22–0.51;  $p < .001$ ), which led to the early termination of the study. Researchers also found that 1- and 2-year PFS rates were longer with gefitinib than with chemotherapy (42% vs. 3.2%, 8.4% vs. 0%, respectively). Response rates were doubled in the gefitinib group when compared to the chemotherapy group (73% vs. 30.7%,  $p < .001$ ). OS was not statistically significant, although patients receiving gefitinib lived for a median 30.5 months while patients treated with standard chemotherapy lived for a median 23.5 months. The incidence of grade 3 and 4 toxicities was higher in the standard chemotherapy group (71.7% vs. 41.2%,  $p \leq .001$ ). The authors concluded that first-line gefitinib was superior to standard chemotherapy in prolonging PFS in patients who are harboring sensitive EGFR mutations. This was the first phase 3 trial in advanced NSCLC that selected patients specifically based on EGFR mutations and its results further support the subgroup analysis data from the IPASS study.

The results of the INTEREST and IPASS trials led to a resubmission of licensing in Europe in late 2008. In June 2009 the European Medicines Agency (EMA) approved marketing authorization for gefitinib in patients with advanced or metastatic NSCLC whose tumors have EGFR mutations across all lines of therapy.<sup>12</sup> This marks the first time an agent used to treat NSCLC has been granted licensing with a requirement for molecular testing. The future for gefitinib in the United States remains to be seen. Unlike erlotinib (Tarceva®), which was approved based on a comparison against placebo, gefitinib has the distinction of having demonstrated non-inferiority compared to standard chemotherapy. However, the wide acceptance of erlotinib as a second-line, third-line, and maintenance option, coupled with a demonstrated survival benefit versus placebo,<sup>13</sup> may make it more challenging for gefitinib to gain approval. The ongoing OPTIMAL<sup>14</sup> and EURTAC<sup>15</sup> trials, which are comparing erlotinib to standard chemotherapy in patients harboring EGFR mutations, could also muddy the waters if positive results are found.

At the very least, the results of the INTEREST, IPASS, and NEJ002 trials shed new light on the potential role of gefitinib in the treatment of advanced NSCLC. The INTEREST trial demonstrates that gefitinib is a viable option in the second-line setting with the added advantage of comparable efficacy, improved tolerability, and an enhanced quality of life when compared to second-line chemotherapy. The results of the IPASS and NEJ002 also suggest a potential role for gefitinib in the first-line setting in

a selected group of patients with EGFR mutations. Ultimately, the approval of gefitinib in the advanced or metastatic setting could create a competitive landscape among the oral tyrosine kinase inhibitors used in the treatment of NSCLC. These results further underscore the importance of molecular testing prior to treatment initiation to select patients who would benefit the most from anti-EGFR oral tyrosine kinase inhibitor therapy.

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## Fleeing the United States: Gemtuzumab Ozogamicin Withdrawn from the Market

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In June of this year, the U.S. Food and Drug Administration (FDA) and Pfizer, Inc., announced the withdrawal of gemtuzumab ozogamicin after postapproval clinical trials demonstrated that it provided no clinical benefit to patients with acute myeloid leukemia (AML).<sup>1,2</sup>

Gemtuzumab ozogamicin is a monoclonal antibody that binds to the CD33 antigen expressed by hematopoietic cells. It was initially approved in May of 2000 through an accelerated approval program for the treatment of AML. Initially, the approval was for AML patients in first relapse who were 60 years of age or older and not candidates for other chemotherapy. This approval was based on data from three clinical trials using the surrogate endpoint of response rate observed in 142 patients with AML.

The FDA's accelerated approval regulations program was developed in 1992 to allow patients with life-threatening diseases earlier access to medications for which early evidence may suggest that the agent may improve survival or reduce symptoms. The medication is expected to be superior to available treatments, but confirmatory studies have yet to demonstrate clinical benefits. After being granted an accelerated approval, the manufacturer is required to conduct postmarketing trials to demonstrate a clinical benefit. If clinical benefit is not shown, the FDA may require the medication to be withdrawn from the market.<sup>3</sup>

In 2004 a postapproval clinical trial (SWOG S0106) was initiated to investigate the benefit of gemtuzumab ozogamicin as a first-line therapy in patients younger than 65 years. The SWOG S0106 study was a phase 3, randomized, controlled trial comparing the disease-free survival of untreated de novo AML

with induction cytarabine and daunorubicin with or without gemtuzumab ozogamicin in 627 adult patients. When the addition of gemtuzumab ozogamicin to standard induction chemotherapy failed to demonstrate an increase in survival time, the trial was concluded early. It was also found that toxicity rates were significantly higher in the gemtuzumab arm.<sup>4</sup> Considering the lack of benefit and potential harm, the new drug application and product were voluntarily withdrawn.

Gemtuzumab ozogamicin will no longer be commercially available to new patients. The FDA recommends that for patients who are currently being treated, therapy may be completed with close follow-up with their healthcare professional. Further use of gemtuzumab ozogamicin will require an investigational new drug application to the FDA.

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## Breast Cancer and Bevacizumab: The FDA Takes a Mulligan

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The U.S. Food and Drug Administration (FDA) has recently extended its review of bevacizumab in the treatment of metastatic breast cancer until December 17, 2010, because new clinical trials have not shown a statistically significant benefit in overall survival (OS).

In February 2008 the FDA issued an accelerated approval of the use of bevacizumab combined with paclitaxel for first-line treatment of HER-2-negative metastatic breast cancer based on the encouraging results of the E2100 trial conducted in 722 patients.<sup>1,2</sup> In comparison to paclitaxel alone, the addition of bevacizumab yielded improved progression-free survival (PFS), radiographic response rates, and time to progression (TTP). This accelerated approval was contingent on additional clinical trials demonstrating

efficacy for this indication. To convert the accelerated approval status to a full approval, Genentech submitted two supplemental biologics license applications (sBLA), providing findings from the AVADO and RIBBON-1 trials.<sup>3,4</sup> Data from these studies have resulted in the advisory committee questioning the OS benefit from this combination therapy.

In the AVADO trial, which randomized 736 patients to receive docetaxel 100 mg/m<sup>2</sup> every 3 weeks with either bevacizumab or placebo, patients showed improvement in PFS by 0.79 months ( $p = .0318$ , 95% CI, 0.63–0.98) for the lower dosage (7.5 mg/kg every 3 weeks) and by 0.72 months ( $p = .0099$ , 95% CI, 0.57–0.90) at the higher dose (15 mg/kg every 3 weeks). Results from the RIBBON-1 trial, conducted in 1,237 patients with HER-2-negative disease, showed that bevacizumab (when added to conventional chemotherapy with taxane or anthracycline) improved PFS by 2.4 months ( $p = .0054$ ) and 2.9 months ( $p = .0097$ ) when added to capecitabine. OS was not a primary endpoint in AVADO or RIBBON-1 trials. There were no significant differences in OS, which was a secondary endpoint in both trials.<sup>3,4</sup>

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## BOARD AND COMMITTEE UPDATES

### Board Update

Rowena (Moe) Schwartz, President, HOPA

In March, I thought one of the challenges of the upcoming year would be transitioning from DesignWrite to our new association management company, AMC. I was partially correct—but not in the way I had imagined. AMC is an experienced association management company that has a broad understanding of the issues involved with associations, including strategies for transitions. AMC's experience has allowed HOPA to make a relatively smooth transition of our business issues. I had anticipated there being several months during which HOPA would not be able to focus on anything but the transition. The actual time period during which our sole focus was the transition only lasted a matter of weeks, and during that time, HOPA business did continue.

