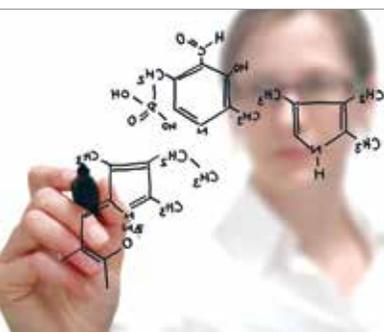




Immunotherapy for Cancer Named Advance of the Year by ASCO

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Immunotherapy has been a cancer treatment strategy since the late 19th century, though not widely implemented into practice until today. In 1891, New York surgeon William Coley injected bacteria into a patient's tumors in an attempt to elicit an immune response targeting the infection as well as the tumor.¹ Several methods to harness the immune system to attack cancer cells have been investigated over the decades, including stimulating the actions of specific components within the immune system or thwarting signals made by cancer cells to suppress the immune response.² Unfortunately using the body's own immune system to target cancer cells is not an easy feat to master. Cancer cells may evade the immune system by concealing themselves to make it difficult for T cells to identify them, or by expressing proteins that suppress T cells in the surrounding environment.



Numerous immunotherapy treatment methods have been researched and refined leading to U.S. Food and Drug Administration (FDA) approved treatment options. Immune checkpoint modulators are agents that modulate certain proteins to limit the strength and duration of the immune response.² By blocking these proteins, the immune system is no longer in check and can fully attack and destroy cancer cells. Ipilimumab was the first medication approved that inhibits the checkpoint CTLA4. Nivolumab and pembrolizumab are the most recently approved agents that act on a different checkpoint, PD-1.

Adoptive cell transfer (ACT) is another exciting area of immunotherapy research. One form of this treatment collects tumor-infiltrating lymphocytes (TIL) from a patient's tumor, manipulates and grows them in the lab with cytokines, and infuses them back into the patient.² The theory behind this approach is that the TILs have the ability to target the tumor cell, but may not be enough to kill the tumor or overcome the immune system

Contents

The New Oncology Pharmacy Updates Course	3	Drug Update: Elotuzumab	17
HOPA 12th Annual Conference Goes Beyond Expectations.....	4	Drug Update: Ixazomib.....	20
Board Update	6	Drug Update: Marizomib.....	22
Recalls and Safety Alerts from the FDA	10	Drug Update: Necitumumab	24
New Drugs and Drug Updates.....	13	Drug Update: Osimertinib.....	26
Drug Update: Alectinib.....	13	Drug Update: Uridine Triacetate	28
Drug Update: Daratumumab	14		



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inhibiting their activity. Administering a large amount of these cells can overcome obstacles to shrink or kill the cancer. Another approach utilizing ACT is chimeric antigen receptor (CAR) T cell therapy, which takes a patient's own T cells and modifies them in a lab to express a protein, or CAR. These altered T cells are multiplied and then infused into the patient to attach to proteins on the surface of the cancer cell. Once the cells are bound together, the engineered T cell is activated and kills the cancer cell.

Several therapeutic antibodies have been in practice for decades, but modifications have recently been introduced. Antibodies are designed to attack specific antigens found on cancer cells and other noncancer cells and proteins in order to kill cancer cells.³ Naked monoclonal antibodies (mAb) are most commonly used and work on their own. They induce apoptosis, antibody-dependent cell-mediated cytotoxicity, and complement-dependent cytotoxicity.² Conjugated monoclonal antibodies are mAbs that are joined to a chemotherapy agent or radioactive particle to deliver the toxic substance directly to the cancer cell.³ The newest kind of mAb is the bispecific monoclonal antibody, which combines two different mAbs allowing the drug to bind to two different proteins at the same time. Blinatumomab is an approved agent that binds to both CD19 and CD3.

Therapeutic cancer vaccines also have been an area of research for decades. The first approved therapeutic vaccine was sipuleucel-T.³ To engineer this vaccine, cells are taken from the patient and treated prior to being reinfused and helping the immune system attack the cancer. Many different types of cancer vaccines (tumor cell vaccines, antigen vaccines, dendritic cell vaccines, vector-based vaccines) are currently being investigated in a variety of malignancies including brain, breast, and lung cancer. It is an exciting area of development.

The American Society of Clinical Oncology (ASCO) has named cancer immunotherapy the advance of the year due to the number of improvements made to the immunomodulatory process and the clinical implementation of immunotherapy strategies into multiple disease states.³ Research is expanding the number of patients who may benefit from these strategies and developing ways to minimize adverse effects to improve tolerability. 

