



Brief Update on Newly Approved Agents for the Treatment of Chronic Lymphocytic Leukemia

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Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) accounts for approximately 7% of newly diagnosed cases of non-Hodgkin's lymphoma (NHL)¹ and is the most common leukemia diagnosed in the Western world.² CLL and SLL basically are the same disease and are treated similarly (unless otherwise indicated, however, this article will focus on SLL). With CLL, the disease burden primarily is in the bloodstream and bone marrow, and with SLL, the lymph nodes are involved.³ In the United States, 15,720 new diagnoses and 4,600 new deaths from CLL are predicted to occur in 2014.⁴ CLL is considered an indolent NHL with median age at diagnosis of 72 years.⁵ Signs and symptoms of this malignancy are vague and include weakness, weight loss, fever, night sweats, enlarged lymph nodes, and early satiety,

but patients also may be asymptomatic when they are diagnosed.⁶

Diagnosis typically involves evaluation of the patient's complete blood count (CBC) with differential, peripheral blood smear, immunophenotype of the circulating lymphocytes, and a thorough physical exam. Molecular cytogenetics are also performed to assess for specific gene mutations, such as deletion 11q or 17p, which are poor prognostic indicators. Unmutated IgVH (immunoglobulin heavy chain variable region) and high expression of Zap70 or CD38 also are poor prognostic factors. Bone-marrow biopsies are not required for diagnosis of CLL but may be completed in select patients. Excisional lymph node biopsies are required for the diagnosis of SLL.^{3,6,7}

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The National Cancer Institute–sponsored Working Group (NCI-WG) on CLL published revised guidelines for the diagnosis and management of this malignancy in 2008.⁷ To determine response to therapy (**Table 1**), assessment must include physical examination and evaluation of blood parameters. Response assessments should be conducted at least 2 months after treatment is completed. *Stable disease* (SD) is when patients do not have progressive disease (PD) but do not meet the criteria for complete response (CR) or partial response (PR). *Relapse* is described as evidence of disease progression after 6 or more months following an initial CR or PR. *Refractory disease* is expressed as failure to achieve a response or having disease progression within 6 months of the last treatment.^{3,7}

Treatment Options

Treatment options for CLL have progressed during the past several decades, particularly in recent years. Several ongoing clinical trials are evaluating the efficacy of novel drug combination regimens and agents targeting unique pathways in B-cell malignancies. Treatment of this NHL subtype ranges from close observation with supportive-care measures to a variety of more intense therapeutic options. CLL is generally incurable, occurs in older patients, and progresses slowly. Therefore, it is often treated conservatively with careful consideration of the patient's performance status and comorbidities.^{3,8}

Patients who are asymptomatic may be observed but not treated until they become symptomatic, whereas patients with significant disease-related symptoms should be treated. Several pieces of clinical information should be considered if a patient is to be treated for CLL. Age, comorbidities, performance status, and presence of specific chromosomal abnormalities and gene mutations all should be evaluated when electing treatment regimens on an individual basis. Enrollment in a clinical trial should always be considered.^{3,6} Despite numerous available

Table 1. Response Definitions After Treatment^{3,7}

Parameter	Complete Response (CR)*	Partial Response (PR)*	Progressive Disease (PD)*
*CR: All criteria must be met and patients must be without disease-related constitutional symptoms; PR: At least two criteria from group A and one criterion from group B must be met and patients must be without disease-related constitutional symptoms; PD: At least one criterion from group A or B must be met.			
Group A			
Lymphadenopathy	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly		Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly		Decrease ≥ 50%	Increase ≥ 50%
Marrow	Normocellular, < 30% lymphocytes, no B-lymphoid nodules; hypocellular, marrow defines CR with incomplete marrow recovery (CRi)	50% reduction in marrow infiltration or the presence of B-lymphoid nodules	
Blood lymphocytes	< 4,000/mm ³	Decrease ≥ 50% over baseline	Increase ≥ 50% over baseline
Group B			
Platelet count without growth factors	> 100,000/mm ³	> 100,000/mm ³ or increase ≥ 50% over baseline	Decrease ≥ 50% over baseline secondary to CLL
Hemoglobin without transfusions or growth factors	> 11 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease > 2 g/dL from baseline secondary to CLL
Neutrophils without growth factors	> 1,500/mm ³	> 1,500/mm ³ or > 50% improvement over baseline	

treatment options, some patients may be refractory to therapy, needing alternative treatment options, or require allogeneic hematopoietic stem cell transplantation (HSCT) for disease control. New agents have recently been added to the treatment armamentarium, which has improved patient options and prolonged survival.

Obinutuzumab (Gazyva)

Obinutuzumab is a humanized, glycoengineered IgG1 type 2 antibody targeted against CD20. Obinutuzumab has high-affinity binding for the type 2 epitope leading to 5- to 100-fold greater antibody-dependent cytotoxicity than rituximab.^{8,9} Obinutuzumab was approved by the U.S. Food and Drug Administration (FDA) in November 2013 for use in combination with chlorambucil for the treatment of patients with untreated CLL.¹⁰

Obinutuzumab was studied in a multinational trial (189 centers in 26 countries) that enrolled untreated patients with CD-20 positive CLL, Binet stage C, or symptomatic disease. Patients were also required to have a clinically meaningful burden of coexisting conditions, defined as a score higher than 6 on the Cumulative Illness Rating Scale (CIRS). Patients who did not have a high enough comorbidity score were also eligible if they had a creatinine clearance of 30–69 mL/min calculated with the Cockcroft-Gault formula. This open-label, three-group study randomized patients in a 1:2:2 manner: (a) chlorambucil alone, (b) obinutuzumab plus chlorambucil, and (c) rituximab plus chlorambucil, respectively; all regimens were given in six 28-day cycles. Chlorambucil was administered at 0.5 mg/kg orally once on days 1 and 15. Obinutuzumab was administered at 1,000 mg intravenously on days 1, 8, and 15 during cycle 1, then only on day 1 during all subsequent cycles. The first infusion was divided over 2 days for cycle 1 after a protocol amendment to help decrease the rates of infusion reactions. Rituximab was administered at 375 mg/m² intravenously on day 1 during cycle 1, then 500 mg/m² during all subsequent cycles.⁹

After 118 patients had been assigned to the chlorambucil arm, this arm was closed early due to predefined stopping criteria. The protocol was revised to randomize patients in a 1:1 ratio into the remaining arms stratified by geographic region and stage. Patients in the single-agent chlorambucil arm were allowed to cross over to the obinutuzumab-plus-chlorambucil arm if they had PD during treatment or within 6 months of the end of treatment.⁹

A total of 781 patients were enrolled in the three study arms. Baseline characteristics among the three groups were well balanced, with a median age of 73 years, creatinine clearance of 62 mL/min, and a CIRS score of 8. The site investigator determined that progression-free survival (PFS) was the primary end point. There was significant improvement in PFS for the combination arms over the arm receiving chlorambucil alone—26.7 months for obinutuzumab plus chlorambucil versus 11.1 months for chlorambucil alone (hazard ratio [HR] = 0.18; 95% confidence interval [CI]: 0.13–0.24; $p < .001$) and 16.3 months for rituximab plus chlorambucil (HR = 0.44; 95% CI: 0.34–0.57; $p < .001$). Patients with deletion 17p were the only subgroup who did not experience this benefit in PFS. PFS was also significantly longer when obinutuzumab plus chlorambucil was compared with rituximab plus chlorambucil: 26.7 versus 15.2 months (HR = 0.39; 95% CI: 0.31–0.49; $p < .001$). Additionally, obinutuzumab in combination with chlorambucil resulted in higher rates of overall, complete, and molecular responses.

At the time of publication, the most recent data for overall survival (OS) revealed a significant improvement for the obinutuzumab plus chlorambucil arm over the chlorambucil monotherapy arm; 9% versus 20% (HR for death = 0.41; 95% CI: 0.23–0.74; $p = 0.002$). There was no significant OS difference in the combination therapy arms.⁹

Adverse reactions occurred most commonly in the obinutuzumab plus chlorambucil arm, including neutropenia, anemia, thrombocytopenia, leukopenia, and infusion-related reactions. Infection grade 3–5 ranged from 11% to 14% and was not significantly different between groups, with the majority of infections being bacterial in nature. Twenty percent of patients experienced grade 3–4 infusion reactions with the first infusion of obinutuzumab, yet no grade 3–4 reactions occurred during subsequent cycles. Patients in the rituximab plus chlorambucil arm were the least likely of all groups to discontinue therapy early due to adverse events. The primary reason for discontinuation in the obinutuzumab plus chlorambucil group was infusion-related reactions, which decreased with the divided dosing on day 1 of cycle 1 (100 mg on day 1 and 900 mg on day 2).⁹

Obinutuzumab plus chlorambucil has been added to the National Comprehensive Cancer Network (NCCN) guidelines as a preferred treatment option for first-line therapy of CLL.³ The infusion-related adverse reactions are manageable with appropriate premedications of acetaminophen, antihistamine, and corticosteroid.⁹ Obinutuzumab is being evaluated in the relapsed/refractory setting as well as in various combinations in both the relapsed/refractory and untreated setting.¹¹

Ibrutinib (Imbruvica)

Ibrutinib is an oral agent that inhibits Bruton's tyrosine kinase (BTK). This enzyme target is essential for B-cell receptor signaling, proliferation, and survival.^{12,13} The FDA approved ibrutinib in February 2014 for the treatment of patients with CLL who have received at least one previous therapy.¹³ In July 2014, it was also approved for treatment of patients with deletion 17p CLL.¹⁴

Ibrutinib was evaluated in RESONATE, a phase 3, multicenter, open-label, randomized trial that enrolled patients with relapsed or refractory CLL or SLL. RESONATE compared ibrutinib, 420 mg orally once per day, with ofatumumab, 300 mg intravenously week 1 followed by 2,000 mg intravenously weekly for 7 weeks, then every 4 weeks for 16 weeks. From 67 sites in the United States, Australia, and seven European countries, 391 patients were stratified according to purine analog chemoimmunotherapy resistance and presence of 17p13.1 deletion. Due to positive results from the phase 2 trial with ibrutinib, the trial was revised to allow crossover of patients from ofatumumab to ibrutinib.¹³