### The Good News

The wonderful news for our organization is that AMC has vast experience in areas of associations that HOPA had not previously considered. The staff and leadership of AMC have worked collaboratively with the HOPA Board to not only maintain business as usual but to implement some essential structures and supports for HOPA during the organization's growth.

- HOPA now has a budget. We have worked with AMC to create a budget to better coordinate HOPA activities and efforts. The budget will be an essential part of implementing the strategic plan and ensuring that the organization stays solvent during these challenging economic times.
- HOPA has an updated strategic plan.
  - The combined efforts of committee leadership, past leadership, individual HOPA members, the board of directors, and AMC staff have resulted in an updated strategic plan for HOPA. With the help of AMC, we engaged a dynamic leader to facilitate the strategic planning process. The work of this group has been developed into a written plan that will allow the ideas of the members to be the driving

force of the organization for the next 5–10 years. (You will hear much more about the plan once the board has approved it.)

- The board is evaluating the current functions of the board, committees, and workgroups to determine the best way to utilize the organization's resources and ensure that HOPA's efforts reinforce the strategic plan.
- The key word here is focus. HOPA is fortunate to be an organization with many opportunities, but we have struggled with utilizing resources effectively. Our structure does not easily support the ability of committees or the board to mobilize or utilize our resources effectively. The strategic plan brings a focus to the organization and will help us prioritize efforts. It is wonderful to be a large, enthusiastic group rich in diversity. The challenge will be making sure that we do not spread our resources so thin that we limit our accomplishments.

### HOPA's Challenge

I often hear about the difficulty that HOPA and HOPA members experience as the organization changes. HOPA is fortunate to have grown so fast; however, to be successful with this growth we must modify the way we do business. It may seem like we change the way something is done before we have had the opportunity to thank those who were involved in developing the original process. It is important to realize that change isn't a sign that something was done poorly, and, in the case of HOPA, it is often an indication that we need to accommodate for further growth and progress.

- Thank you to everyone who has helped HOPA reach this point in our growth.
  - HOPA has grown because of the work and partnerships with Syntaxx and DesignWrite. HOPA exists today in large part due to the enthusiastic efforts of Terri and Ross Davidson, owners of Syntaxx Communications. We were extremely fortunate to have had Terri participate in the stra-

tegic planning this October. The dedicated team at DesignWrite was instrumental in supporting HOPA during the early years as we grew into an organization of more than 1,400 members.

- Members are what make HOPA successful. It is the work of the HOPA membership that has helped take HOPA from a wonderful idea to a large organization.
- AMC is a resource for HOPA members.
  - AMC is a resource for your questions. The person on the phone may not always know the answer, but they are able to triage to the appropriate person.
  - If you have an idea, or if you are contacted with a request for HOPA, please contact AMC to ensure that this request is coordinated within the HOPA organization.
- Please help us with the challenges associated with the growth and development of HOPA.
  - HOPA has partnered with an association management company to help support the growth of our organization. Their expertise in association management will help us be successful. This partnership will bring changes, new people, and new ideas. At times there may be bumps as the methods of the past will be reevaluated and strengthened. I ask that our membership work collaboratively with AMC and realize that the relationship is developing.



## COMMITTEE UPDATES

### BCOP Recertification Committee

*Julianna Burzynski, Chair*

*Ryan Bookout, Vice Chair*

The Oncology Pharmacy Specialty Sessions for Board Certified Oncology Pharmacist (BCOP) recertification continuing education credit were presented at the 2010 HOPA Annual Meeting in New Orleans, LA, and the 2010 American College of Clinical Pharmacy (ACCP) Annual Meeting in Austin, TX. If you are attending the American Society of Health System Pharmacists (ASHP) Midyear Clinical Meeting in Anaheim, CA, the lectures will be repeated in the "Oncology Pharmacy Specialty Sessions: Part 1," December 7, 2010, from 8–11 am, and "Part 2" on December 7, 2010, from 2–5 pm. Updates to some of the presentation slides have been made and are available on the HOPA University website ([www.hopau.org](http://www.hopau.org)). The BCOP examination questions were not affected by these changes. A friendly reminder for all those individuals who have already attended the sessions as well as those planning to attend at ASHP, the deadline for completing the exam to obtain BCOP recertification credit is December 31, 2010. A link to the exam has been sent to those who are eligible to take it. Accreditation Council for Pharmacy Education credit is also available at [www.hopau.org](http://www.hopau.org) for those who attend the sessions but do not take the exam.

Currently, the BCOP recertification committee is working diligently to continue the forward momentum for the 2011 Oncology Pharmacy Specialty Sessions to be provided at the 2011 HOPA Annual Conference in Salt Lake City, UT; the 2011 ACCP Annual Conference in Pittsburgh, PA; and the 2011 ASHP Midyear Clinical Meeting in New Orleans, LA. Speakers and topics for the 2011 sessions include

- Rebecca Greene, PharmD BCOP: "Castration-Resistant Prostate Cancer"
- Ashley Morris Engemann, PharmD BCOP: "Chronic Lymphocytic Leukemia Treatment Update"
- Courtney Bickford, PharmD BCPS: "The Heart of the Matter: When Targeted Cancer Therapies Cause Off-Target Toxicities"

- Michael J. Berger, PharmD BCOP: "Updates in the Treatment of Metastatic Breast Cancer"
- Kamakshi V. Rao, PharmD BCOP CPP: "Immunizations in Cancer Patients—Recommendations for Vaccine-Preventable Diseases in the Immunocompromised Population"
- Kellie L. Jones, PharmD BCOP: "Germ Cell Tumors: A Focus on Testicular Cancer."

The speakers are currently developing their presentations and creating BCOP recertification examination questions for their topics. The committee is actively recruiting field testers for the 2011 BCOP Recertification lectures early this winter; if you are interested in participating in field testing part of the examination, please contact Ryan Bookout at [Ryan.Bookout@moffitt.org](mailto:Ryan.Bookout@moffitt.org).

We'd like to thank the speakers of the 2010 Oncology Pharmacy Specialty Sessions for their continued hard work and dedication this year. We'd also like to extend our appreciation to the 2011 speakers for their commitments to HOPA for 2011.

### Education Committee

*Susannah Kootz, Chair*

*Helen Marshall, Vice Chair*

The Education Committee had a busy start to the fall season, which culminated in submitting two proposals to the board for future annual meeting programs. The first proposal, authored by Helen Marshall in conjunction with David Gregornick, Marc Takemoto, Katie Tipton, Mallika Weant, and Laura Wiggins, was to include a best practices program as part of the 2012 Annual Conference. The best practices program would allow selected practitioners to share with HOPA members the ways in which their respective institutions address clinical and administrative issues encountered in everyday practice. The suggested topic for the next best practices session is the Risk Evaluation and Mitigations Strategies program. The other proposal submitted by the Education Committee was a request to conduct another Oncology Boot Camp symposium prior to the start of the 2012 Annual Conference. Susannah Koontz, in collaboration with Tony Jarkowski, Dan Sageser, Angela Urmanski,

and Poppy Wilson, crafted this proposal to build on the success of the first Oncology Boot Camp conducted at the 2010 Annual Conference in New Orleans last March. The next Oncology Boot Camp, which is an educational program aimed at pharmacy trainees and new practitioners, will focus on nontraditional cancer therapies, namely monoclonal antibodies, tyrosine kinase inhibitors, and mTOR inhibitors.