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The New Oncology Pharmacy Updates Course

Christy Harris, PharmD BCOP BCPS
Associate Professor of Pharmacy Practice
MCPHS University
Boston, MA

An exciting new program is coming this summer, the Oncology Pharmacy Updates Course. This annual 2-day conference will be directed toward the advanced board certified hematology/oncology pharmacy (BCOP) practitioner. We know that our membership is very diverse and we hope that this program will fill a gap that has not yet been addressed by any other BCOP recertification program.

The Oncology Pharmacy Updates Course is not designed as an introduction to the content, nor is it intended to replace a board certification preparatory review course. Each session will be literature-focused, discussing studies and results that have been published or are ongoing. This course will ensure that all core topics and domains are covered, as specified by the Board of Pharmacy Specialties and the Oncology Pharmacy Specialty Council. The course curriculum will be

changed and content updated yearly with all core topics covered in a 3-year cycle. The course will provide 10 BCOP continuing education (CE) and professional development hours per year.

This year there are some great topics that will be presented, including a less commonly covered disease, soft tissue sarcomas, which have had a remarkable year with one new drug approval and one added indication in the past 12 months. Other sessions will break down the new data and discuss the sequence of therapies or special circumstances in malignancies such as prostate cancer and melanoma. The speakers are knowledgeable veterans in practice and we look forward to hearing about the new literature and current developments and learning how to incorporate this new information into practice. 



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Oncology Pharmacy Updates Course

HOPA 12th Annual Conference Goes Beyond Expectations

Everything was sweet in “The Big Peach” during the 12th HOPA Annual Conference! A record-setting 1,040 registrants gathered in Atlanta this past March for cutting-edge education and valuable networking. Hematology/oncology pharmacists from across the nation gathered to explore current information about new and emerging therapies for hematology/oncology patients and review recent developments in medical literature. The nation’s leading experts shared their knowledge in more than 45 educational sessions over 3.5 days. Conference attendees also took advantage of Atlanta’s beautiful weather and exciting tourist attractions.

Pulitzer Prize winner Siddhartha Mukherjee, MD PhD, delivered the John G. Kuhn Keynote Lecture. His address analyzed the role of the pharmacist in the changing landscape of cancer care. For a donation to the HOPA Research Fund, a small group of individuals had the opportunity to meet and talk with Dr. Mukherjee after the event and obtain a signed copy of his Pulitzer Prize-winning book, *The Emperor of All Maladies: A Biography of Cancer*.

As part of the all-new HOPA BCOP Recertification Program, HOPA offered eight specialty sessions for a total of eight (8) hours of BCOP recertification credit. Topics included haploidentical stem cell transplant, triple negative breast cancer, medical marijuana, and more. In case you missed these valuable sessions, they will be repeated live in Chicago on September 22 and will be available online later this year.

HOPA offered several preconference events, allowing attendees to maximize their time in Atlanta. This included a tour of the Phase 1 Clinical Trials Unit at the nearby Winship Cancer Institute of Emory University. Also new this year, attendees received complimentary professional headshots at the attendee lounge. The Attendee Lounge was the meeting place for the Big Idea project. HOPA Board Members were available to answer questions about the new Big Idea project to help HOPA achieve its strategic plan.



Dr. Siddhartha Mukherjee delivers the John G. Kuhn Keynote Lecture.



The Attendee Lounge provided a great place for networking.

In addition to the eight BCOP specialty sessions and 10 breakout sessions, HOPA was pleased to offer a breadth of general session topics delivered by industry experts throughout the conference. A few of the speaker highlights were:

Significant Papers in Hematology/Oncology

Chris Fausel, PharmD MHA BCOP; Susan Goodin, PharmD BCOP FASHP FCCP

Practice Panel: The Cost of Cancer Care

Timothy Tyler, PharmD; Michael Kolodziej, MD; Ed Li, PharmD MPH BCOP; Thomas Smith, MD FAAHPM FACP FASCO

Management of Acute Lymphoblastic Leukemia in the Elderly

Cindy Ippoliti, PharmD

State of the Art in Oncology Pharmacy Research

Susan Goodin, PharmD BCOP FASHP FCCP; Judith Smith, PharmD BCOP CPHQ FCCP FISOPP RPh

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

HOPA President Scott Soefje, PharmD MBA BCOP, delivered exciting highlights from the year during his member address, including the launch of the HOPA BCOP Recertification Program, the inaugural class of Fellows of HOPA, a completely rebranded HOPA logo and look, and the success of our first annual report. Dr. Soefje commented on HOPA's many collaborations in 2015, noting that HOPA interacted with 20 different advocacy and professional organizations on a variety of endeavors. With a renewed strategic plan under our belt, Soefje stated, "we have made great strides toward our goal of supporting the research efforts of hematology/oncology pharmacists to optimize the care of individuals affected by cancer."