The baseline characteristics of patients were well matched between the two groups. Patients in the ibrutinib group received a median of 8.6 (0.2–16.1) months of therapy, and patients in the ofatumumab group received 5.3 (0–7.4) months of therapy. The primary end point of PFS was significantly prolonged in the ibrutinib group: 9.4 months versus 8.1 months for the ofatumumab group (HR for progression or death = 0.22; 95% CI: 0.15–0.32; $p < .001$ by log-rank test). Ibrutinib's impact on PFS was seen regardless of baseline clinical characteristics or molecular features. OS was also significantly prolonged in the ibrutinib arm (HR = 0.43; 95% CI: 0.24–0.79; $p = .005$). The improvement in OS was maintained in all subgroups according to the pretreatment and genetic abnormalities.¹³

Lymphocytosis occurred in 69% of patients in the ibrutinib arm and was not considered disease progression. This lymphocytosis is a result of the lymphocytes leaving the nodal compartments and resolves within 8 months in most patients.¹⁵ The most common nonhematologic adverse events occurring in at least 20% of patients were diarrhea, fatigue, pyrexia, and nausea in the ibrutinib arm and fatigue, infusion-related reactions, and cough in the ofatumumab arm. Grade 3 or higher adverse events occurring more often in the ibrutinib arm included diarrhea (4% versus 2%) and atrial fibrillation (3% versus 0%). Any grade bleeding-related adverse events were more common in the ibrutinib group (44% versus 12%). Additional adverse events more common in the ibrutinib arm included rash (8% versus 4%), pyrexia (24% versus 15%), infection (70% versus 54%), and blurred vision (10% versus 3%). Study treatment discontinuation due to adverse events occurred in 4% of patients in each arm.¹³

Ibrutinib is an effective therapy for patients with relapsed or refractory CLL/SLL and patients with deletion 17p. It has been added to the most recent version of the NCCN guidelines as a category 1 recommendation for patients with relapsed or refractory disease.³ Ibrutinib is also being evaluated in untreated patients with CLL or SLL and in various combination therapies in the relapsed/refractory setting.¹¹

Ofatumumab (Arzerra)

Ofatumumab is an IgG kappa human monoclonal antibody that binds to a distinct epitope composed of both small and large loops on the CD20 molecule. Ofatumumab has increased binding and more potent complement-dependent cytotoxicity than rituximab.^{16,17}

Ofatumumab was initially approved by the FDA in October 2009 for the treatment of patients with CLL refractory to fludarabine and alemtuzumab on the basis of durable tumor reduction in a single-arm study. Ofatumumab was administered in eight weekly intravenous infusions followed by four monthly infusions with the first dose being 300 mg and doses 2 through 12 being 2,000 mg each. Patients experienced a 42% (99% CI: 26–60) investigator-determined objective response rate (ORR) and 6.5-month (95% CI: 5.8–8.3) median duration of response (DOR). All responses were partial.^{16,17}

Ofatumumab received FDA approval for an additional indication in April 2014. It is now also approved for use in combination with chlorambucil for first-line treatment of CLL in patients for whom fludarabine-based therapy is considered inappropriate,¹⁸ based on results presented at the 2013 American Society of Hematology (ASH) Annual Meeting and Exposition.

A multicenter, randomized, open-label study was conducted in 447 patients randomized in a 1:1 manner comparing ofatumumab plus chlorambucil to chlorambucil alone. Patients were considered inappropriate for fludarabine-based therapy due to advanced age and/or comorbidities. Chlorambucil was administered at 10 mg/m² orally on days 1 through 7 of each 28-day cycle, and ofatumumab was administered intravenously at 300 mg on day 1 and 1,000 mg on day 8 of cycle 1, followed by 1,000 mg on day 1 of subsequent cycles. Patients were treated for a minimum of three cycles, and treatment was continued until best response to a maximum of 12 cycles. Baseline demographics were well matched between treatment arms, with a median age of 69 years, 82% of patients aged 65 years or older, and/or having two or more comorbidities.¹⁹

The primary end point of PFS assessed by an independent review committee revealed a significantly longer PFS in the combination-therapy arm compared with the single-agent chlorambucil arm (22.4 versus 13.1 months; HR = 0.57, 95% CI: 0.45–0.73, $p < .001$). The secondary end point of overall response rate was also improved in the ofatumumab plus chlorambucil arm (82% versus 69%; OR 2.16; $p = .001$). CR rate was superior in the combination arm compared with the chlorambucil-alone arm: 12% versus 1%, respectively. At a median follow-up time of 29 months, the median OS was not reached for either arm; the trial concluded before survival time could be assessed. The median duration of treatment for both arms was six cycles, with 82% of patients receiving six or more cycles of ofatumumab plus chlorambucil.¹⁹

There were similar rates of grade 3 or higher adverse events occurring from the start of treatment through 60 days from the last dose (50% in ofatumumab plus chlorambucil versus 43% chlorambucil alone). The most common grade 3 or higher adverse event occurring in both groups was neutropenia (26% in the combination arm versus 14% in the single-agent arm) followed by infection (15% versus 14%, respectively). Ten percent of patients in the combination-therapy arm experienced grade 3 or higher infusion reactions despite premedication with acetaminophen, an antihistamine, and glucocorticoid; none were fatal.¹⁹

Ofatumumab is an important addition to the treatment options for patients with untreated CLL who are not candidates for fludarabine-based therapy. With CLL being diagnosed in older patients with comorbidities, this is an important advance in CLL therapy. Ofatumumab has not been added to the current version of the NCCN guidelines for this setting, but an update is in progress.³

Idelalisib (Zydelig)

Idelalisib is an oral, highly selective PI3K (PI3 kinase) inhibitor approved in July 2014. It is indicated for the treatment of relapsed CLL in combination with rituximab for patients for whom rituximab alone would be considered inappropriate treatment and as monotherapy for patients with relapsed SLL.²⁰

Study 116 was a phase 3, randomized, double-blind, placebo-controlled trial conducted at 90 centers in the United States and Europe comparing idelalisib plus rituximab to placebo plus rituximab in patients with relapsed CLL. Patients were given idelalisib, 150 mg orally twice daily, or placebo with rituximab, 375 mg/m² followed by 500 mg/m² every 2 weeks for four doses and then every 4 weeks for three doses (a total of eight infusions). Patients were stratified by presence of 17p deletion or other TP53 mutations or the lack of IgHV mutation. Patients had to have been treated with a CD20 antibody or at least two previous cytotoxic regimens and be ineligible to receive cytotoxic therapy for any of the following reasons: severe neutropenia or thrombocytopenia from previous therapies, creatinine clearance less than 60 mL/min, or CIRS score higher than 6. Patients in the placebo group who experienced disease progression while enrolled in Study 116 were permitted to enroll in Study 117 to receive idelalisib. Patients with progression on idelalisib were allowed a dose increase to 300 mg orally twice daily.²¹

The groups were well matched with 110 patients randomized to each study arm. The median time on study was short because of early stopping parameters being met due to response. Patients received study treatment for 3.8 months in the idelalisib group and 2.9 months in the placebo group. Results were positive, with the idelalisib combination arm

having a significantly improved primary end point of PFS (combination arm, not reached versus placebo arm, 5.5 months; HR = 0.15; $p < .001$), overall response (81% versus 13%; OR, 29.92; $p < .001$), and OS at 12 months (92% versus 80%; HR = 0.28; $p = .02$). Patients receiving idelalisib also experienced lymphocytosis, but this was lessened with the addition of rituximab. Lymphocytosis rates peaked at week 2 and resolved by week 12. Serious adverse-event rates were comparable between groups: 40% in the idelalisib plus rituximab group versus 35% in the placebo plus rituximab group. The most common adverse events in the idelalisib group were pyrexia, fatigue, nausea, chills, and diarrhea.²¹


Idelalisib's accelerated approval for relapsed SLL is based on data from a single-arm, phase 2 study (101-09; DELTA) conducted at 41 U.S. and European sites in patients with relapsed indolent lymphoma refractory to rituximab and alkylating-agent containing chemotherapy. Idelalisib was administered at 150 mg orally twice daily until the disease progressed, unacceptable toxicities occurred, or the patient died. A total of 26 patients with SLL were included in this study, and they had an overall response rate of 58% (37%–77%), which was the primary end point. All 15 responses seen in patients with SLL were PRs with a median duration of response of 11.9 months (0–14.7 months). The median duration of treatment was 6.6 months (0.6–23.9 months), and the mean duration was 8.1 ± 5.7 months. The most common adverse events ($\geq 20\%$) seen in all grades included diarrhea, fatigue, nausea, cough, and pyrexia.^{20,22}

Idelalisib is an important addition to the available therapies for CLL/SLL, having a distinctive mechanism of action. Idelalisib has yet to be added to the NCCN guidelines due to its recent approval and the guideline update currently in progress. It is included in several ongoing clinical trials in combination therapy and untreated patients.^{3,11,23}

Future Directions

There are several new agents that have the potential to provide additional options for the management of CLL. The B-cell lymphoma 2 (Bcl-2) family of regulator proteins is highly involved in apoptosis and is a potential pathway to target in CLL because Bcl-2 is highly expressed in this disease. There are several small-molecule Bcl-2 inhibitors under investigation. The B-cell receptor (BCR) pathway is an additional potential target, as B cells rely on signaling mediated by BCR for maturation, proliferation, survival, and death. Some tyrosine kinases involved in this signaling include spleen tyrosine kinase (SYK), PI3K, and BTK. Inhibitors of these tyrosine kinases are already under investigation.^{3,11}

Conclusion

CLL is a common subtype of NHL and is incurable with current treatment options outside of an allogeneic HSCT. Chemoimmunotherapy has improved OS for patients with CLL, but patients who experience relapsed or refractory disease continue to have poor outcomes. Because of the age of patients at diagnosis, it is important to consider several patient-specific factors and implement appropriate supportive-care measures when selecting a treatment option.³ Identifying treatment alternatives with improved side-effect profiles and patient tolerability is an important next step for management of this malignancy. The recently approved and in-development targeted therapies have the goal of filling this niche. 