For the remainder of the fall, the Committee's efforts will return to drafting patient education sheets, creating oncology resources lists, and further developing the HOPA U website. Common adult and pediatric regimens have been identified to serve as prototypes for the creation of patient education sheets summarizing common toxicities associated with a particular regimen rather than single treatment entities. As part of this process, standard toxicity language is being drafted to use in the sheets. An oncology resources list for pharmacy trainees and new practitioners covering general principles and practices relating to care of hematology and oncology patients is almost completed. Finally, the Committee continues to look for additional programs to offer on HOPA U and ways to enhance the HOPA U website. If you have any suggestions for changes to the HOPA U website, please feel free to contact the Education Committee.

### Finance Committee

*Antoinette Lavino, Chair*

*Caren Hughes, Vice Chair*

In the past quarter, the Finance Committee voted on some timely issues that will have a major impact on HOPA's revenue. It analyzed membership fees and registration fees for the upcoming annual conference.

First, the Finance Committee (in collaboration with the Membership Committee) analyzed membership fees and existing categories (i.e., full, associate, technician, and student) from 2005–2010. We compared membership fees charged by other professional pharmacy organizations to benchmark HOPA's current offerings. The Finance Committee chose to modify membership fees; however, we wanted to ensure fees remained less than other organizations to maintain affordability. All recommended changes were accepted by the HOPA Board.

## COMMITTEE UPDATES

The membership incentives (e.g., signing up for 2-year membership to receive a 5% discount, group rates) will remain in place. The committee recommended that these fees be re-evaluated again in 3 years.

Next, the Finance Committee (in collaboration with the Program Committee) completed a similar analysis of the fees for attending the HOPA annual conference. We wanted to accomplish the following with the fee restructure: (1) encourage membership, (2) encourage early registration, and (3) provide all members with an opportunity to register at an affordable price. It was understood that annual conference registration fees can serve as a major barrier to registration and attendance. In addition, the Finance Committee recommended increasing the window of time for early-bird registrations to help registrants take advantage of the lowest prices. The proposed fee changes were accepted by the HOPA Board.

Event cancellation insurance, a topic that had been discussed the previous year, was discussed recently and has been purchased by HOPA.

The Finance Committee is now moving toward evaluating and choosing an independent auditor for HOPA's fiscal year 2010 review.

### Legislative Affairs Committee

*Scott Savage, Chair*

*Ali McBride, Vice Chair*

The Legislative Affairs Committee has been focusing on several key issues that affect our members, including medication shortages, Risk Evaluation and Mitigation Strategies (REMS), and safe handling of hazardous drugs.

Medication shortages have become a major issue of late as numerous institutions and centers have been faced with having to delay or alter care to our patients. The ability to provide care without access to needed medications has not only been frustrating, but has placed undue pressure on clinicians and managers to explore alternative means of procuring medications and alternative medication therapies. On November 5, 2010, HOPA participated in the ASHP/U.S. Food and Drug Administration/Institute

for Safe Medication Practices/American Society of Clinical Oncology/American Society of Anesthesiologists Drug Shortages Summit to evaluate methods to identify and prevent current and future drug shortages. HOPA will continue its collaborative efforts with ASHP and other professional organizations to help ease the burden of medication shortages for patients and clinicians.

REMS are a particularly important issue for oncology and for HOPA members. REMS continue to be a priority topic in cancer care. HOPA conducted a member survey earlier this year, which provided the opportunity for members to ask questions about REMS. The HOPA Legislative Affairs Committee is currently reviewing the submitted questions and will post the answers to the HOPA website in the near future.

The committee has also developed smaller task force-driven initiatives that focus on key legislative initiatives including oral chemotherapy payment equity, comparative effectiveness research, and the healthcare reform bill.

### Membership Committee

*Karen Smethers, Chair*

*Meredith Toma Moorman, Vice Chair*

The membership committee has been working hard to increase the number of active members. We successfully contacted PGY-2 oncology residency program directors to encourage their residents to participate in HOPA. This effort contributed to a 38% increase in trainee membership since May. As a reminder, the membership fee for students and trainees is priced to foster trainee participation in our organization. Please encourage your pharmacy residents to join!

Committee members are also continuing to identify and contact our BCOP colleagues who are not current members of HOPA. In addition, we have been working to update the HOPA Travel Grant Program to support member attendance at this year's HOPA Annual Conference in Salt Lake City, UT. We will continue to keep you informed as these initiatives come to fruition.

The Membership Committee is excited to serve you this year. Remember to encourage your colleagues, including pharmacists, students, trainees, and technicians to join HOPA!

### Nominations and Awards Committee

*Karen Fancher, Chair*

*Laura Jung, Vice Chair*

The Nominations and Awards Committee is pleased to report that we have chosen the winners for the 2010–2011 HOPA Awards. We will be notifying the winners in early November, and will announce the results to the membership in January 2011. The winners will formally receive their awards at the 2011 HOPA Annual Conference.

In addition, we recently closed nominations for the board of directors. We will be setting the slate for the elections in early November; the general election will open in January 2011. Please be sure to vote for your new board of directors!

Thank you to everyone who has nominated a colleague this year—we appreciate your efforts!

### Program Committee

*Lauren Decloe, Chair*

*Jill Rhodes, Vice Chair*

The 2011 Annual Conference is rapidly approaching! The Program Committee is excited to provide a diverse offering of educational topics. The annual John G. Kuhn Keynote lecture will kick off the conference. This year's address is "The Cost of Cancer Therapy."

Other conference highlights include

- a preconference morning workshop that will be hosted by the Research Committee on Wednesday, March 23
- committee meetings on Wednesday, March 23
- Oncology Interest Groups led by the Professional Affairs Committee on Friday, March 25
- HOPA's partnership with the British Oncology Pharmacy Association (BOPA) for our 1st Annual Speaker Exchange
- the popular Controversies in Care sessions, which will be expanded to include supportive care topics
- trainee and research posters, which will be conducted by the Research Committee
- the presentation of the HOPA research award

## COMMITTEE UPDATES

- more than 18 hours of CE and 6 hours of BCOP credits!

Conference registration began on November 4, 2010. Please continue to visit the HOPA website to view the preliminary schedule and conference updates!

### Publications Committee

*Brooke Bernhardt, Chair*  
*Stacy Shord, Vice Chair*

The Publications Committee has been busy with three major endeavors this fall: the HOTopics Webinar, the listserv, and the newsletter.

We hope you were able to join us for the Fall 2010 Webinar, "Understanding the Role of Genetic Testing in Community Pharmacy and Adverse Events Associated with Anticancer Therapy," on November 10. We would like to thank our speakers, Christine Walko and Kristine Crews, for an excellent presentation. If you were able to participate, please remember to fill out the post-webinar survey. If you were not able to participate, please let us know how we can better meet your educational needs.

Last, we hope you are enjoying this newsletter. We have several very talented contributors, and we hope that you find the newsletter informational and educational. To ensure we provide the highest quality product to our audience, we have been busy creating standard operating procedures regarding the selection of contributors and the peer-review process for newsletter articles. If you have any suggestions for future newsletter content or format, [please do not hesitate to let us know](#).