Thank you to all who attended the 2016 HOPA Annual Conference. We hope to see you next year at the 13th HOPA Annual Conference, taking place March 29–April 1, 2017, at the Disneyland® Hotel in Anaheim, CA.



There was great conversation and networking during the receptions.



Attendees gather around to check out all the conference has to offer.



Members are stylin' with the new HOPA logo on their conference bags.



Exhibitors and attendees spend quality time together in the Exhibit Hall.

Welcome 2016–2017 Board of Directors

HOPA is pleased to acknowledge the contributions of board members who worked diligently throughout their time in office, and whose terms have come to a close:

Michael Vozniak,
Past President



Jill Rhodes,
At-Large Member



HOPA thanks you all for your leadership, service, and commitment! This year, Dr. Soefje's term as president came to a close and he welcomed our new HOPA President, Sarah Scarpace, PharmD MPH BCOP. Dr. Scarpace's career is filled with numerous milestones and contributions to the field of hematology/oncology pharmacy, as she

has dedicated her career to academia and serving as a mentor and advisor to students entering the profession. HOPA is thrilled to welcome Dr. Scarpace as the leader of our organization. As the previously mentioned board members completed their leadership service to the organization, HOPA is delighted to welcome several new board members. The Board of Directors for 2016–2017 is

- President, Sarah Scarpace, PharmD MPH BCOP
- President-Elect, Susanna Koontz, PharmD BCOP FHOPA
- Past President, Scott Soefje, PharmD MBA BCOP
- Secretary, Helen Marshall, PharmD BCOP BCPS
- Treasurer, Jolynn Sessions, PharmD BCOP CPP
- At-Large Member, David DeRemer, PharmD BCOP
- At-Large Member, Ryan Bookout, PharmD BCOP BCPS
- At-Large Member, Heidi Finnes, PharmD BCOP
- At-Large Member, Ed Li, PharmD MPH BCOP

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



Introducing the 2016–2017 HOPA Board of Directors. Top row (pictured left to right): Susanna Koontz, David DeRemer, Scott Soefje, Ryan Bookout, Jolynn Sessions. Bottom row (pictured left to right): Helen Marshall, Heidi Finnes, Sarah Scarpace, Edward Li.

Congratulations to the 2016 HOPA Member Award Winners

Recognition Chair Stephanie Sutphin and President Scott Soefje were pleased to present the HOPA Member Awards at the members' meeting held at the 12th HOPA Annual Conference.



Meghana V. Trivedi, PharmD PhD BCOP
2016 Basic Science and Clinical Research Literature Award



Benyam Muluneh, PharmD BCOP CPP
2016 Patient Advocacy Award



Ginah Nightingale, PharmD BCOP
2016 Oncology Pharmacy Practice Literature Award



Edward D. Gormley, Jr., BS CPhT
2016 Technician Award



Kristin Held Wheatley, PharmD BCOP
2016 New Practitioner Award



Niesha L. Griffith, MS RPh FASHP
2016 Award of Excellence

NZW-Hamburg 2016

Lisa Holle, PharmD BCOP
Assistant Clinical Professor, Department of Pharmacy Practice
University of Connecticut School of Pharmacy
Storrs, CT

Following the 11th Annual HOPA meeting, I was invited by Klaus Meier, president of the German Society for Oncology Pharmacy (Deutsche Gesellschaft für Onkologische Pharmazie [DGOP]) and the European Society of Oncology Pharmacy (ESOP) to give a short greeting from HOPA to both DGOP and ESOP and to present my work on oral chemotherapy disposal (originally presented at the 11th Annual HOPA meeting) at the 24th NZW-Hamburg conference. NZW-Hamburg was held January 29–31, 2016, in Hamburg, Germany, and sponsored by the local Hamburg pharmacy association Apothekerkammer Hamburg, DGOP, and ESOP. Over 1,000 oncology pharmacists, physicians, and researchers from around the world attended the conference.

It was a terrific opportunity to introduce HOPA to a global pharmacy audience and to learn more about other oncology pharmacy organizations and oncology pharmacy practice in a variety of countries and settings. Similar to the Annual HOPA Meeting, the topics of the main conference were wide-ranging, including an overview of interactions of herbal medicines and oncology, the controversy of using generic tyrosine kinase inhibitors, an overview of the quality standards of the new ISO 9001, and updates on new drugs, cancer immunotherapy, end-of-life care, and oral chemotherapy. DGOP offers a certificate course for oncology pharmacists and NZW-Hamburg offered several certificate course sessions on aseptic work, clinical case reports, psycho-oncology, and risk management.