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HOPA Publishes Investigational Drug Service Best Practice Standards

We are pleased to announce the HOPA Standards Committee has completed the HOPA Investigational Drug Service Best Practice Standards, the first of its kind that provides the best practice standards and guidance for pharmacists and institutions that conduct clinical trials. The HOPA Investigational Drug Service Best Practice Standards emphasizes the critical role of the pharmacist in the investigational drug service from protocol concept to close-out. This document provides a foundation for pharmacy to be involved very early in protocol development and review, to ensure that the trial meets institutional medication guidelines, is executed efficiently, and adheres to all regulations and standards. In addition, the guidelines provide an outline for the role of the pharmacy technician which is unique to this document. These guidelines address various best practices for pharmacy operations and provide ancillary information about the different mechanisms for obtaining investigational drugs for a single patient, and provide a concise summary of and reference source for the procedures for obtaining investigational drugs on a "compassionate" basis. This best practice guideline should be used in conjunction with other applicable state and federal guidelines.

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You can access the HOPA Investigational Drug Service Best Practice Standards on HOPA's website.

Controversial Medicare Part D Rule Placed on the Back Burner

On March 10, 2014, the Centers for Medicare & Medicaid Services (CMS) issued a memorandum to all Part D plan sponsors and Medicare hospice providers clarifying the criteria for determining payment responsibility under the Part A hospice benefit and Part D for drugs for hospice beneficiaries. The memorandum, “Part D Payment for Drugs for Beneficiaries Enrolled in Hospice—Final 2014 Guidance,” established that as of May 1, 2014, all prescribed medications for hospice patients billed to Medicare Part D initially will be denied coverage. This is in response to the issue of duplicative payments. Insurance companies were paying for drugs that already were covered under the hospice benefit, or waived through the beneficiary’s hospice election. Requiring prior authorization for all prescribed medications for hospice patients places an undue burden on the patient. Denial of coverage places the patient in the middle of potential payer disputes between hospice providers and the Part D plan.

In response to this memorandum, HOPA joined with more than 40 state and national organizations in signing a [letter](#)¹ facilitated by the Center for Medicare Advocacy. The letter urges CMS to suspend the current policy directing Part D plans to place prior authorization requirements on all prescriptions for hospice beneficiaries as well as to bring together relevant stakeholders to collectively work through the issues. Overall, the supporting organizations believe that the Final

2014 Guidance is premature, subject to differing interpretations, and already creating barriers for dying patients who are trying to access necessary medications.

CMS listened to our voices and is modifying the rules so that additional authorization would only be required for four types of hospice-related medications: pain relievers, anti-nauseants, laxatives, and anti-anxiety drugs. Speaking on the rule revision, Medicare spokesman Raymond Thorn said, “Based on discussions with stakeholders, we are adjusting our rules so that beneficiaries enrolled in hospice will continue to have access to their medications while balancing recommendations by the inspector general meant to safeguard the Medicare program.” This is a great win for patients and a true testament to the power of a collective voice and HOPA’s advocacy efforts. 

Reference

1. Center for Medicare Advocacy. Letter to Marilyn Tavenner. [Accessed 2014 June 11]. www.hoparx.org/uploads/Health_Policy/2014/Hospice_Part_D_sign-on_6_11_14_FINAL_00072459.pdf.

2014 ASCO Annual Meeting Review

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The American Society of Clinical Oncology (ASCO) held its 50th Annual Meeting in Chicago, IL, May 31–June 3, 2014. The official theme of this year’s meeting was “Science and Society” and focused on opportunities for the community of clinicians and researchers to lead society in the quest for knowledge and insight as it pertains to cancer. The meeting certainly delivered on its theme, presenting a diverse array of trial results that will affect practice and guide future research. The following is a summary of a few of the important findings presented.

LBA1: Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer Patients

The combined results of two phase 3 trials, Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT), were presented during the plenary session. The trials compared 5 years of adjuvant exemestane plus ovarian suppression with tamoxifen plus estrogen suppression in 4,690 premenopausal women. The method of ovarian suppression was based on physician

and patient preference and included triptorelin, oophorectomy, or ovarian irradiation. Disease-free survival at 5 years was superior in the exemestane group (91.1% versus 87.3%; hazard ratio [HR] for disease recurrence, second invasive cancer, or death = 0.72; 95% confidence interval [CI]: 0.60–0.85; $p < .001$).

LBA4: Disappointing Final Results of ALTO Trial

This trial examined the benefit of adding lapatinib to trastuzumab, either concurrently or sequentially, in the adjuvant treatment of HER2-positive breast cancer. Unfortunately, lapatinib did not increase disease-free survival compared with trastuzumab alone. These results were disappointing and unexpected given the significantly increased pathologic complete response rates reported from the addition of lapatinib to trastuzumab in the neoadjuvant setting (reported previously in the NeoALTO trial, available in *Lancet* 2012;379:633–640).

LBA505: Prevention of Early Menopause Study (POEMS)

In this trial, women younger than 50 years with stage I, II, or IIIa ER/PR-negative breast cancer were randomized to receive a

cyclophosphamide-based adjuvant chemotherapy regimen with or without goserelin at a dose of 3.6 mg monthly, starting 1 week before chemotherapy. The primary endpoint was rate of premature ovarian failure (POF). Rate of POF was 22% in the standard arm and 8% in the goserelin arm (OR = 0.30, 95% CI: 0.10–0.87; $p = .03$). A secondary endpoint in this trial was rate of pregnancy. Roughly the same proportion of women in each arm reported that they attempted to conceive after treatment, and more women in the goserelin arm were able to become pregnant (21% versus 11%; OR = 2.45; $p = .03$).

LBA 9500: Zoledronic Acid Every 4 Weeks Versus Every 12 Weeks

In this prospective, randomized, double-blind trial, women with bone metastases from breast cancer who previously received approximately 1 year of monthly intravenous (IV) bisphosphonate (either zoledronic acid or pamidronate) were randomized to receive either zoledronic acid 4 mg intravenously every 4 weeks or every 12 weeks for 1 year. There were no differences between the arms in rates of skeletal-related events. Treatment-related adverse events were similar in both arms; however, there were two cases of osteonecrosis of the jaw in the every-4-week arm and none in the every-12-week arm.

Abstracts 8002 and 8003: Important Data for Patients with ALK Translocation Positive NSCLC

In abstract 8002, the PROFILE 1014 trial confirmed that in first-line treatment, crizotinib is superior to doublet chemotherapy in patients with advanced anaplastic lymphoma kinase (ALK)-positive, nonsquamous non-small cell lung cancer (NSCLC). The study met its primary objective of prolongation of progression-free survival (PFS), demonstrating superiority of crizotinib over chemotherapy (median PFS 10.9 versus 7.0 mo; HR = 0.454; 95% CI: 0.346–0.596; $p < .0001$). The overall response rate was also significantly higher with crizotinib (74% versus 45%; $p < .0001$). Overall survival data are not yet mature, however, overall survival is a secondary endpoint, and the trial has a crossover design.

Abstract 8003 reported results from the expansion phase of the ASCEND-1 trial of ceritinib (formerly LDK378) in ALK-positive lung cancer patients (phase 1 results available in *NEJM* 2014;370:1189-1197). In the 180 patients evaluated, overall response rate was 60%. Of the 121 patients who had previously received crizotinib, the response rate was 55.4%, with a median duration of response of 7.4 months. Ceritinib gained U.S. Food and Drug Administration (FDA) approval in April 2014 for treatment of ALK-positive lung cancer patients previously treated with crizotinib.

Abstract 8005: Erlotinib Plus Bevacizumab Versus Erlotinib Alone as First-Line Treatment for Advanced EGFR Mutation-Positive Nonsquamous NSCLC

This open-label trial randomized epidermal growth factor receptor (EGFR)-positive advanced or metastatic NSCLC patients to receive


either erlotinib 150 mg by mouth daily or the same dose of erlotinib combined with bevacizumab 15 mg/kg intravenously every 3 weeks. Progression-free survival was superior in the combination arm (16.0 months versus 9.7 months; HR, 0.54; 95% CI: 0.36–0.79; log-rank $p = .0015$). Response rates were similar, and adverse events were considered manageable in the combination arm.

LBA2: Impact on Overall Survival with Chemohormonal Therapy Versus Hormonal Therapy for Hormone-Sensitive Newly Metastatic Prostate Cancer: An ECOG-Led Phase 3, Randomized Trial

In this potentially practice-changing trial, 790 men with metastatic hormone-sensitive prostate cancer who received androgen-deprivation therapy (ADT) were randomized to ADT alone or ADT plus docetaxel 75 mg/m² every 3 weeks for six cycles. Patients receiving docetaxel were required to start chemotherapy within 4 months of initiation of ADT. The primary endpoint of overall survival demonstrated superiority of combination chemohormonal therapy compared with ADT alone (median overall survival was 52.7 months versus 42.3 months; $p = .0006$). Of note, patients who progressed on the ADT-alone arm were eventually given docetaxel as per the current standard of care. Survival benefit was most profound in men with high-volume disease, with an increase in survival of 17 months. Data are currently insufficient to determine whether men with low-volume disease would benefit from this strategy.

LBA3: CALGB/SWOG 80405 Phase 3 Trial of FolFIRI or FolFOX with Bevacizumab or Cetuximab for Patients with KRAS Wild-Type Untreated Metastatic Colorectal Cancer

Results from the CALGB/SWOG 80405 trial (LBA3) found that for first-line treatment of metastatic colorectal cancer in patients who are KRAS wild-type, overall survival for cetuximab plus chemotherapy is equivalent to bevacizumab plus chemotherapy (approximately 29 months in both arms). It should be noted that the selection of FolFOX or FolFIRI as the first-line chemotherapy backbone was at the discretion of the treating physician and that there was a strong preference for FolFOX (73.4%). This is particularly important because previous studies have suggested that the cetuximab plus FolFOX combination may be inferior to FolFOX alone in the first-line setting.

As usual, the ASCO Annual Meeting presented clinicians with an enormous amount of data to digest. While not discussed in this review, excitement about immunotherapy continued to grow at ASCO 2014. We will likely see the first of the PD-1 inhibitors approved in late 2014, and I encourage readers to review abstracts related to these agents in melanoma and in other disease states. Also of note, value in cancer care was a recurrent theme at the meeting, which is not surprising given ASCO's recent launch of the strategic Value in Cancer Care Initiative. 