### Standards Committee

*Myke Green, Chair*  
*Jamie Poust, Vice Chair*

The HOPA Standards Committee has been diligently working on the development of its first standard operating procedure (SOP). This SOP will focus on the development of evidence-based guidelines. After the SOP is finalized, work will begin on the renal dosing guideline that was initiated by last year's committee. The committee is also in the process of looking at other potential documents that the Standards Committee would

consider publishing in the future. These include documents such as white papers and consensus statements. The HOPA Standards Committee is moving forward with the development of the investigational drug task force. Currently, the foundation of this task force is being established.

The 2010–2011 Standards Committee members are Matthew Christianson, Mandy Gatesman, Eileen Herbeck, Kathy Hogan, Alex Kappelman, Lyndsay Koberinski, Diana Kostoff, Lisa Langston, Andrea Ledford, Theresa Mays, Michael Newton, Kelly Rio, Jim Schwartz, and Peter Tortorice.

## Membership Now

You can now become a HOPA member and enjoy an entire year's worth of benefits anytime you join! HOPA now offers its members and prospective members the opportunity to join for a full year at any time during the calendar year. This means that your membership year begins the day you join HOPA. Special membership discounts are still available when you join for 2 years. Encourage your colleagues to join HOPA today!

[www.hoparx.org](http://www.hoparx.org) • 877.467.2791



HOPA UNIVERSITY

### Planning to Recertify in 2010?

**Be sure to take the BCOP test by December 31, 2010**

BCOP Exam: \$45

The link to access the exam was sent to those who attended the six specialty sessions during this year's HOPA, ACCP or ASHP meetings. If you did not receive the link, contact member services at 877.467.2791.

Not taking the exam but need CPE credits?  
Visit HOPA U at [www.hopau.org](http://www.hopau.org).

## Breast Cancer and Bevacizumab: The FDA Takes a Mulligan

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Despite its controversial role in treating breast cancer, bevacizumab has demonstrated activity in breast cancer when combined with standard taxane-based chemotherapy in several phase 3 clinical trials. In one phase 3 trial of bevacizumab as the first-line treatment of HER-2-negative breast cancer, 736 patients were randomized to docetaxel 100 mg/m<sup>2</sup> with either placebo or bevacizumab given at 7.5 mg/kg or 15 mg/kg every 3 weeks. The combination of bevacizumab 15 mg/kg every 3 weeks and docetaxel increased PFS compared to placebo meeting criteria for statistical significance (8.1 months vs. 10.0 months, hazard ratio = 0.67,  $p < .001$ ).<sup>5</sup> The ATHENA study was a large ( $n = 2,251$ ), open-label safety study that assessed first-line bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks with taxane-based chemotherapy) for locally recurrent or metastatic breast cancer, a routine practice in adult oncology. This study also reported increased PFS (9.5 months; 95% CI, 9.1–9.9), consistent with results from other randomized first-line trials without additional safety concerns.<sup>6</sup> In each of these trials, the improvement in PFS was much smaller than in the E2100 trial in which bevacizumab nearly doubled median PFS when added to paclitaxel (5.8 months vs. 11.3 months).

These conflicting results provide evidence that reflect a critical need to restructure future clinical trials. PFS is used as a primary endpoint in many oncology trials for locally advanced and metastatic cancers. Although the gold standard for efficacy in oncology is improvement in OS (as evidenced with trastuzumab in HER-2-positive breast cancer), this endpoint is often difficult to use given concerns of slowing drug development and approval. A doubled PFS and response rate from the E2100 trial has been reflected in community practice, and as with other novel targeted therapy agents, more comprehensive data are now available to determine its “true” clinical benefit to patients. Although added toxicities from bevacizumab therapy represent a real concern to oncologists, standardized uniform guidelines to manage these toxicities are urgently needed.

Based on the recent clinical trials and the FDA’s key role in the regulation of pharmaceuticals, it is reasonable for the FDA to reevaluate the role of bevacizumab for breast cancer before making a final decision regarding the indication of bevacizumab for

HER-2-negative breast cancer. For incurable disease, bevacizumab may continue to be a “favorable” treatment option compared with other cytotoxic agents. Identifying individual patients who may benefit from an angiogenesis inhibitor will become more feasible as molecular characterizations improve and allow us to identify patients who may benefit from these targeted therapies.

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## Emerging Role of Gefitinib (Iressa®) in the Treatment of Advanced Non-Small-Cell Lung Cancer

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## DRUG UPDATES

### Denosumab (Prolia™, Xgeva™)

**Class:** Human IgG2 monoclonal antibody with affinity for nuclear factor-kappa ligand (RANKL)

**Indication:** Treatment of osteoporosis in postmenopausal women at high risk for fracture

**Treatment of osteoporosis in postmenopausal females (Prolia™):** SubQ: 60 mg as a single dose, once every 6 months

**Prevention of skeletal-related events in bone metastases from solid tumors (Xgeva™):** SubQ: 120 mg every 4 weeks

**Dose modifications:** Dose adjustment is not needed for renal impairment; monitor calcium in patients with severe impairment ( $Cl_{Cr} < 30$  mL/minute or on dialysis)

**Common adverse effects:** Dermatitis, eczema, rash, limb pain, hypercholesterolemia, hypocalcemia

**Serious adverse effects:** Infections, osteonecrosis of the jaw, secondary malignancies

**Drug interactions:** Denosumab may enhance the effects of immunosuppressants, including the risk of serious infections.

Denosumab is a human IgG2 monoclonal antibody that inhibits binding of receptor activator of nuclear factor kappa-B ligand (RANKL) to RANK receptors located on the surface of osteoclasts and their precursors. RANKL is a part of the tumor necrosis factor family. This inactivation prevents the formation, function, and survival of osteoclasts, which then reduces bone resorption, allowing for growth in cortical and trabecular bone.<sup>2</sup> An improvement in BMD has been demonstrated with the use of denosumab.

Serum type 1 C-telopeptide (CTX), a bone resorption marker, adequately measures denosumab activity. Three days following a single injection, CTX levels are reduced by 83%. A maximum reduction in CTX levels was noted in 1 month and ranged from 45%–80% during the 6-month dosing interval. Bone formation markers such as osetocalcin and procollagen type 1 N-terminal peptide (PINP) were also noted to decrease, indicating the coupled action of bone remodeling.<sup>2</sup> Studies have shown that denosumab is not incorporated into bone, therefore, accumulation is not a factor.