Two interesting joint professional organization endeavors were prominent during the conference. Empowering Pharmacists to Improve Healthcare for Oral Chemotherapy Patients: Establishment of a European Best Practice Model, also known as EPIC, is a joint project of the DGOP, ESOP, Slovene Chamber of Pharmacists, and Association of Estonian Hospital Pharmacists. The EPIC project conducted several seminars to display its work within specific case studies, drug information, dysphagia, and psychosocial aspects. Another joint initiative



From left to right: Amalia Papanikolopoulou (Athens, Greece), Lisa Holle (HOPA), and Bogumila Julia Sobkowiak (Lublin, Poland)

by DGOP and the German Cancer Society (DKG) is the oral cancer treatment project, aimed at optimizing oral chemotherapy by a safe, economical team-based approach that improves quality of life and minimizes drug-related problems.

ESOP hosted a short lecture session during the conference that included updates on the EPIC and Cytotoxic Drug Contamination in European Hospitals projects and presentations on the role of the pharmacist in hypothermic intraperitoneal chemotherapy (HIPEC) treatment, effect of disease state on the pharmacokinetics and efficacy of monoclonal antibodies like bevacizumab and cetuximab, disposal of oral chemotherapy drugs, and use of glutamine to prevent radiation-induced side effects. This session also included clinical pharmacy practice model examples from Japan, Egypt, and Croatia, which provided the audience with novel and innovative methods of oncology pharmacy practice. For example, Shinya Suzuki from Japan described the development of patient-friendly materials to manage adverse effects in the outpatient setting, which have become nationally accepted. Vesna Pvalica and colleagues presented on the recent creation of an oncology pharmacy team that spans community, hospital, and clinics to offer clinical oncology pharmacy services. Within 4 months of this service starting, the Croatian government approved payment for their services.

As with most conferences, the networking opportunities at NZW-Hamburg were just as important as the scientific information gained. I made connections with other oncology pharmacists and physicians from over 15 countries. I've encouraged them to come to a HOPA meeting some day and plan to keep in touch to foster international collaborations.

If you haven't attended an international oncology pharmacy meeting, I would certainly encourage you to do so. It always is a treat to meet folks, collaborate, and gain so much from the great work being done around the globe. The next DGOP meeting will be NZW-Dresden on June 17–18, 2016, in Dresden, Germany, and the next ESOP meeting will be ECOP3 in Dubrovnik, Croatia on May 19–21, 2016. For more information about NZW-Dresden visit <http://www.nzw.de/nzw-dresden.php> and for ECOP3 visit <https://ecop2016.wordpress.com/>.



Lisa Holle presenting "Ins and Outs of Disposing Oral Chemotherapy"



Board Update: Why Will Patients Ask for You...By Name?

Sarah Scarpace, PharmD MPH BCOP, HOPA President

In my remarks at the 12th HOPA Annual Conference, I challenged all of you to think about ways in which our patients will ask for us, their oncology pharmacists, by name. The profession has been working diligently for the last few years to seek “provider status” by amending the Social Security Act to include pharmacists in the list of providers who can bill Medicare Part B for clinical services. Members of the HOPA Board of Directors and Health Policy Committee participated in our second annual Hill Day on April 27, 2016, to advocate for H.R. 592 and S. 314, the Pharmacy and Medically Underserved Areas Enhancement Act. We also advocated for the Cancer Drug Coverage Parity Act (H.R. 2739/S. 1566), explained the role of the hematology/oncology pharmacist, and provided updates on the new CMS Part B “demonstration project.”

HOPA is a member of the Patient Access to Pharmacists’ Care Coalition, which is a collaboration of multiple pharmacy organizations who lobby year-round to support this legislation. While the profession has aimed specifically these past few years on bills that have been gaining increasing bipartisan support, this effort is not new. In fact, when I was in pharmacy school, I remember being told that we would be entering an era of “pharmaceutical care” and pharmacists would one day “bill for cognitive services.” In addition to 47 states and the District of Columbia, California and Washington recently authorized provider status legislation allowing pharmacists to practice under collaborative drug therapy management protocols, many of which predate the newest provider status initiative by many years. However, I’ve met HOPA members who have shared that they never have the opportunity to meet their patients. I’ve met friends, family members, and other colleagues who had not met their oncology pharmacist during their cancer journey, and were unaware that one was available to them.

As we continue to advocate for the opportunity to bill for these services, it is imperative that we start working toward including our most important advocate—our patients. I have yet to meet a patient who was not appreciative of the interactions that I or other pharmacists have had with them in the clinic. We all have different roles; some of us are working in very busy infusion centers and perhaps are the only pharmacist working to ensure that orders and drug therapy are written, dosed, and prepared safely. Imagine what an impact you could have if you took the time to meet just one patient—maybe that very last patient at the end of the day when you are getting orders ready for the next day—just to introduce yourself and say, “Hi Mrs. Smith. I’m Sarah Scarpace, and I’m your pharmacist. What questions do you have about your medications? How did that last cycle of chemo go for you? What side effects or symptoms do you have that I can help you with?”