Board Update

Michael Vozniak, PharmD BCOP, HOPA President



HOPA had a busy and productive summer! In July, HOPA hosted its 4th Annual Industry Relations Council (IRC) Summit. Representatives from thirteen of the 15 IRC participants joined us in Chicago. HOPA provided an update on the organization, and board members led focused discussions on clinical pathways, oral chemotherapy, and patient advocacy. The summit was very informative and provided the board of directors with good insight to help move HOPA forward in the ever-evolving healthcare environment.

One of the most active and visible HOPA member benefits is the HOPA Listserv. The HOPA Listserv is a great forum for getting answers to practice questions and learning from others. However, the current Listserv has some limitations. The board reviewed and discussed alternative platforms that will provide a better member experience and more functionality and has decided to replace the Listserv with a product from Higher Logic. A few of the benefits of the Higher Logic product include

- a more comprehensive community experience
- resource libraries where members can post documents to share
- additional options for discussion delivery methods
- adaptive design, which allows users to fully interact on smart phones and tablets
- space for electronic advertising and association-related news.

Higher Logic's functionality is broader than a Listserv's. HOPA will assess how to best utilize the product for our members and work on the design and implementation in the months to come.


In other HOPA news, the Standards Committee has released the *HOPA Investigational Drug Services Best Practice Standards* document and will develop follow-up webinars to inform target audiences about these guidelines in the fall. In addition, the Standards Committee helped appoint a work group to review, comment on, and consider endorsing the U.S. Pharmacopeial (USP) Convention, General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings Guideline. Ryan Forrey, Richard Cleveland, and Susan Spivey served on the work group and provided detailed comments that were submitted to USP in July. The comments also have been posted on the HOPA website for member review.

The 2nd Annual HOPA Oncology Pharmacy Practice Management Program was held September 19–20 in Chicago. In addition to extending the program to 2 days, there was a preconference workshop, "Oncology Residency and Preceptor Program Development," offered. We also are excited about HOPA's upcoming 11th Annual

Conference, which is being held March 25–28, 2015, in Austin, TX. Both programs offer great educational content, networking opportunities, and the chance to engage with pharmaceutical industry representatives in the exhibitor halls.

HOPA's Health Policy Committee has been actively monitoring the Provider Status initiative and will soon reach out to the HOPA membership to solicit support. In addition, the Health Policy Committee traveled to Washington, DC, in September with our health policy consultants from the District Policy Group. The committee and our consultants met with members of Congress to seek their support for H.R. 4190 and recognize pharmacists as providers under Medicare Part B. Please stay tuned for opportunities to support H.R. 4190.

HOPA has created and appointed a new Recognition Committee. The committee will be led by Stephanie Sutphin, chair, and David DeRemer, vice chair. The committee is responsible for directing our HOPA membership awards program, which was the task of the former Nominations and Awards Committee. The committee will be charged with developing processes and procedures for a new HOPA Fellows Program. The goal is to recognize the first class of fellows at the 2016 Annual Conference.

As HOPA celebrates its 10th anniversary, it is an opportune time to reflect on the association's progress over the years and to envision HOPA's future. HOPA has enjoyed tremendous growth in our membership, engagement, and participation in both advocacy and the pharmacy profession in recent years. We continue to provide quality continuing education programs that have expanded in content and variety. HOPA's growth and maturation is a result of the association fulfilling its goals and objectives outlined in the strategic plan revolving around the four goal areas: professional development, research, advocacy, and hematology/oncology pharmacy practice standards. HOPA's strategic plan was created in 2010 and was revised in November 2012. As HOPA looks toward its future, the board of directors has decided to formally review and update the strategic plan in early 2015. This will allow the association to reflect on changes in our environment, assess our progress on our goals, and set or revise goals that work toward our envisioned future when all individuals affected by cancer have a hematology/oncology pharmacist as an integral member of their care team. 

Recalls, Withdrawals, and Safety Alerts from the FDA

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Exemestane (Aromasin)

The “Warnings and Precautions” section for exemestane now recommends that women with osteoporosis or those at risk of osteoporosis undergo a formal assessment of their bone mineral density by bone densitometry when initiating therapy. Patients should be monitored for bone mineral density loss and treated as indicated. Additionally, postmarketing reports of paresthesia and acute generalized exanthematous pustulosis have been added to the prescribing information.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm250607.htm>

Crizotinib (Xalkori)

The “Clinical Pharmacology Drug Interactions” section of the package insert has been revised to include information regarding the potential for crizotinib to inhibit uridine diphosphate glucuronosyl-transferase (UGT) enzymes, as well as other hepatic and renal transporters. Additionally, updated safety margins for pregnant and pediatric patient populations have been included within the “Use in Specific Populations” section of the package insert.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm295722.htm>

Docetaxel Intoxication

The U.S. Food and Drug Administration (FDA) has issued a safety announcement to warn that docetaxel contains ethanol and may cause patients to feel intoxicated or drunk during and after treatment. Product label revisions are being made to warn about the risk. Healthcare professionals (HCPs) should take this into consideration when prescribing and administering docetaxel, especially in patients in whom alcohol intake should be avoided or minimized, and when used in combination with certain drugs. Patients should be monitored for signs of alcohol intoxication during and after treatment. Alcohol content may vary between formulations. In patients who experience this adverse reaction, HCPs may consider using a docetaxel formulation with the lowest alcohol content and slowing the infusion rate during administration. Patients should be notified about the alcohol content in docetaxel and the potential for this to affect the central nervous system. Patients should be advised to avoid driving, operating machinery, and performing activities that are dangerous or require skill for 1 to 2 hours after the infusion.

<http://www.fda.gov/Drugs/DrugSafety/ucm401752.htm>

Gemcitabine (Gemzar)

The “Warnings and Precautions,” “Adverse Reactions,” and “Dose Modifications” sections of gemcitabine’s prescribing information have been updated to include information on the risk for posterior reversible encephalopathy syndrome (PRES). PRES has been reported with single-agent gemcitabine, as well as in combination

with other chemotherapy agents. If PRES develops during therapy with gemcitabine, it is recommended to permanently discontinue the agent.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm356107.htm>

Denosumab (Xgeva) Hypocalcemia with Renal Dysfunction

The prescribing information for denosumab (Xgeva) has been revised to update information on the risk for hypocalcemia in the “Warnings and Precautions” and “Use in Specific Populations” sections. There is an increased risk for the development of hypocalcemia in patients with renal dysfunction, most commonly in patients with severe impairment—defined as those with a creatinine clearance less than 30 mL/min and/or those on dialysis—and with inadequate or no calcium supplementation. Calcium levels should be monitored and supplemented with calcium and vitamin D as needed.

<http://www.fda.gov/safety/medwatch/safetyinformation/ucm343116.htm>

Denosumab (Prolia) Musculoskeletal Pain

The “Warnings and Precautions” section of the prescribing information for denosumab (Prolia) has been revised to include postmarketing reports of severe and possibly incapacitating bone, joint, and muscle pain. Severe symptoms may warrant therapy discontinuation.

<http://www.fda.gov/safety/medwatch/safetyinformation/safety-relateddruglabelingchanges/ucm307218.htm>

Eculizumab (Soliris) Recall

Alexion Pharmaceuticals, Inc., has issued a voluntary recall of certain lots of eculizumab distributed in the United States. This was due to the use of a process component during vial filling that resulted in the presence of visible particles. The company has identified the problem and is implementing a process change. There have been no safety risks identified in patients who have received eculizumab. There are no anticipated interruptions in patient supply.

<http://www.fda.gov/safety/recalls/ucm399527.htm>

Sunitinib (Sutent) Proteinuria and Dermatologic Toxicities

Proteinuria and dermatologic toxicities, including Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, and necrotizing fasciitis, have been added to the “Warnings and Precautions and Medication Guide” of sunitinib’s package insert.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm224050.htm>

Docetaxel Respiratory Adverse Reactions

There have been additional respiratory adverse reactions reported in postmarketing surveillance of docetaxel. The package insert has been updated and now includes the following statement: “Dyspnea, acute

pulmonary edema, acute respiratory distress syndrome/pneumonitis, interstitial lung disease, interstitial pneumonia, respiratory failure, and pulmonary fibrosis have rarely been reported and may be associated with fatal outcome. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.”
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm396551.htm>

Temozolomide (Temodar) Hepatotoxicity

The “Warnings and Precautions” section for temozolomide’s package insert has been updated to include the risk of fatal and severe hepatotoxicity reported in patients receiving this agent. Recommended monitoring includes liver function tests at baseline, midway through the first cycle, prior to each subsequent cycle, and approximately 2 to 4 weeks after the last dose of temozolomide. A case control study is being conducted to determine the correlation between temozolomide and severe acute liver injury.
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm211909.htm>

Thalidomide Venous and Arterial Thromboembolism Update

Updates have been made to the “Warnings and Precautions—Venous and Arterial Thromboembolism” section of the package insert for thalidomide. The update includes the following information: “Ischemic heart disease (11.1%), including myocardial infarction (1.3%) and stroke (cerebrovascular accident, 2.6%) have also occurred in patients with previously untreated multiple myeloma treated with Thalomid and dexamethasone compared to placebo and dexamethasone (4.7%, 1.7%, and 0.9%, respectively) in one clinical trial.”
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm402899.htm>

Topotecan (Hycamtin) Renal Impairment

Revisions to the dosing recommendations in renal impairment for oral topotecan have been made in the package insert.
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm279915.htm>

Pazopanib (Votrient) Drug Interactions

The solubility of pazopanib is pH dependent. Concomitant administration of pazopanib with drugs that raise gastric pH should be avoided. A drug interaction trial demonstrated a decrease in the exposure of pazopanib by approximately 40% (AUC and C_{max})

when administered with esomeprazole. If therapy with these agents is necessary, short-acting antacids instead of PPIs and H₂ receptor antagonists should be used whenever possible. The administration of antacids and pazopanib should be separated by several hours.
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303649.htm>

Obinutuzumab (Gazyva) Thrombocytopenia and Hemorrhagic Events

Updated safety data include reports of fatal hemorrhagic events during cycle 1 in patients treated with obinutuzumab. It is recommended to monitor all patients frequently, especially during the first cycle, for thrombocytopenia and hemorrhagic events. Dose delays of obinutuzumab and chlorambucil or dose reductions of chlorambucil can be considered in patients with grade 3 or 4 thrombocytopenia. Consideration should be made to withholding concomitant agents that increase bleeding risk, especially during the first cycle of therapy.
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm404996.htm>

ISMP Medication Safety Alerts (March–June)

May 8, 2014 (Volume 19, Issue 9)

The Institute for Safe Medication Practices (ISMP) has asked the FDA and Teva to investigate commas that have replaced decimals on tbo-filgrastim (Granix) syringes. The outer carton and peel-away prefilled syringe wrappers list the syringe volume using a decimal point (e.g., 300 mcg per 0.5 mL). However, the barrel of the syringe uses commas for volume increments (e.g., 0,5 mL). The use of a comma rather than a decimal has caused problems in the past. To prevent inadvertent errors from occurring, ISMP has requested further investigation.