To treat osteoporosis, denosumab is administered as a 60 mg subcutaneous injection from a prefilled syringe every 6 months in the upper arm, upper thigh, or abdomen. To prevent skeletal-related events in patients with metastatic (to bone) breast and prostate cancer, the approved dose is 120 mg administered subcutaneously monthly. Co-administration of calcium 1,000 mg and vitamin D 400–800 IU daily is also recommended. Dose reductions are not required in renal or hepatic impairments unlike the bisphosphonates. Clearance occurs through the reticuloendothelial system ending with renal filtration and excretion.<sup>3</sup> Currently, studies have not identified any specific drug-drug interactions. Safety and efficacy in pediatrics has not been evaluated. It is a pregnancy category C and possibly transmitted via breast milk.<sup>2</sup>

Denosumab is contraindicated in patients with preexisting hypocalcaemia. It is recommended that calcium levels be corrected before initiation and monitored during therapy. Many precautions have been identified—suppression of bone remodeling, pre-existing mineral abnormalities, serious infections, dermatologic reactions, and osteonecrosis of the jaw (ONJ). Bone remodeling suppression can contribute to ONJ, atypical fractures, and delayed fracture healing. In patients with mineral metabolism disturbances such as hypoparathyroidism, malabsorption syndromes, and thyroid/parathyroid surgery, monitoring calcium and mineral levels is recommended. Infections of the abdomen, urinary tract, ear, and skin were noted in clinical trials. Serious infections leading to hospitalizations can occur. The incidence of opportunistic infections was balanced between placebo and denosumab patients, and the overall incidence of infections was similar between the treatment groups. Patients taking concomitant immunosuppressant therapy and/or who have impaired immune systems may also be at greater risk. Clinical trials also noted epidermal and dermal adverse events such as dermatitis, eczema, and rashes. Injection site reactions were reported most often. Dental examinations should be conducted prior to initiation and patients should be counseled on good oral hygiene to prevent ONJ. It is important to use clinical judgment regarding continued therapy for patients requiring invasive dental procedures.<sup>2</sup>

### Denosumab: A Review of Its Pharmacology and Clinical Implications

*Russell S. Crawford, BPharm BCOP*

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Osteoporosis is characterized by low bone mass, deterioration of bone tissue and architecture, compromised bone strength, and an increase in fracture risk.<sup>1</sup> The World Health Organization (WHO) defines osteoporosis by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the young normal mean reference population. It affects nearly 10 million Americans, and, according to the National Osteoporosis Foundation, nearly 34 million are at risk for developing it. Although women have a greater incidence, men can also be affected.<sup>1</sup> Postmenopausal women require special attention because of decreases in estrogen levels; increasing the rate of bone remodeling causes an imbalance between osteoblasts and osteoclasts. Several measures are key to prevention (e.g., adequate intake of calcium and vitamin D, weight-bearing exercises, fall prevention) and treatment (e.g., oral/parenteral bisphosphonates, calcitonin, estrogen/hormone therapy, parathyroid hormone).<sup>1</sup>

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## DRUG UPDATES

The most common adverse reactions reported with denosumab are back pain, asthenia, extremity pain, musculoskeletal pain, upper respiratory infections, nasopharyngitis, fatigue, hypercholesterolemia, nausea/vomiting, and cystitis. Serious adverse reactions included endocarditis, cellulitis, dermatitis, rash, serious infections, cancer, pancreatitis, and hypocalcaemia. The most common adverse reactions leading to discontinuation of denosumab were progression of breast cancer, back pain, and constipation.<sup>2,4</sup>

### Current Indications

In 2009 the results of the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months trial (FREEDOM), a large international, randomized, placebo-controlled trial, were published.<sup>3</sup> During this trial, patients were randomly assigned to either denosumab 60 mg subcutaneously or placebo every 6 months for 36 months. All patients received daily supplements containing at least 1,000 mg of calcium and vitamin D supplementation determined by the baseline labs. Patients were eligible for the trial if they were 60–90 years old with a bone mineral density T-score of less than -2.5 at the lumbar spine or total hip. Patients who had previously used bisphosphonates for less than 3 years were eligible for the study if they had not received bisphosphonate therapy for the previous 12 months. Exclusion criteria for the study included previous oral bisphosphonate use for more than 3 years, intravenous bisphosphonates within the previous 5 years, fluoride or strontium in the previous 5 years, or a vitamin D level less than 12 ng/mL. The primary endpoint for the trial was the presence of new vertebral fractures, evaluated by annual lateral spine radiographs. Secondary endpoints were the time to the first nonvertebral fracture and time to the first hip fracture. The efficacy endpoints were evaluated based on the intention-to-treat analysis, and safety analyses included all patients who had received at least one dose of a study drug. A total of 7,868 women were enrolled in the study. The average age in both groups was 72.3 ± 5.2 years, and the groups were well matched in terms of baseline characteristics. At the end of the 36-month study period, 82% of patients had completed the study and 76% had completed all planned injections. The endpoint results of the study are shown in **Table 1**. The risk reduction for vertebral fractures seen in the denosumab group is similar in magnitude to intravenous zoledronic acid and greater than the oral bisphosphonates.

**Table 1. Effect of Denosumab on the Risk of Fracture at 36 Months**

Outcome	Denosumab n (%)	Placebo n (%)	Difference in Rate (95% CI)	Relative Risk or Hazard Ratio (95% CI)	p Value
<b>Primary end point</b>					
New vertebral fracture	86 (2.3%)	264 (7.2%)	4.8 (3.9–5.8)	0.32 (0.26–0.41)	<.001
<b>Secondary end points</b>					
Non-vertebral fracture	238 (6.5%)	293 (8.0%)	1.5 (0.3–2.7)	0.80 (0.67–0.95)	.01
Hip fracture	26 (0.7%)	43 (1.2%)	0.3 (-0.1–.7)	0.60 (0.37–0.97)	.04
<b>Other fracture end points</b>					
New clinical vertebral fracture	29 (0.8%)	92 (2.6%)	1.7 (1.1–2.3)	0.31 (0.20–0.47)	<.001
Multiple (≥2) new vertebral fractures	23 (0.6%)	59 (1.6%)	1.0 (0.5–1.5)	0.39 (0.24–0.63)	<.001

The denosumab group had a similar risk reduction to alendronate, risedronate, and zoledronic acid in regard to nonvertebral fractures. There were no significant differences between the denosumab and

**Table 2. Adverse Events**

Event	Denosumab (n = 3,886)	Placebo (n = 3,876)	p Value
All	3,605 (92.8)	3,607 (93.1)	0.91
Serious	1,004 (25.8)	972 (25.1)	0.61
Fatal	70 (1.8)	90 (2.3)	0.08
Leading to study discontinuation	93 (2.4)	81 (2.1)	0.39
Leading to discontinuation of a study drug	192 (4.9)	202 (5.2)	0.55
<b>Adverse Events</b>			
Infection	2,055 (52.9)	2,108 (54.4)	0.17
Cancer	187 (4.8)	166 (4.3)	0.31
Hypocalcaemia	0	3 (0.1)	0.08
Osteonecrosis of the jaw	0	0	NA
<b>Serious adverse events</b>			
Cancer	144 (3.7)	125 (3.2)	0.28
Infection	159 (4.1)	133 (3.4)	0.14
Cardiovascular event	186 (4.8)	176 (4.6)	0.74

placebo groups in terms of adverse events. There were significantly more patients in the denosumab group that developed eczema (3% vs. 1.7%). The incidence of selected adverse events is shown in **Table 2**.

Also in 2009, the results of a phase 3 randomized, double-blind study comparing 12 months of therapy with either denosumab (60 mg subcutaneously every 6 months) or alendronate (70 mg orally every week) were published.<sup>5</sup> Eligible patients were postmenopausal women with a T-score ≤2.0 at the total hip or lumbar spine. Patients were excluded if they had previously received treatment with intravenous bisphosphonates, fluoride, or strontium. In addition to the study treatment, patients were instructed to take daily calcium supplements along with ≥500 mg of calcium and vitamin D supplements based on the baseline 25(OH)D levels. The primary endpoint of the study was the percentage change from baseline of the total hip BMD at month 12. Secondary endpoints included the percentage change from baseline in BMD at the femoral neck, trochanter, lumbar spine, and one-third radius at month 12. A total of 1,189 subjects were enrolled in the study. The groups had similar baseline characteristics. The mean BMD percent change at the total hip from baseline was significantly higher in the denosumab group (3.5%) compared to the alendronate group (2.6%,  $p < .0001$ ) at month 12. Patients treated with denosumab had significantly greater increases in BMD compared to patients treated with alendronate at the trochanter (4.5% vs. 3.4%;  $p < .0001$ ) and one-third radius (1.1% vs. 0.6%;  $p = .0001$ ), in addition to the gains at the total hip. These results were consistent between the intention-to-treat analysis and per protocol populations. There were no significant differences in overall adverse events between

the denosumab- and alendronate-treated patients (80.9% vs. 82.3%;  $p = .60$ ). The incidence of serious adverse events was also similar between groups.