It is incredible what you will learn from that personal interaction with your patients. These are the stories that I told legislators on the Hill in April—and these are the ones that matter. No one cares about how much education, training, or experience we have. They want to know the actual impact that we make. Describing the patient experience to legislators would pale in comparison to an actual patient writing a letter to describe how your interventions mattered to their care. We will need these stories, letters, and support to make provider status a reality, but moreover, we will need them as new payment models focusing on quality, value, outcomes, and impact rather than the quantity of services provided.

Speaking of Hill Day, we had a very successful and busy day on the Hill. We met with over 30 legislative offices from 13 states and learned within days of our visits that four legislators signed on to either the Provider Status or Oral Chemotherapy Parity bills! I asked those who attended for their thoughts on improving Hill Day for the future and one consistent message was to consider expanding participation to include more HOPA members. This is not surprising, given the standing-room only attendance at the advocacy session at this year’s annual conference and that 57 HOPA members have expressed interest in joining the Health Policy Committee through the volunteer activity center. While the board considers this suggestion and thinks of creative ways to implement it in a fiscally responsible manner, I strongly encourage you to consider meeting with your senator or representative while they are home during the summer recess (July 15–September 6 for the House of Representatives and July 18–September 5 for the Senate) on issues that matter to you. The HOPA Health Policy agenda, which includes briefs on a variety of issues with talking points and links to the actual pieces of legislation, and a link to find your senator and representative, can be found on the banner of HOPA’s current website (look for our new website in August!).

As HOPA’s new president, I am looking forward to providing leadership on a number of initiatives, some new and some that started during Scott Soefje’s term: revising the committee structure to be implemented in March 2017 to better coordinate communication among committees; revisiting the Scope of the Hematology/Oncology Pharmacist to work on “part 2”—a more granular and detailed version; publication of the Oral Chemotherapy Medication Therapy Management standard and development of tools, resources and perhaps even a “summit” to promote the standard and the pharmacists who provide services in this area; establishing hematology/oncology pharmacy competencies for pharmacy school graduates; enhancing our external collaborations and tangible projects with other pharmacy organizations as well as our partners in hematology/oncology medicine and nursing; implementing the selected Big Idea(s); and of course, monitoring the first year of our excellent BCOP Recertification Program involving over 50 HOPA members.



Recalls and Safety Alerts from the FDA

Jennifer Kwon, PharmD BCOP
Hematology/Oncology Clinical Pharmacy Specialist
VA Medical Center
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RECALLS

Baxter Recall on IV Solutions

Baxter International Inc. issued a voluntary recall on two lots of intravenous (IV) solutions due to the potential presence of particulate matter. The particulate matter has been determined to be an insect and was identified from a customer complaint. There have been no adverse events reported. For a full list of recalled products, visit <http://www.fda.gov/Safety/Recalls/ucm479877.htm>.

Downing Labs Recall in Texas

Downing Labs, LLC, in Farmers Branch, TX, voluntarily recalled all lots of sterile products compounded and packaged by Downing Labs due to concerns of sterility assurance. These products were distributed in the United States and the United Kingdom to patients and providers between April 20, 2015, and September 15, 2015. The recall does not affect any nonsterile, compounded medications prepared by Downing Labs. There have been no adverse events reported related to this recall.

<http://www.fda.gov/Safety/Recalls/ucm468215.htm>

Medistat RX Recall in Alabama

Medistat RX, LLC, in Foley, AL, issued a voluntary recall of all non-expired products produced for sterile use due to possible contamination. These products were distributed between November 1, 2014, and September 3, 2015. The U.S. Food and Drug Administration (FDA) has received reports of several adverse events that are possibly associated with Medistat drug products. Healthcare professionals and patients are encouraged to report adverse reactions or quality problems experienced with the use of drug products produced by Medistat to the FDA's MedWatch Adverse Event Reporting program.

<http://www.fda.gov/Safety/Recalls/ucm461939.htm>

Medline Industries Recall on Acetaminophen

Medline Industries, Inc. announced a voluntary nationwide recall on lot #45810 of Acetaminophen tablets, 500 mg, uncoated compressed tablets. This recall was due to an error in labeling. The Acetaminophen tablets of 500 mg are incorrectly labeled as being 325 mg. The recalled lot was distributed nationwide from June 12, 2015–September 18, 2015. There have been no adverse events reported related to this recall.