May 22, 2014 (Volume 19, Issue 10)

The ISMP reported a dosing error that occurred with nilotinib (Tasigna). A patient was instructed to take once-daily dosing because of previous intolerance to twice-daily dosing. The pharmacy filled the prescription with instructions to take once daily. However, the preprinted dosing instructions on the manufacturer’s blister packaging provide instructions to take the medication every morning and evening. This led to confusion; the patient took nilotinib twice daily instead of once daily. The ISMP has notified the FDA and Novartis about the incident.

The Resident's Cubicle: Research Projects

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The residency year starts each July with a new crop of bright-eyed oncology pharmacy residents and a flurry of activity to prepare for the coming year. Residents often are expected to complete multiple projects throughout their 1-year residency—from medication usage evaluations to administrative projects to their main research project. They usually are expected to hit the ground running with early project selection and institutional review board (IRB) submission, all while getting acclimated to new practitioners, computer systems, and institutional practices. This edition of *The Resident's Cubicle* will focus on tips to help residents with their post-graduate year 2 (PGY-2) research projects.

Residents entering their PGY-2 should be comfortable completing various projects given experiences from their first year of residency; however, they should be ready for the increased expectations and demands of PGY-2. Projects completed in the first year may not have been oncology focused and may have been the resident's first experience with completing a major research project. With the transition to PGY-2, residents should be prepared to complete a high-quality project, which may require broadening their oncology knowledge base. Preceptors may also expect that the project will be completed with more independence and at a higher level than was expected during the previous year. Residents should be prepared to undertake a project that holds potential benefits for their own learning, their institution, and, ideally, oncology pharmacy practice. Although this may seem overwhelming at the beginning of the year, breaking the project down into smaller steps that can be accomplished throughout the year can make it more manageable.

Project Selection

Most residents will be presented with a list of possible project ideas at the beginning of their PGY-2—a result of preceptor brainstorming during the prior year. The number and type of team members (physicians, pathologists, nurses, etc.) involved with the project will vary based on the complexity of the project and subject matter. It is important that all of the key practitioners are involved; having a large research team can be helpful when brainstorming ideas and delegating project tasks. However, a large team also can be challenging because it is difficult to please everyone when ideas differ among team members. An additional challenge for incoming residents at a different institution than in their first year is getting a good feel for the preceptors and practitioners with whom they will be working on each project. Prior residency alumni are a great resource and often are willing to give candid advice about strengths and weaknesses of specific projects or preceptors. It is important to ensure that the resident selects a preceptor with whom they feel comfortable, because the project will require frequent interactions with other project team members and open communication at all times. Ultimately, it is important for all parties to remember that this project is the resident's, and he or she should have the final say in project and research team selection.

Many oncology residents enter their second year of training with a specific area of focus for their residency year and, potentially, their career. However, with the uncertainty of the job market from year to year, it is important that residents' projects are diverse and that they exit the year as well-rounded oncology pharmacy clinicians. If the resident decides to complete a solid tumor medication usage evaluation, he or she may want to consider a research topic that is in another area, such as hematology or stem cell transplant. Ultimately, it is important for the resident to be passionate about the topic he or she chooses. The major research project will require countless hours to complete, and the project quality will likely correlate with the interest level the resident has. In addition, a resident will be most proud of a project that holds meaning for him or her.

Last, when considering project ideas, it is important for the resident to consider the feasibility of project completion within a 1-year time frame. Feasibility is often incorporated into project idea review by residency preceptors prior to the PGY-2 resident's arrival; however, the true feasibility of an individual project will vary based on the caliber of the resident and his or her time management skills. Residents often are ambitious and want to complete meaningful, large-scale projects. Ambition in residents is highly desirable; however, it is very undesirable if the project cannot be completed as planned. Meetings with the entire project team at the beginning of the year can help establish timelines and outline project expectations to ensure the project is completed as planned.

Project Timeline

Establishing a timeline for project milestones—such as IRB submission, completion of data collection, meeting with statisticians, abstract submission to a national meeting, and manuscript preparation—can be extremely helpful for staying on track throughout the year. During the first year of residency, residents often focus on presentation of their project at a regional residency conference. One difference that PGY-2 oncology residents may face is the shortened time frame for project completion if the resident is expected to present his or her project results at the HOPA Annual Meeting in March. Residents should meet with his or her program director and research team early in the year to decide where the project will be presented, and the resident should adjust his or her timeline accordingly.

The research team also should decide early on whether manuscript submission to a peer-reviewed journal is the ultimate goal, and, if so, the target journal should be determined. There may be multiple journals to consider based on what the research project aims to accomplish. Members of the team may already have a target journal in mind; however, if that is not the case, the resident should research journals to determine the most appropriate one based on journal scope and impact factor, design of the research project, and project findings. Selecting the target journal early will be helpful to guide formatting when preparing the manuscript. Even if the project does not end up showing a significant

change or difference, it is still important to consider submitting the manuscript to inform other practitioners and institutions of the findings.

Residents should schedule regular meetings with other project team members throughout the year to ensure adherence to the project timeline. It also may be advisable to keep minutes from each meeting and e-mail them to team members to make sure everyone is on the same page. It is important that IRB submission be completed early in the year because unexpected delays are a common obstacle. Most importantly, any delays the resident encounters during the year should be quickly communicated to the rest of the research team. Residency project mentors are selected to teach research skills and guide the resident through the project. Although more independence may be expected from a PGY-2 resident, mentors can likely help get the project back on track as long as there is open communication at all times and willingness from both parties to stay actively involved.

Take-Home Points

The PGY-2 pharmacy research project should be meaningful and contribute to the advancement of oncology pharmacy practice. When the project has been completed, it is important that these data are presented to the institution's hospital staff. The goal behind completing the project is usually to improve or change a process at the hospital, and disseminating the findings will hopefully contribute to improving patient care. If a change is implemented as a result of the project, that

information could be included in the manuscript so that other institutions can determine whether a similar change would be beneficial. Ultimately, the project may have the potential to make an impact both locally and nationally.

Residents should not lose track of the fact that this project is also a learning experience. Although project outcomes are certainly important, the research skills that can be learned from completing the project, no matter the topic, are at least as valuable. Residents will soon find themselves in the role of preceptor and project mentor to other residents and students. It is imperative that residents take full advantage of the top-notch physicians and experienced pharmacist preceptors with whom they have the opportunity to work and absorb all of the wisdom and knowledge that can be learned throughout the year.

Although it may be overwhelming to consider at the beginning of the year the entirety of the project that needs to be completed, focusing on smaller aspects of the research project timeline can help to restore sanity. The demands of PGY-2 certainly keep residents busy, and the year will fly by. Before residents realize it, they will be presenting the results of their long hours of research to their colleagues and wondering where the year went. I urge current residents to take advantage of meetings attended throughout the year to network with other current and future hematology/oncology pharmacists. Research projects require a lot of hard work, and maybe a sleepless night or two, but aspects of the project can certainly be fun, too!

New Drugs and Drug Updates: Changes in Labeling, Indications, and Dosage Forms

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Purixan® (Mercaptopurine)

In April 2014, the U.S. Food and Drug Administration (FDA) approved an oral suspension formulation of mercaptopurine. Previously, this drug had only been available as a 50-mg tablet; however, many patients have difficulty swallowing tablets. Oral mercaptopurine suspensions, not commercially available at the time, had to be prepared in compounding pharmacies to obtain an accurate dose for a particular patient.

Mercaptopurine is indicated for the treatment of patients with acute lymphoblastic leukemia as part of a combination regimen.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205919s000lbl.pdf

Arzerra® (Ofatumumab)

In April 2014, the FDA approved a new indication for Arzerra®. The drug had previously been approved for the treatment of refractory chronic lymphocytic leukemia (CLL). The new indication calls for the use of Arzerra®, in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate. The approval was based on the

results of a multicenter, randomized, open-label trial comparing ofatumumab in combination with chlorambucil to single-agent chlorambucil. Median progression-free survival was 22.4 months (95% confidence interval [CI]: 19.0–25.2 months) for patients receiving ofatumumab in combination with chlorambucil versus 13.1 months (95% CI: 10.6–13.8 months) for patients receiving single-agent chlorambucil (hazard ratio = 0.57; 95% CI: 0.45–0.72; stratified log-rank $p < .001$). Additional post-marketing requirements were also added for the drug.

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125326Orig1s060ltr.pdf

Gleostine® (Lomustine)

In May 2014, the FDA approved a request to modify the package insert to include a new proprietary name, Gleostine®. In addition, some editorial changes were made in the “How Supplied, Stability” section of the package insert.

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/017588Orig1s040ltr.pdf

Vectibix® (Panitumumab)

In May 2014, the FDA granted Amgen's request for a new indication to be added to the package insert of Vectibix®. It is now indicated as monotherapy for the treatment of patients with wild-type KRAS (exon 2 in codons 12 or 13) metastatic colorectal cancer, as determined by an FDA-approved test for this use, following disease progression on fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. It had previously only been approved for use in combination with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) as first-line treatment.

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125147Orig1s186ltr.pdf

Alvocidib

In April 2014, the FDA granted orphan drug designation to alvocidib for the treatment of acute myeloid leukemia (AML). Alvocidib is a potent cyclin-dependent kinase small-molecule inhibitor and is being tested in patients with either intermediate- or high-grade AML. There are relatively few treatment options for this subset of patients, causing poor prognosis in those with intermediate- or high-grade AML.