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In addition to its current FDA-approved indication for use in the management of osteoporosis, denosumab has also been approved by the FDA for another indication—the prevention of skeletal-related events (SREs) in patients with breast and prostate cancers that have metastasized to the bones.<sup>6</sup> Results of several phase 2 and 3 trials have been recently published, or have been presented at national oncology meetings but are only currently available in abstract form.

### Metastatic Breast Cancer

To date, there is one large, randomized phase 3 study and several phase 2 trials that have evaluated the efficacy of denosumab in women with breast cancer that has metastasized to the bone. In these patients there is increased osteoclast activity at the site of bone metastases, resulting in local bone destruction and the potential for skeletal complications.

A randomized, double-blind phase 3 trial was conducted by Stopek and colleagues in patients with advanced breast cancer and bone metastases to evaluate the impact of denosumab in preventing or delaying SREs.<sup>7,8</sup> In this study, an SRE was defined as either a pathological fracture, need for radiation or surgery to bone for an impending fracture, or spinal cord compression. The study was designed as a noninferiority trial comparing denosumab to zoledronic acid with time to first SRE (on study) as the primary endpoint of the trial. Secondary endpoints of this trial included a demonstration of superiority of denosumab over zoledronic acid with respect to time to first SRE (on study), time to first and subsequent SREs, and a safety and tolerability assessment. Patients were required to be naïve to previous treatments with intravenous bisphosphonates, and were encouraged to take a minimum of 500 mg of calcium and 400 IU of vitamin D daily.

A total of 1,026 patients were randomized to the denosumab/zoledronic acid placebo arm, and 1,020 were randomized to the zoledronic acid/denosumab placebo arm. Denosumab was administered every 4 weeks at a dose of 120 mg given SQ, while zoledronic acid was given on the same 4-week dosing schedule at 4 mg. At an average follow-up period of 34 months, denosumab was found to be superior to zoledronic acid in preventing first on-study SREs (primary outcome), an 18% reduction in incidence ( $p = .01$ ). In the zoledronic acid group, the median time to first on-study SRE was determined to be 26.5 months; in the denosumab arm, median time to first on-study SRE had not yet been reached at the time of the analysis. The secondary endpoint of time to first and subsequent SREs was also found to be superior in the denosumab-treated patients, with a 23% improvement in this study outcome favoring denosumab ( $p = .001$ ). There were no differences noted in time to disease progression or overall survival between the two treatment arms.<sup>7,8</sup>

In terms of safety and tolerability, there were no differences in the overall reported adverse events; 96% of denosumab-treated patients and 97% of zoledronic-acid-treated patients experienced at least one on-study adverse event. There were also no differences in the rates of serious adverse events reported (44% vs. 46%), infection rates (46% vs. 49%), or serious infections (7% vs. 8%) when comparing denosumab to zoledronic acid, respectively. The reported incidence of ONJ was similar between the two arms, with a 2% incidence in the denosumab arm and a 1.4% incidence in the zoledronic acid arm ( $p = .39$ ). Renal-related complications to treatments slightly favored the denosumab-treated patients, with a 4.9% incidence

compared to an 8.5% incidence in the zoledronic acid arm. The authors concluded that denosumab was superior to zoledronic acid in delaying the time to first on-study SRE and the time to both first and subsequent SREs.<sup>7,8</sup>

A multicenter, randomized, blinded phase 2 trial conducted by Lipton and colleagues evaluated the efficacy and safety of five different dosing levels of denosumab compared to an intravenous bisphosphonate in patients with breast cancer and bone metastases who had not received prior intravenous bisphosphonate therapy.<sup>9,10</sup> The primary endpoint of this study was the percentage change in urinary N-telopeptide (corrected for urine creatinine [uNTx/Cr]), which is a marker for bone turnover, from baseline to week 13. Patients with elevated levels of NTx have been shown to be at an increased risk for developing skeletal-related complications, disease progression, and death. Two hundred fifty-five patients were randomized to either denosumab 30 mg SQ every 4 weeks ( $n = 42$ ), 120 mg every 4 weeks ( $n = 42$ ), 180 mg every 4 weeks ( $n = 43$ ), 60 mg every 12 weeks ( $n = 42$ ), or 180 mg every 12 weeks ( $n = 43$ ). Forty-three patients were randomized to receive an intravenous bisphosphonate, zoledronic acid, pamidronate, or ibandronate depending on site-specific labeling and commercial availability. Patients were also instructed to take the same oral calcium and vitamin D supplementation as described above in the phase 3 trial conducted by Stopek and colleagues.<sup>9,10</sup> Secondary endpoints of efficacy assessed at 25 weeks (end of treatment) included the percentage change from baseline in uNTx levels, the proportion of patients with a >65% reduction in uNTx from baseline, the median time to a >65% reduction in NTx from baseline, the percentage of patients with at least one on-study SRE, and the overall incidence of adverse events and safety through the end of the follow-up period (57 weeks). The study endpoint was a 65% reduction in NTx levels; this was chosen because it was the average decrease reported in the literature for patients with bone metastases treated with an intravenous bisphosphonate.

Two hundred fifty-five women with bone metastases secondary to advanced breast cancer were enrolled in the study. Demographics were generally well balanced, although the denosumab-treated patients were slightly older than those in the bisphosphonate group. The majority of patients had skeletal metastases at more than two separate sites. Suppression of NTx occurred at all doses of denosumab administered, but the 120-mg dose given every 4 weeks resulted in the greatest overall median suppression of NTx at 13 weeks; computer estimates projected that approximately 95% of patients treated at a dose of 120 mg every 4 weeks would achieve >90% suppression of NTx. Overall, a greater than 65% reduction in NTx/Cr occurred in 74% of all denosumab-treated patients compared to 63% of those treated with an intravenous bisphosphonate. The median time from randomization to achievement of a greater than 65% reduction in NTx/Cr was 13 days in the denosumab-treated cohorts compared to 29 days for the bisphosphonate cohort. Time to first on-study SRE was similar between the two groups, with 9% of denosumab- and 16% of bisphosphonate-treated patients experiencing a first on-study SRE. The most commonly experienced SRE was fracture.<sup>9,10</sup> The incidence and severity of reported adverse events were similar between the groups, and there was no apparent relationship between the dose of denosumab administered and the development of adverse events. Pyrexia, arthralgias, and asthenia were more commonly reported in the bisphosphonate group, while nausea and fatigue were more common in the denosumab cohorts.

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The authors concluded that denosumab and intravenous bisphosphonates appeared similar in regard to the suppression of uNTx/Cr, but that the 120-mg dose of denosumab administered every 4 weeks resulted in a numerically greater degree of suppression of uNTx/Cr than the other doses or dosing interval combinations of denosumab and that was the dose that should be studied in future phase 3 trials.