<http://www.fda.gov/Safety/Recalls/ucm467049.htm>

Pharmedium Recall on Norepinephrine Bitartrate

Pharmedium Services, LLC, in Lake Forest, IL, has recalled 29 lots of 4 mg norepinephrine bitartrate (16 mcg/mL) added to 0.9% sodium chloride in 250 mL Viaflex Bag and three lots of 8 mg norepinephrine bitartrate (32 mcg/mL) added to 0.9% sodium chloride in 250 mL Viaflex Bag distributed to hospitals. This recall was due to discoloration in the admixture, which could be indicative of degradation leading to

decreased potency. There have been no adverse events reported related to this recall. For a full list of affected products, visit <http://www.fda.gov/Safety/Recalls/ucm479677.htm>.

Sanofi Recall on Auvi-Q®

Sanofi US issued a voluntary recall on all Auvi-Q® (epinephrine injection, USP), including all Auvi-Q® currently on the market, due to inaccurate dosage delivery. The lot numbers involved are 2081278 through 3037230 with expiration dates of October 2015 through December 2016. The recall applies to both the 0.15 mg and 0.3 mg strengths for hospitals, retailers, and consumers. As of October 26, 2015, Sanofi has received 26 reports of suspected device malfunctions in the United States and Canada, but these device malfunction reports have not yet been confirmed. No fatal outcomes have been reported in these cases.

<http://www.fda.gov/Safety/Recalls/ucm469980.htm>

US Compounding, Inc. Recall in Arkansas

US Compounding, Inc. (USC) of Conway, AR, voluntarily recalled all lots of sterile products compounded and packaged by USC. This recall was due to the lack of sterility assurance. These products were distributed nationwide to patients, providers, hospitals, and clinics between March 14, 2015, and September 9, 2015. The recall does not apply to any nonsterile compounded medications made by USC.

<http://www.fda.gov/Safety/Recalls/ucm464071.htm>

SAFETY ALERTS

Afatinib (Gilotrif®)

The updated adverse reactions section of the drug labeling includes the incidence of nausea and vomiting seen in clinical trials experience. Reports of pancreatitis have been added to the postmarketing experience.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm480999.htm>

Azacitadine (Vidaza®)

The postmarketing experience has been updated to include reported cases of necrotizing fasciitis.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm289980.htm>

Bendamustine (Treanda®)

The warnings and precautions section of the package labeling for bendamustine has been revised to include the risk for reactivation of infections including hepatitis, cytomegalovirus, mycobacterium tuberculosis, and herpes zoster. Clinical and laboratory monitoring, prophylaxis, and treatment should be provided for infection and infection reactivation prior to administration of the drug.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm204021.htm>

Bevacizumab (Avastin®)

Nonmandibular osteonecrosis and posterior reversible encephalopathy syndrome (PRES) are now included in the postmarketing experience section of the prescribing information. Nonmandibular osteonecrosis can be found in the pediatric use section, as well. The risk of renal injury has been added to the adverse reactions section of the drug labeling.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm275758.htm>

Bortezomib (Velcade®)

The updated prescribing information for bortezomib includes use in the pediatric population. This update was based on a pediatric study, Study AALL071P1, which was a phase 2 pilot trial using bortezomib in combination with intensive reinduction therapy for children with relapsed acute lymphoblastic leukemia and lymphoblastic lymphoma.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyRelatedDrugLabelingChanges/ucm123444.htm>

Clofarabine (Clolar®)

Hepatobiliary disorders have been added to the postmarketing experience under the adverse reactions section of the package labeling. The warnings and precautions now include the risk of hepatitis and hepatic failure.

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

Crizotinib (Xalkori®)

The warnings and precautions section of the prescribing information for crizotinib has been updated to include a subsection for severe visual loss, inclusion of safety information across multiple clinical studies, and modifications to the embryofetal toxicity subsection. The use in specific populations has also been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

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

Deferasirox (Jadenu®)

Renal tubular necrosis and gastrointestinal perforation has been added to the postmarketing experience. In the warnings and precautions section of the prescribing information, the risk of gastrointestinal (GI) hemorrhage, and severe skin reactions are now listed. Reports have been made including deaths from GI hemorrhage, especially in elderly patients who had advanced hematologic malignancies or low platelets. Patients on deferasirox therapy should be monitored for signs and symptoms of GI ulceration and hemorrhage. The risk of GI hemorrhage may be increased with concurrent administration of drugs that have hemorrhagic potential, such as nonsteroidal anti-inflammatory drugs, corticosteroids, oral bisphosphonates, or anticoagulants. Rash may occur while on deferasirox therapy. For mild to moderate rashes, deferasirox may be continued since the rash will likely resolve on its own. Severe skin reactions, including Stevens-Johnson syndrome and erythema multiforme, have been reported. If any of these serious skin reactions are suspected, deferasirox should be discontinued immediately.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm472530.htm>

Docetaxel (Taxotere®)

Reported cases of permanent alopecia have been added in the postmarketing experience for docetaxel.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm212079.htm>