<http://genericbusiness.net/04/23/14/alvocidib-gets-orphan-status-fda-acute-myeloid-leukemia#.U9v1G-NdVGM>

Custirsen

In April 2014, OncoGenex Pharmaceuticals' investigation of custirsen (OGX-011) received Fast Track designation by the FDA when used in combination with cabazitaxel and prednisone for the treatment of men with metastatic castration-resistant prostate cancer (CRPC) following prior treatment with a docetaxel-containing regimen. The international, randomized, open-label phase 3 AFFINITY trial is designed to evaluate whether custirsen, when combined with second-line chemotherapy cabazitaxel and prednisone, has the potential to improve survival outcomes for prostate cancer patients compared with second-line chemotherapy alone.

Custirsen has also received Fast Track designation from the FDA for the treatment of patients with metastatic non-small cell lung cancer as part of the phase 3 ENSPIRIT trial and for men with metastatic CRPC as part of the phase 3 SYNERGY trial.

<http://www.oncogenex.com/physicians/custirsen-ogx-011>

KRN5500

In June 2014, the FDA granted orphan drug status to an experimental compound currently being studied as a potential treatment for multiple myeloma. Dara BioScience's KRN5500 had received orphan drug designation earlier in the year for the treatment of chemotherapy-induced neuropathic pain refractory to conventional analgesics in patients with cancer. This agent appears to impair myeloma cells and osteoclasts, which are responsible for the dissolution and absorption of bone.

<http://multiplemyelomablog.com/2014/06/fda-grants-orphan-drug-designation-for-krn5500.html>

Sylvant™ (Siltuximab)

In April 2014, the FDA approved siltuximab for the treatment of patients with multicentric Castleman's disease who are human immunodeficiency virus (HIV) negative and human herpes virus-8 negative.

For more information, see "Drug Update—Siltuximab" on page 20.

<http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm394522.htm>

Zykadia (Ceritinib)

In April 2014, the FDA granted accelerated approval of ceritinib for the treatment of patients with anaplastic lymphoma kinase-positive, metastatic non-small cell lung cancer with disease progression on, or who are otherwise intolerant to, crizotinib.

For more information, see "Drug Update—Ceritinib" on page 15.

<http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm395386.htm>

Cyramza (Ramucirumab)

In April 2014, the FDA approved Cyramza for the treatment of patients with advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

For more information, see "Drug Update—Ramucirumab" on page 17.

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394107.htm>

Ceritinib (Zykadia™)

Class: Tyrosine kinase inhibitor; anaplastic lymphoma kinase (ALK) inhibitor

Indication: Treatment of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or who are intolerant to crizotinib

Dose: 750 mg orally once daily on an empty stomach

Dose modifications: Interrupt therapy for the following toxicities: alanine aminotransferase (ALT) or aspartate transaminase (AST) elevation > 5 times upper limits of normal (ULN) with total bilirubin elevation < 2 times ULN; severe or intolerable nausea, vomiting, or diarrhea; persistent hyperglycemia \geq 250 mg/dL; or QTc interval > 500 msec on at least two separate electrocardiograms. Therapy may be resumed with a 150-mg dose reduction as follows: upon the return of liver function tests to baseline, or to no higher than three times the ULN; improvement of nausea, vomiting, or diarrhea; adequate control of hyperglycemia; or recovery of QTc interval to < 481 msec. Therapy should be permanently discontinued for ALT or AST elevation > 3 times ULN with total bilirubin elevation > 2 times ULN in the absence of cholestasis or hemolysis. Therapy should be permanently discontinued for treatment-related interstitial lung disease (ILD) or pneumonitis of any grade; QTc interval prolongation in combination with Torsade de pointes, polymorphic ventricular tachycardia, or a serious arrhythmia; or if severe or life-threatening bradycardia occurs in the absence of a contributing concurrent medication.

Common adverse effects: Diarrhea, nausea, vomiting, abdominal pain, constipation, fatigue, anorexia, and decreased hemoglobin

Serious adverse effects: Increased risk of hepatotoxicity, pneumonitis, QTc interval prolongation, and hyperglycemia

Drug interactions: Substrate of CYP3A4 and P-glycoprotein, inhibitor of CYP3A4 and CYP2C9; avoid concurrent use with strong CYP3A inhibitors and inducers, substrates of CYP2C9, medications known to prolong the QTc interval or cause bradycardia, and grapefruit or grapefruit juice

Ceritinib for ALK-Positive Metastatic Non-Small Cell Lung Cancer

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The treatment of non-small cell lung cancer (NSCLC) has had several breakthroughs in recent years. Genetic alteration of the anaplastic lymphoma kinase (ALK) gene was found to cause expression of a potent oncogenic driver, echinoderm microtubule-associated

protein-like 4-anaplastic lymphoma kinase (EML4-ALK).¹ ALK rearrangement has been implicated as the cause of approximately 5% of NSCLC cases. In the United States, this represents more than 10,000 patients annually² who tend to have a unique set of clinical features such as young age at onset, absence of smoking history, and adenocarcinoma histology. The tyrosine kinase inhibitor crizotinib (Xalkori®) was the first drug in its class approved to treat this unique subset of patients. Unfortunately, the majority of patients with an initial response to crizotinib develop resistance, with a median duration of clinical benefit of 10 months.³ This short-lived benefit led to the search for new ALK inhibitors that could overcome the intrinsic or acquired resistance to crizotinib.

Ceritinib (Zykadia™, Novartis) is an oral, small-molecule, adenosine triphosphate-competitive tyrosine kinase inhibitor of ALK. In contrast to crizotinib, ceritinib inhibits the insulin-like growth factor 1 (IGF-1) receptor and ROS1, but it does not inhibit the kinase activity of MET. The differences in receptor targets lead to slightly different adverse effect profiles. In addition, enzymatic assays have demonstrated a potency of ceritinib that is 20 times greater than crizotinib against ALK. These differences suggest that ceritinib may be active in patients who have progressed on crizotinib and in those who are crizotinib naïve. Ceritinib was granted breakthrough therapy designation by the U.S. Food and Drug Administration (FDA) on March 6, 2013, and gained accelerated approval on April 29, 2014.⁴

Accelerated approval of ceritinib was based on the results of a multicenter, single-arm clinical trial of 246 patients with metastatic, ALK-positive NSCLC, of which 163 patients had progressed on or were intolerant to crizotinib and 66 patients were crizotinib naïve.¹ Shaw and colleagues conducted this phase 1 study in two parts: a dose-escalation phase followed by an expansion phase. In the dose-escalation phase, patients received a single dose of ceritinib, followed by a 3-day pharmacokinetic evaluation period, and then patients continued with daily oral dosing for the remainder of a 21-day cycle. The starting dose was 50 mg daily, and determination of the maximum tolerated dose (MTD) was based on 54 patients per protocol who were evaluated for dose escalation. The MTD was determined to be 750 mg daily and became the starting dose for all patients in the expansion phase.

Among the 114 patients with NSCLC who received ceritinib > 400 mg per day, the response rate was 58%. Complete response was observed in 1 patient (1%), a partial response was achieved in 65 patients (57%), and disease stability was seen in 25 patients (22%). Median progression-free survival was 7 months (95% confidence interval [CI]: 5.6–9.5), with a median duration of response of 8.2 months (95% CI: 6.9–11.4) in patients who experienced a complete or partial response. A slightly higher response rate (62%) and median progression-free survival of 10.4 months was noted in the 34 patients who had not received previous crizotinib therapy. Similar response rates were seen in the subgroup of 78 patients who received ceritinib 750 mg daily.

The most common adverse events of any grade were nausea (82%), diarrhea (75%), vomiting (65%), elevated glucose levels (49%), fatigue (47%), and increased alanine aminotransferase (ALT) levels (35%).⁵

The most common grade 3 or 4 adverse events were increased ALT levels (21%), elevated glucose levels (13%), increased aspartate aminotransferase (AST) levels (11%), diarrhea (7%), and increased lipase levels (7%). All adverse events were reversible on discontinuation of treatment.

Hyperglycemia can occur in any patient taking ceritinib, with a 6-fold increase in risk of grade 3-4 hyperglycemia in patients with diabetes or glucose intolerance. Initiation or optimization of antihyperglycemic medications provides adequate glucose control in most patients. Four cases of interstitial lung disease (ILD) and one case of asymptomatic grade 3 QTc prolongation were reported; all resolved with the discontinuation of therapy and administration of standard treatments. Dose reduction was required in 66 of 130 patients (51%), with a median duration of treatment interruption of 7.3 days. Ceritinib was permanently discontinued secondary to an adverse event in eight patients (6%); no treatment-related deaths occurred.

Ceritinib is categorized as pregnancy category D. Animal studies have demonstrated increases in skeletal anomalies at maternal plasma exposures below the recommended human dose of 750 mg daily. Females of reproductive age should be advised to use effective contraception during treatment and for at least 2 weeks following completion of therapy.

Ceritinib is a substrate of CYP3A and should not be administered with strong inhibitors or inducers of this enzyme. Solubility is pH dependent, and bioavailability may be reduced if given concomitantly with gastric acid-reducing agents. No studies have been conducted to evaluate the effect of gastric acid reducers on bioavailability. Systemic exposure of ceritinib is increased when administered with food. A food effect study conducted in healthy subjects demonstrated increased ceritinib area under the curve (AUC) and C_{max} with both low- and high-fat meals when compared with fasting state. It is recommended that the drug be administered on an empty stomach (i.e., do not administer within 2 hours of a meal). Ceritinib is supplied in 150-mg capsules and should be administered once daily. Missed doses can be

made up unless the next dose is due within 12 hours. No data are currently available regarding extemporaneous preparations of ceritinib.

The success of the phase 1 study has provided evidence to support the approval of this important new drug. Ceritinib is currently being investigated in two phase 3 trials. One is a comparison of ceritinib to standard chemotherapy (pemetrexed with either cisplatin or carboplatin) in first-line treatment of stage IIIB or IV NSCLC, and the second is a comparison of ceritinib to either docetaxel or pemetrexed in patients who have previously been treated with chemotherapy and crizotinib. The early approval provides access to an important and much needed new drug for crizotinib-resistant NSCLC but also demands confirmatory trials of the clinical activity and relative safety of ceritinib.