### Metastatic Prostate Cancer

Fizazi and colleagues conducted a phase 3 study in patients with metastatic prostate cancer and bone metastases that was identical in both design and outcome measures to Stopek and colleagues' study (described above) for metastatic breast cancer. Their study was also a randomized, placebo-controlled, multicenter, double-blind, noninferiority trial comparing denosumab dosed at 120 mg SQ monthly to zoledronic acid 4 mg IVPB also given monthly. The primary endpoint was to evaluate whether denosumab was noninferior to zoledronic acid with respect to time on-study of first SRE. Definition of SRE, along with additional secondary outcomes, was also identical to the Stopek study.<sup>7,8,12,13</sup>

Use of denosumab resulted in an 18% decrease in the risk of first on-study SRE in this study ( $p = .008$ ), with the median time to first on-study event being 20.7 months in the denosumab arm compared to 17.1 months in the zoledronic acid arm. Denosumab also demonstrated superiority in the time to first and subsequent SRE over zoledronic acid, an 18% risk reduction ( $p = .004$ ). Time to disease progression and overall survival were similar in the two groups. This study also evaluated uNTx levels, and found greater suppression of this bone turnover marker occurred in the patients randomized to denosumab.

Similar to the Stopek study, there were no significant differences in adverse events experienced from the study drugs. Adverse events were reported in 97% of patients in both arms, with slightly more asymptomatic hypocalcaemia in the denosumab arm (12.8% vs. 5.8%) and more acute phase reactions in the zoledronic acid arm (17.8% vs. 8.4%). There were also no significant differences in the incidence of ONJ in this study, with 2.3% of denosumab patients and 1.3% of zoledronic acid patients developing ONJ. As was the case in the Stopek study, the authors concluded that denosumab was superior to zoledronic acid in delaying the time to first on-study SRE and the time to both first and subsequent SREs.<sup>12,13</sup>

### Other Potential Uses

Fizazi and colleagues also performed a randomized phase 2 study in patients with bone metastases from prostate, breast, and other malignancies that had elevated uNTx levels despite receiving intravenous bisphosphonate therapy. Elevated NTx levels represent excessive bone resorption, and these are the patients at greatest risk for developing SREs, cancer progression, and cancer-associated death.<sup>11</sup>

The study was a randomized, open-label, multicenter trial conducted at 26 centers in Europe and North America. One hundred eleven patients were randomized to three different treatment arms: continuation of an every-4-week intravenous infusion of a bisphosphonate ( $n = 37$ ), denosumab 180 mg SQ every 4 weeks ( $n = 38$ ), or every 12 weeks ( $n = 36$ ). Patients were required to have a uNTx level  $>50$  nmol/L/mM at screening despite having received intravenous bisphosphonate therapy for at least 8 weeks. The primary endpoint of the study was the proportion of patients with a uNTx level  $<50$

nmol at week 13 (treatment phase). Secondary endpoints included a variety of other assessments of uNTx levels in terms of time to response and percentage change of this marker. Time to first on-study SRE and safety were also secondary endpoints of the study. Besides breast and prostate cancers, multiple myeloma was the next most common malignancy (8% of the patients had the diagnosis).

At week 13 the primary endpoint of a uNTx level  $<50$  was achieved in 71% of the denosumab-treated patients compared to 29% in the intravenous bisphosphonate arm. The median percentage reduction in uNTx levels at 13 weeks also favored denosumab, with a 78% reduction for denosumab compared to 33% for the bisphosphonate group. Last, the estimated median time to obtaining a reduction in uNTx levels  $<50$  was 9 days in the denosumab arm compared to 65 days for the IV bisphosphonate arm. All other measurements of marker activity favored the denosumab-treated patients.<sup>11</sup>

During the 25-week treatment period, the percentage of patients experiencing a first on-study SRE was 8% in the denosumab treatment arm compared to 17% for the bisphosphonate arm. Rates of adverse events were similar between the study arms; 55% of the denosumab-treated patients reported grade 3–5 adverse events compared to 71% of the bisphosphonate-treated patients. The authors concluded that denosumab normalized elevated uNTx levels more frequently than bisphosphonate treatment in patients with bone metastases who have elevated uNTx levels despite bisphosphonate therapy. The ability for denosumab to further suppress markers of bone resorption despite previous bisphosphonate therapy indicates a different mechanism of action responsible for these effects.<sup>11</sup>

Giant cell tumors are tumors of the bone that are generally considered to be benign; however, if treatment is warranted, it has traditionally focused on either a surgical or radiation (or both) approach. A recent phase 2 trial conducted by Thomas and colleagues evaluated the effects of monthly denosumab on 38 patients with giant cell tumors.<sup>14</sup> Patients were initially treated with a "loading dose" of denosumab administered SQ on Days 1, 8, and 15 at a dose of 120 mg. After the initial loading-dose phase, patients then received a monthly SQ injection of 120 mg. Treatment was continued for a minimum of 25 weeks or until complete tumor resection was possible, disease progression without clinical benefits, elective patient discontinuation, or death. The primary endpoint of this study was tumor response, which was defined as elimination of at least 90% of giant cells or no radiological progression of the target lesions up to week 25 of treatment. Thirty-five patients were assessable for response; 30 of 35 (86%) had had a tumor response. Treatments were well tolerated with only five serious adverse events reported, none of which were felt to be treatment related. The most common adverse events experienced in this trial were extremity and back pain and headache.<sup>14</sup>

Patients with multiple myeloma with bone metastases may also benefit from RANKL inhibition. In theory, the same mechanisms and scientific premise behind the use of denosumab in patients with breast and prostate cancers that have metastasized to the bone would also apply to the management of patients with multiple myeloma who have demonstrated skeletal lytic lesions on their bones. RANK Ligand is a crucial regulator of osteoclast activity and the cycle of bone destruction and the balance between osteoblast and osteoclast activity. Currently, denosumab is not indicated for preventions of SREs in patients with multiple myeloma.

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### Conclusion

Denosumab provides a new mechanism for treating osteoporosis in postmenopausal women based on data that led to FDA approval. In addition to being an option for osteoporosis treatment, denosumab has shown benefits in treating bone metastases from a variety of cancers and also carries an FDA indication in the prevention of SREs in these patients. Depending on the bisphosphonate it was compared to, the efficacy of denosumab has equaled or surpassed the efficacy demonstrated by bisphosphonates when used for similar indications. To date, denosumab has been well tolerated in all clinical trials. In conclusion, oncology pharmacists will likely see an increase in the use of denosumab for patients with bone metastases and osteoporosis.

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## DRUG UPDATES

### Romidepsin (Istodax®)

**Class:** Histone deacetylase inhibitor

**Indication:** Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy

**Dose:** 14 mg/m<sup>2</sup> given as an intravenous infusion over 4 hours on days 1, 8, and 15 of a 28-day cycle

#### Dose modification

*Nonhematologic toxicities except alopecia*

- Grade 2 or 3 toxicity: Treatment should be delayed until toxicity returns to ≤1 or baseline; then restart therapy at 14 mg/m<sup>2</sup>. If grade 3 toxicity recurs, delay treatment until toxicity returns to ≤1 or baseline and the dose should permanently be reduced to 10 mg/m<sup>2</sup>.
- Grade 4 toxicity: Treatment should be delayed until toxicity returns to ≤1 or baseline and the dose should be permanently decreased to 10 mg/m<sup>2</sup>.
- Romidepsin should be discontinued if grade 3 or 4 toxicities recur after dose reduction.
- Hematologic toxicities
- Grade 3 or 4 neutropenia or thrombocytopenia: Treatment should be delayed until the specific cytopenia returns to ANC ≥1.5 x 10<sup>9</sup>/L and/or platelet count ≥75 x 10<sup>9</sup>/L or baseline, and then therapy may be restarted at 14 mg/m<sup>2</sup>.
- Grade 4 febrile (≥38.5°C) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment should be delayed until the specific cytopenia returns to ≤grade 1 or baseline; then the dose should be permanently reduced to 10 mg/m<sup>2</sup>.