Everolimus (Zortress®)

The risk of interstitial lung disease and noninfectious pneumonitis has been added to the warnings and precautions section of the package labeling for everolimus.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303659.htm>

Granisetron (Sancuso®)

The warnings section of the package labeling for granisetron patch has been edited to address external heat sources to the patch. A heat pad should not be applied over or near the granisetron patch as heat exposure increases the drug plasma concentrations. Application site reactions (i.e., pain, erythema, rash, irritation, urticarial) and cardiac disorders (i.e., bradycardia, chest pain, palpitations) have been added to the postmarketing experience under the adverse reactions section of the package labeling.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm466191.htm>

Ipilimumab (Yervoy®)

Major edits were made to the following sections under the warnings and precautions part of the labeling information: immune-mediated enterocolitis, immune-mediated hepatitis, immune-mediated dermatitis, immune-mediated neuropathies, and immune-mediated endocrinopathies. The embryo-fetal toxicity section has been added to address the risk of fetal harm ipilimumab could cause when given to pregnant women. Education should be provided to females of reproductive potential to use effective contraception during treatment with an ipilimumab-containing regimen and for 3 months after the last dose of ipilimumab.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm328023.htm>

Methotrexate Injection

The boxed warning for methotrexate now has information to use the preservative-free formulation for intrathecal and high-dose therapy. There is a warning to avoid using the preserved formulation for intrathecal or high-dose therapy because it contains benzyl alcohol.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm476298.htm>

Nivolumab (Opidvo®)

The prescribing information for nivolumab has been revised to update information on several immune-mediated adverse reactions. Across the clinical trial experience, 0.4% of patients with solid tumors receiving nivolumab as a single agent experienced fatal immune-mediated pneumonitis. In patients with melanoma receiving nivolumab in combination with ipilimumab, fatal immune-mediated pneumonitis occurred in 0.5% of the patients across the clinical trial experience. Immune-mediated colitis can occur when administering nivolumab in combination with ipilimumab and therapy should be held for

moderate colitis. For any severe or life-threatening colitis, nivolumab should be permanently discontinued. Immune-mediated endocrinopathies, including hypophysitis, adrenal insufficiency, and hypothyroidism, have occurred with nivolumab treatment. Patients should be monitored for immune-mediated rash with nivolumab therapy. Corticosteroids should be administered for severe (Grade 3) or life-threatening (Grade 4) rash, or nivolumab should be held or discontinued depending on the severity of the rash. Immune-mediated encephalitis is another adverse reaction that can occur with nivolumab treatment. Patients with new-onset moderate to severe neurological signs or symptoms should undergo therapy. Nivolumab should be permanently discontinued for immune-mediated encephalitis. From the clinical studies, less than 1% of the patients receiving nivolumab had encephalitis. Other clinically significant, immune-mediated adverse reactions seen in less than 1% of patients receiving nivolumab as a single agent or in combination with ipilimumab in the clinical trials were uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatic, autoimmune neuropathy, Guillain-Barre syndrome, and hypopituitarism.

Infusion-related reactions (e.g., fevers, chills, rigors, flushing, rash, hypotension), including severe and life-threatening reactions, have been reported in patients on therapy with nivolumab. Discontinue the drug for any severe or life-threatening infusion-related reactions.
<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm472431.htm>

Obinutuzumab (Gazyva®)

The warnings and precautions section of the package labeling for obinutuzumab has been revised to include the fatal cases from tumor lysis syndrome (TLS). Patients with high tumor burden, high circulating lymphocyte count ($>25 \times 10^9/L$), or renal impairment are at greater risk for TLS and appropriate TLS prophylaxis should be implemented prior to administering obinutuzumab. The use in specific populations in the prescribing information has also been updated to comply with PLLR.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm404996.htm>

Oxaliplatin (Eloxatin®)

The updated warnings and precautions section of the prescribing information for oxaliplatin addresses severe neutropenia, cardiovascular toxicity, and rhabdomyolysis. There have been reports of sepsis, neutropenic sepsis, and septic shock in patients treated with oxaliplatin, including fatal outcomes. Recommendations to delay oxaliplatin until neutrophils are equal to $1.5 \times 10^9/L$, withhold treatment for sepsis and septic shock, and dose reduce after recovery from Grade 4 neutropenia or febrile neutropenia have been added. Due to reports of QT prolongation and ventricular arrhythmias, even fatal Torsade de Pointes after oxaliplatin administration, there are recommendations to monitor the electrocardiogram in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong QT interval, and

electrolyte abnormalities. Oxaliplatin should not be used in patients with congenital long QT syndrome. Reports have been made of rhabdomyolysis, including fatal cases in patients treated with oxaliplatin. Therapy should be discontinued if any signs or symptoms of rhabdomyolysis occur.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm287508.htm>