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Ramucirumab (Cyramza™)

Class: Vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist

Indication: Advanced gastric cancer or gastroesophageal junction adenocarcinoma, as a single agent after prior fluoropyrimidine- or platinum-containing chemotherapy

Dose: 8 mg/kg intravenous infusion over 60 minutes every 2 weeks

Dose modifications: Has not been studied in patients with renal or hepatic impairment. Dose reductions and treatment interruptions may be necessary in the presence of infusion-related reactions, severe hypertension, or proteinuria (urine protein levels ≥ 2 g/24 hours). Therapy must be withheld prior to surgery and resumed once the surgical wound is fully healed. Treatment should be permanently discontinued in the presence of nephrotic syndrome, arterial thrombotic events, grade 3 or 4 bleeding, gastrointestinal perforation, or reversible posterior leukoencephalopathy syndrome (RPLS).

Common adverse effects: Hypertension, diarrhea, decreased red blood cells requiring transfusion, and infusion-related reactions

Serious adverse effects: Hemorrhage, arterial thromboembolic events, gastrointestinal perforation, impaired wound healing, and RPLS

Drug interactions: Ramucirumab may enhance the adverse, toxic effects of belimumab. It may also increase the risk for osteonecrosis of the jaw if used in combination with bisphosphonate derivatives.

Ramucirumab for Advanced Gastric Cancer or Gastroesophageal Junction Adenocarcinoma

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Although the incidence of gastric cancer has been declining since World War II, it is still a major problem for many countries around the world, including China and Japan.¹ In the United States, it is estimated that more than 22,000 people will be diagnosed with gastric cancer and nearly 11,000 people will die of this disease in 2014.² It is often diagnosed at an advanced stage, posing a major challenge for health-care professionals. Environmental risk factors include *Helicobacter pylori* (*H. pylori*) infection, smoking, heavy alcohol drinking, high salt intake, and other dietary factors. Treatment for patients with locally advanced or metastatic gastric cancer usually involves combination chemotherapy, which can provide palliation and improved survival and quality of life. First-line therapy with two-drug chemotherapy regimens (e.g., fluoropyrimidine plus platinum) is usually preferred because single-agent chemotherapy has shown little, if any, impact on

overall survival. Three-drug regimens should be reserved for medically fit patients with good performance status.¹

With the exception of trastuzumab, targeted therapies have not been a mainstay of therapy. Bang and colleagues assessed the efficacy of trastuzumab in patients with human epidermal growth factor receptor-2 (HER2)-positive tumors in a randomized, controlled, phase 3 trial, ToGA.³ Trastuzumab showed a 2.7-month improvement in overall survival (OS) compared with placebo. Unfortunately, less than 20% of patients in Western countries demonstrate enough HER2 positivity to warrant treatment with this agent, leaving most patients with few second-line options.¹ Vascular endothelial growth factor (VEGF)- and vascular endothelial growth factor receptor-2 (VEGFR-2)-mediated signaling have been shown to have an important role in the pathogenesis of gastric cancer.^{4,5} Studies have shown that patients with circulating and tumoral concentrations of VEGF demonstrate increased tumor aggressiveness and reduced survival.⁵ Several trials have looked at the addition of bevacizumab, an IgG1 humanized monoclonal antibody which binds to and neutralizes VEGF, to standard chemotherapy regimens used in gastric cancer.⁶⁻⁸ The largest of these trials showed no difference in OS and only a 1.4-month benefit in progression-free survival (PFS) compared with chemotherapy alone.⁸ Other targeted therapies, including erlotinib, cetuximab, and sorafenib, also have failed to demonstrate the desired clinical benefit.⁹⁻¹⁵

Ramucirumab is a fully human IgG1 monoclonal antibody VEGFR-2-antagonist that prevents ligand binding and receptor-mediated pathway activation in endothelial cells.^{16,17} On April 21, 2014, the U.S. Food and Drug Administration (FDA) approved ramucirumab (Cyramza™) for use as a single agent for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose disease had progressed during or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy.¹⁸ The approval was based on the results of the REGARD trial.⁵ In this randomized, placebo-controlled, phase 3 trial, Fuchs and colleagues assessed the safety and efficacy of ramucirumab in 355 patients with advanced gastric or gastroesophageal junction adenocarcinoma who had progressed after first-line chemotherapy. Patients aged 24 to 87 years with metastatic or unresectable, locally recurrent gastric or gastroesophageal junction adenocarcinoma and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 were eligible for inclusion. Patients also had to have disease progression within 4 months of the last dose of first-line platinum- or fluoropyrimidine-containing chemotherapy for metastatic disease or within 6 months of the last dose of platinum- or fluoropyrimidine-containing adjuvant treatment. Exclusion criteria included poorly controlled hypertension, grade 3 or higher gastrointestinal (GI) bleeding within 3 months before randomization, or any arterial thromboembolic event within 6 months before randomization. Eligible patients were randomly assigned to best supportive care plus either ramucirumab (8 mg/kg intravenously once every 2 weeks) or placebo.

The study's primary end point was OS. Secondary endpoints included PFS, objective response rate (ORR), duration of response, quality of life, safety, and ramucirumab immunogenicity. OS was significantly improved in patients treated with ramucirumab compared with placebo. Patients in the ramucirumab group had a median OS of 5.2 months (interquartile range [IQR] 2.3–9.9) compared with 3.8 months (IQR 1.7–7.1) in patients in the placebo group (hazard ratio [HR] = 0.776; 95% confidence interval [CI]: 0.603–0.998, $p = .047$). Median PFS also increased in patients treated with ramucirumab compared with placebo (2.1 months versus 1.3 months). Although disease control was significantly higher in patients treated with ramucirumab when compared with placebo, the difference in ORR was not statistically significant. Patients treated with ramucirumab experienced more grade 3 hypertension and thromboembolic events.⁵

Wilke and colleagues conducted a phase 3, randomized, double-blinded study, RAINBOW, of ramucirumab in combination with paclitaxel in a similar population of patients.¹⁹ Eligible patients received paclitaxel (80 mg/m² on days 1, 8, and 15 of a 4-week cycle) plus either ramucirumab (8 mg/kg intravenously every 2 weeks) or placebo. The primary endpoint was OS. Secondary endpoints included PFS, ORR, time to progression (TTP), and safety. Preliminary results presented at the 2014 Gastrointestinal Cancers Symposium demonstrated that patients in the paclitaxel plus ramucirumab group had a statistically significant improvement in OS of >2 months compared with paclitaxel alone. Median PFS (4.4 versus 2.9; $p < .0001$) and ORR were also significantly improved in the combination arm. More neutropenia was seen in the combination arm, although the incidence of febrile neutropenia was similar between groups.

Although ramucirumab was approved by the FDA as single-agent therapy, current treatment guidelines from the National Comprehensive Cancer Network (NCCN) indicate a preference for the use of ramucirumab in combination with paclitaxel due to the more clinically meaningful improvement in OS seen in the RAINBOW trial as compared with REGARD.^{1,5,19}

Additional adverse events include diarrhea, decreased red blood cells requiring transfusion, and infusion-related reactions. Less common adverse effects include headache, skin rash, hyponatremia, intestinal obstruction, proteinuria, neutropenia, anemia, antibody development, and epistaxis. Rare, but significant, adverse reactions include gastrointestinal perforation, hemorrhage, and reversible posterior leukoencephalopathy syndrome.¹⁷⁻¹⁸

Ramucirumab has not been studied in patients with renal or hepatic impairment. The infusion rate should be reduced by 50% in patients experiencing grade 1 or 2 infusion-related reactions. It should be permanently discontinued in patients experiencing grade 3 or 4 infusion-related reactions. Blood pressure should be monitored every 2 weeks or as clinically warranted. Treatment interruption is necessary in patients with severe hypertension until controlled with medical management. Ramucirumab should be permanently discontinued in patients with severe hypertension that cannot be controlled with antihypertensive therapy. Treatment interruption is necessary in patients with

urine protein levels ≥ 2 g/24 hours. Treatment may be reinitiated at a reduced dose of 6 mg/kg every 2 weeks once the urine protein level returns to < 2 g/24 hours. If the protein level ≥ 2 g/24 hours recurs, therapy should be interrupted until urine protein level returns to < 2 g/24 hours. Therapy may be reinitiated at a reduced dose of 5 mg/kg every 2 weeks. For urine protein levels > 3 g/24 hours or in the setting of nephrotic syndrome, ramucirumab should be permanently discontinued. Therapy must be withheld prior to surgery and resumed once the surgical wound is fully healed. Ramucirumab should be permanently discontinued in the setting of arterial thrombotic events, grade 3 or 4 bleeding, gastrointestinal perforation, and reversible posterior leukoencephalopathy syndrome (RPLS).¹⁷⁻¹⁸

Ramucirumab is supplied as an IV solution in 100-mg/10 mL and 500-mg/50 mL vials. All patients should be premedicated with an IV H₁ antagonist prior to infusion. Patients who experience a grade 1 or 2 infusion reaction should also receive dexamethasone (or equivalent) and acetaminophen. Ramucirumab is administered as an IV infusion over 60 minutes. Use of a 0.22-micron protein-sparing filter is recommended. Patients should be counseled on possible side effects, including the risk of infusion-related reactions, hypertension, and diarrhea.¹⁷⁻¹⁸

Monoclonal antibodies, such as ramucirumab, may enhance the toxic effects of belimumab. As an angiogenesis inhibitor, ramucirumab may also enhance the toxic effects of bisphosphonate derivatives. The risk of osteonecrosis of the jaw may increase in patients on this combination.¹⁷⁻¹⁸ For patients receiving the 8-mg/kg dose, the mean half-life is increased from 123 hours with the first infusion to 328 hours following the last infusion.¹⁷⁻¹⁸

Based on the results of the REGARD and RAINBOW trials, current NCCN treatment guidelines now list ramucirumab alone or in combination with paclitaxel as a category 1 recommendation for treatment of patients with advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma who have progressed following fluoropyrimidine- or platinum-containing chemotherapy.¹

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Siltuximab (Sylvant™)

Indication: Treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpes virus 8 (HHV-8) negative

Dose: 11 mg/kg intravenously over 1 hour once every 3 weeks until treatment failure

Dose modifications: No recommended dosing reductions; however, delaying therapy should be considered for severe infections and/or abnormal hematologic counts as outlined in the package insert. Siltuximab has not been studied in patients with creatinine clearance \leq 15 mL/min or in those with severe hepatic impairment.