**Common adverse effects:** Nausea, vomiting, asthenia, fatigue, infections, anorexia, hypomagnesemia, hypokalemia, hypocalcemia, elevations of AST and ALT

**Serious adverse effects:** Thrombocytopenia, neutropenia, leucopenia, anemia, EKG ST-T wave changes

**Drug interactions:** Romidepsin is primarily metabolized by cytochrome P 450 3A4 (CYP3A4). Medications that induce or inhibit CYP3A4 may interact with romidepsin and warrant therapy modification. Elevations of the prothrombin time (PT) and international normalized ration (INR) were observed in patients concomitantly receiving warfarin. PT and INR should be closely monitored. Romidepsin is a substrate of P-glycoprotein (P-gp) and concentrations may be elevated in patients receiving concomitant P-gp inhibitors.

### Romidepsin for Cutaneous T-cell Lymphoma

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Cutaneous T-cell lymphoma (CTCL) is classified as a non-Hodgkin's lymphoma (NHL). It is characterized by infiltration of the skin with malignant T-lymphocytes. An estimated 6.4 million people are diagnosed with CTCL each year, accounting for 4% of all NHL patients. The two most common types are mycoses fungoides (MF), which accounts for 60% of cases, and Sezary syndrome (SS) that accounts for 5% of cases. MF is indolent and only involves the skin while SS is more aggressive, additionally involving the blood.<sup>1,2</sup>

Prognostic factors for survival have been identified as patient age, extent and type of skin involvement, overall stage, presence or absence of extracutaneous disease, and peripheral blood involvement.<sup>1</sup> Depending on the severity of the disease, CTCL can be treated with skin-directed therapy, systemic therapy, or a combination of the two. Early stage disease can be treated with skin-directed therapy with response rates as high as 60%. These include topical steroids, topical retinoids, and topical nitrogen mustard.<sup>1,2</sup>

Systemic therapy is used to treat patients with stage 2 disease or higher or in patients with early stage disease who have become refractory or have had significant toxicity to skin-directed therapies. Extracorporeal photopheresis (ECP) is often the first therapy employed in these patients with a response rate of 78%. However, ECP is invasive and can take 4 to 6 months to begin showing a benefit. Other systemic therapies include bexarotene, denileukin diftitox, vorinostat, as well as cytotoxic therapy, such as gemcitabine and liposomal doxorubicin; however, no standard exists.<sup>1,2</sup>

Romidepsin, a novel histone deacetylase (HDAC) inhibitor, was approved in November 2009 by the U.S. Food and Drug Administration (FDA) for the treatment of CTCL in patients who have received at least one prior systemic therapy. Romidepsin prevents deacetylation of histones and other proteins, preventing the unwinding of chromatin and, thus, gene expression. Romidepsin inhibits class 1 and 2 HDACs, with preclinical studies suggesting it is the most potent of the currently available HDACs.<sup>3,4</sup>

The efficacy and safety of romidepsin was evaluated in two phase 2 single-arm studies. Patients with relapsed, refractory, or advanced CTCL were treated with romidepsin 14 mg/m<sup>2</sup> on Days 1, 8, and 15 of a 28-day cycle. Responses were evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST). The median number of previous therapies received was four in both studies. Overall response rates (ORR) observed in both trials were 41% (95% CI, 22%–61%) and 34% (95% CI, 25%–45%), with most being partial responses (30% and 21%). The median time to response was 2 months (range 0.9–4.8 months) and median time to disease progression was 8 months.<sup>4,5</sup>

Adverse events associated with romidepsin therapy include hematologic toxicities such as leukopenia, thrombocytopenia, and

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anemia. Constitutional adverse events include fatigue, nausea, and vomiting. Most concerning, however, are the cardiac changes that can occur, such as QTc prolongation. Because patients with CTCL are at risk of hypomagnesemia and QTc prolongation, magnesium and potassium levels should be monitored closely and replenished aggressively while receiving romidepsin. The most common grade 3/4 adverse events include lymphopenia, neutropenia, anemia, and thrombocytopenia occurring at rates of 37%, 27%, 16%, and 14%, respectively. Dosage modifications during clinical trials were most commonly required for neutropenia and thrombocytopenia.<sup>3-5</sup>

The recommended dose of romidepsin is 14 mg/m<sup>2</sup> on days 1, 8, 15 of a 28-day cycle. Dosage modifications are necessary for both hematologic and nonhematologic toxicities. Doses should be delayed for grade 3/4 neutropenia and thrombocytopenia and can be resumed when the absolute neutrophil count is  $\geq 1.5 \times 10^9/L$  or platelet count  $\geq 75 \times 10^9/L$  or if the cytopenia returns to baseline. The dose should be reduced to 10 mg/m<sup>2</sup> for grade 4 febrile neutropenia or thrombocytopenia requiring platelet transfusions, as well as grade 4 nonhematologic toxicities.<sup>3</sup>

Romidepsin is metabolized via CYP3A4 and is prone to interactions with medications that induce or inhibit the enzyme. It is also a substrate of P-gp, and concentrations may be elevated in patients receiving P-gp inhibitors. The extent of these interactions has not been adequately studied; as such, there is an absence of recommended dosage modifications. Therefore, therapy modification should be considered to remove the offending agent. Elevations of PT and INR were observed in patients concomitantly receiving warfarin therapy requiring patients to be monitored closely. Finally, because patients are prone to QTc prolongation during therapy, other medications that can prolong the QTc interval should be avoided.<sup>3</sup>

Romidepsin is available as a kit that contains one vial of romidepsin 10 mg and one 2 mL vial of sterile diluent, which contains 80% propylene glycol and 20% dehydrated alcohol. Romidepsin must be reconstituted with the supplied sterile diluents and further diluted in 500 mL of 0.9% sodium chloride. The diluted solution is stable for 24 hours at room temperature and should be infused over 4 hours.<sup>3</sup>

To date, romidepsin has been evaluated in phase 2 studies for a number of tumor types including metastatic colorectal cancer, castration-resistant prostate cancer, multiple myeloma, and small-cell lung cancer. However, it has been unsuccessful in achieving significant responses in any of these tumors. Currently, it is being studied in other types of lymphoma as well as melanoma and glioma.<sup>6-10</sup>

In conclusion, romidepsin is a new histone deacetylase inhibitor indicated for the treatment of CTCL in patients who have been treated with at least one prior systemic therapy. The most common adverse events include nausea, neutropenia, thrombocytopenia, and anemia with a concern for QTc prolongation.<sup>3</sup> It has so far only been studied in phase 2 studies and requires phase 3 comparative trials to fully ascertain its place in therapy. It may also play a role in the treatment of other types of lymphoma for which it is currently under study.

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