Common adverse effects: Rash, pruritus, upper respiratory infection, edema, weight gain, hyperuricemia, and abdominal pain

Serious adverse effects: Severe infection, infusion-related reactions and hypersensitivity, and gastrointestinal perforation

Drug interactions: No in vitro or in vivo drug-drug interaction studies have been performed; however, caution should be used with coadministration of CYP450 substrates.

Siltuximab: First Approved Treatment of Multicentric Castleman's Disease

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Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder that was first described in the 1950s.¹ MCD prevalence and incidence is unknown; however, a recent U. S. analysis estimates that approximately 1,100–1,300 Americans have MCD.² MCD has been strongly associated with immunosuppression and viral infections, including human immunodeficiency virus (HIV) and human herpes virus 8 (HHV-8). The pathogenesis has been poorly understood, but an overproduction of interleukin-6 (IL-6) plays a central role in this disorder. Increased IL-6 levels cause enlargement of the lymph nodes, growth of B lymphocytes and plasma cells, secretion of vascular endothelial growth factor (VEGF), and autoimmune phenomena.³ MCD has been associated with the development of malignancies such as Kaposi's sarcoma and lymphomas.⁴ Roughly two-thirds of patients survive for more than 5 years after diagnosis. The most common causes of mortality in patients with MCD are infection, multiorgan failure, and secondary malignancies.³ Because MCD shares many characteristics with lymphoma and is often associated with its development, MCD treatment is similar to that of lymphoma. Surgery, radiation, traditional chemotherapy, and targeted therapy with monoclonal antibodies have been the mainstays of therapy for MCD; however, there is no standard of care.³

Siltuximab was approved by the U.S. Food and Drug Administration (FDA) on April 23, 2014, for the treatment of patients with MCD.

Siltuximab is a human-mouse chimeric immunoglobulin G1 κ monoclonal antibody that binds human IL-6, preventing IL-6 from binding to both soluble and membrane-bound IL-6 receptors. In a nonclinical study, siltuximab did not bind to viral IL-6; thus, siltuximab was not studied in patients with HIV or HHV-8 and is not indicated for use in this patient population.⁵

Siltuximab gained approval by the FDA based on the results of the MCD2001 study. MCD2001 was a multinational, randomized, double-blinded, placebo-controlled phase 2 study. Seventy-nine patients with newly diagnosed or previously treated MCD were randomized (2:1) to either receive siltuximab at 11 mg/kg intravenously once every 3 weeks plus best supportive care (BSC; $n = 53$) or placebo plus BSC ($n = 26$); treatment in both arms continued until treatment failure. Randomization was stratified by concomitant corticosteroid use at study entry. The primary outcome was durable tumor and symptomatic response, defined as a complete or partial response by modified Cheson criteria, with improvement or stabilization of disease-related symptoms for at least 18 weeks. The primary outcome was met; siltuximab plus BSC was superior to placebo plus BSC in durable tumor and symptomatic response rate (34% versus 0%, $p = .012$). In addition, siltuximab treatment demonstrated significant benefit in the secondary end points of tumor response (38% versus 4%; $p = .0022$), time to treatment failure (not reached versus 134 days; $p = .0084$), and hemoglobin response (61% versus 0%; $p = .0002$) compared with placebo. Fifty percent of patients in the placebo arm crossed over into the siltuximab arm after treatment failure.⁶

The incidence of adverse reactions was similar in the two treatment arms. The most common adverse reactions ($\geq 10\%$) reported more frequently in the siltuximab arm than in the placebo arm were pruritus (42%), maculopapular rash (34%), weight gain (21%), upper respiratory tract infection (36%), localized edema (21%), abdominal pain (15%), thrombocytopenia (15%), nasopharyngitis (15%), and hyperuricemia (13%). Grade 3 or higher adverse reactions ($\geq 5\%$) that occurred more frequently in the siltuximab arm included fatigue (9%) and night sweats (8%).⁶ In another study of the long-term safety of siltuximab therapy, the most common adverse reactions ($\geq 20\%$) were upper respiratory tract infection (63%), diarrhea (32%), pain in extremities (21%), arthralgia (21%), and fatigue (21%).⁵

Warnings and precautions for siltuximab include active severe infections, administration of live vaccines, infusion-related reactions, hypersensitivity, and gastrointestinal perforations. Live vaccines should not be given to patients receiving siltuximab because inhibition of IL-6 may interfere with the immune system's response to new antigens. Although not demonstrated in MCD trials, clinicians should exercise caution because gastrointestinal perforations have been reported in other clinical trials.⁵

Siltuximab does not require dose modifications; however, doses should be delayed if the hematologic parameters listed in the package insert are not met or in the presence of an active, severe infection. Siltuximab should be discontinued if the patient has a severe

infusion-related reaction, if he or she experiences anaphylaxis or a severe allergic reaction, or if cytokine release syndrome is suspected. There are no dose-adjustment recommendations for patients with severe renal dysfunction (creatinine clearance < 15 mL/min) or severe hepatic dysfunction (Child-Pugh Class C) because these patient populations were excluded from the clinical trial.⁵ There have been no drug interaction studies conducted; however, because cytokines such as IL-6 down regulate cytochrome P450 enzymes in the liver, the administration of siltuximab may conversely lead to increased CYP450 activity, which would theoretically affect drugs metabolized by these enzymes. Caution should be exercised when initiating or discontinuing siltuximab or any other CYP450 substrate, especially one with a narrow therapeutic window; patients should be monitored for toxicity, decreased effect, and drug concentrations to properly consider dose adjustments if necessary.⁵

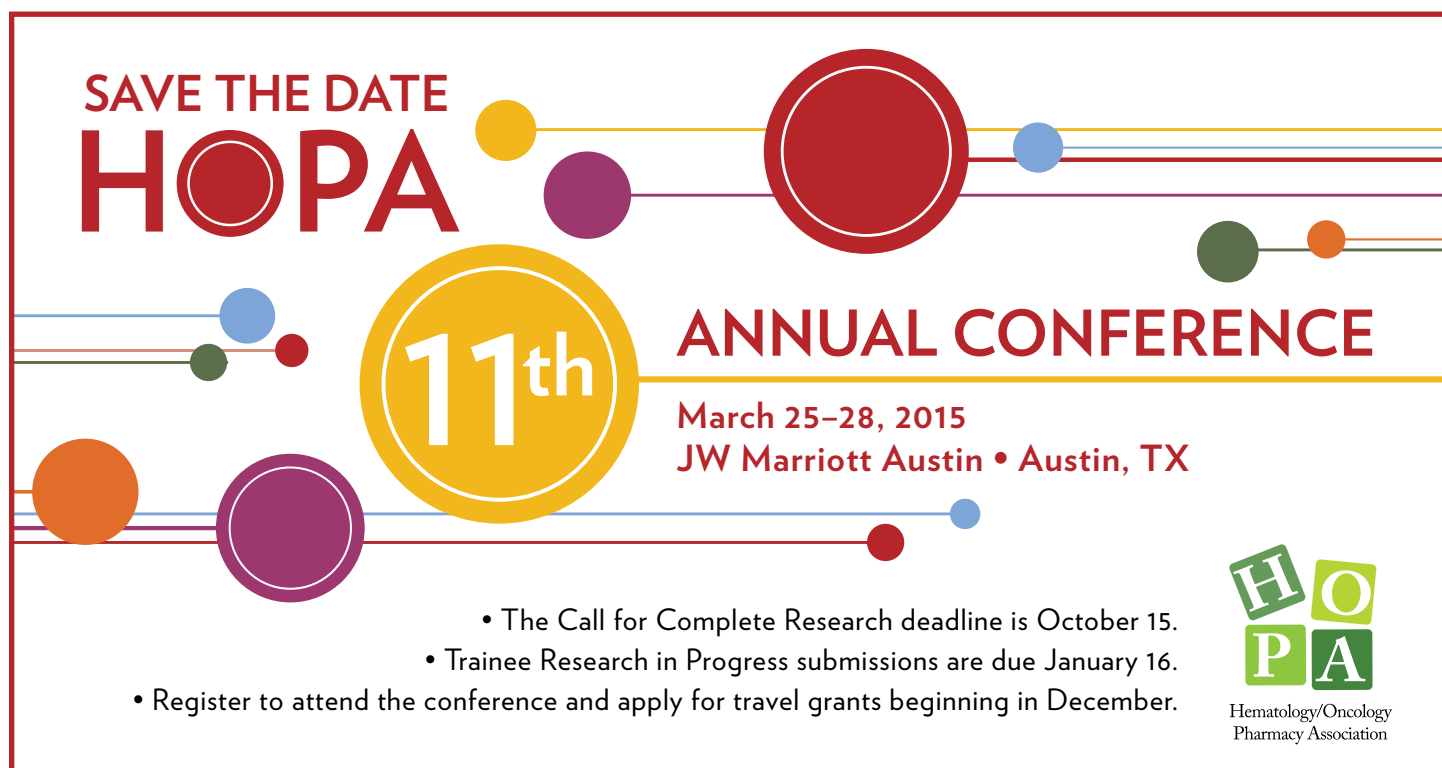
The pharmacokinetic profile of siltuximab was studied in nonhematologic and hematologic malignancies and is described by a linear, two-compartment model with first-order elimination. The maximum serum concentration of siltuximab was reached at the end of the 1-hour infusion. Steady state is achieved by the sixth infusion on an every-3-week infusion schedule. The mean terminal half-life range for siltuximab is 14.2 to 29.7 days. Siltuximab should be administered diluted in dextrose 5% (it is incompatible with normal saline) and administered through a 0.2-micron inline polyethersulfone (PES) filter. The prepared solution should be administered and completed within 4 hours of preparation.⁵

Siltuximab is the only FDA-approved medication for the treatment of MCD. It is an IV infusion that generally is well tolerated. It has

demonstrated benefit in durable tumor and symptomatic response for patients with MCD. According to the clinicaltrials.gov website, siltuximab is currently being studied in the treatment of multiple myeloma, solid tumors (e.g., ovarian, pancreatic, prostate, lung, head and neck, and colorectal), and kidney tumors. Siltuximab could be a potential treatment option for a number of different malignancies.

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