Pazopanib (Votrient®)

Interstitial lung disease (ILD)/pneumonitis is now included in the warnings and precautions section and listed in the adverse reactions section of the package labeling. ILD/pneumonitis occurred in 0.1% of patients treated with pazopanib in clinic trials. Patients should be counseled on reporting pulmonary signs or symptoms indicative of ILD or pneumonitis.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303649.htm>

Pegfilgrastim Injection (Neulasta®)

Updates have been made to the warnings and precautions section of the package insert for pegfilgrastim. The update includes the risk for glomerulonephritis, leukocytosis, and capillary leak syndrome. Glomerulonephritis has been diagnosed based on azotemia, hematuria, proteinuria, and renal biopsy. These events usually are resolved after dose reduction or discontinuation of pegfilgrastim. If glomerulonephritis is suspected due to pegfilgrastim, this medication should be discontinued. White blood cell counts of $100 \times 10^9/L$ or greater have been observed in patients receiving pegfilgrastim. Monitoring of complete blood counts during therapy is recommended. Reports of capillary leak syndrome have been made in patients getting pegfilgrastim injections. Patients who develop capillary leak syndrome, which can be a life-threatening condition, should receive standard symptomatic treatment, which may include intensive care.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm262864.htm>

Ponatinib (Iclusig®)

The updated warning and precautions section of the prescribing information includes vascular occlusion, arterial occlusion and thrombosis, and hypertension. Renal artery stenosis leading to worsening or treatment-resistant hypertension has occurred in patients treated with ponatinib. Treatment should be interrupted if there is significant worsening of hypertension.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm380782.htm>

Temozolomide (Temodar®)

Infections including primary and reactivated cytomegalovirus and reactivation of hepatitis B infections have been added to the postmarketing experience section of the drug labeling.

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm262708.htm>

Alectinib (Alecensa®)

Class: Tyrosine kinase inhibitor (TKI), anaplastic lymphoma kinase (ALK) inhibitor

Indication: ALK-positive metastatic non-small cell lung cancer (NSCLC) after progression on crizotinib

Dose: 600 mg twice daily

Dose modifications: First dose reduction to 450 mg twice daily; second dose reduction to 300 mg twice daily. If patients are unable to tolerate the 300 mg twice daily dose, discontinue. Specific parameters for dose reductions are provided in the package information.

Common adverse effects: Fatigue, constipation, edema, and myalgia

Serious adverse effects: Hepatotoxicity, interstitial lung disease/pneumonitis, bradycardia, severe myalgia, and creatine phosphokinase elevation

Drug interactions: Bradycardia-causing agents

Alectinib for ALK-Positive NSCLC After Progression on Crizotinib

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ALK-positive NSCLC is a rare disease only occurring in an estimated 2%–7% of patients with NSCLC. Crizotinib, the first TKI to specifically target ALK rearrangements in NSCLC, improved response rates to 74% versus 45% with chemotherapy in the first-line setting ($p < .001$). Median time to progression of 7–12 months¹ is an unfortunate expected reality on crizotinib, thus subsequent therapies are needed. Ceritinib was the first subsequent therapy approved by the U.S. Food and Drug Administration (FDA) in April 2014, and most recently alectinib was approved via the FDA's accelerated approval pathway in December 2015. Alectinib is five times more potent than crizotinib against ALK and has shown activity against most of the clinically observed crizotinib-resistance mutations. The phase 2 study leading to alectinib's approval treated patients with ECOG PS of 2 or less, adequate organ function, and measurable disease including stable brain metastases and leptomeningeal disease. Patients were required to have a 7-day washout of crizotinib. Alectinib then was administered as 600 mg twice daily within 30 minutes of eating. Of the 138 patients enrolled across 16 countries, 122 were evaluable for response. The overall response rate (ORR) was 49% (95% confidence interval [CI]: 40%–58%) and median progression free survival (PFS) was 8.9 months (95% CI: 5.6–11.3 months). The activity of alectinib in central nervous system (CNS) disease is impressive. Patients with measurable CNS lesions had a CNS ORR of 57% (95%, 39%–74%) with a duration of response of 10.3 months (95% CI: 7.6–11.2 months).²

Alectinib was well-tolerated, with myalgia (17%), constipation (15%), fatigue (26%), and asthenia (11%) being the most common treatment-related adverse events (AE). Grade 3/4 events were minimal, occurring in <5% of patients. Only one patient died of a treatment-related AE (intestinal perforation). Myalgia usually occurs early with treatment, but tends to resolve within 4 weeks.²

Alectinib is supplied as 150-mg capsules, therefore patients should be counseled they will need to take four capsules twice daily. Doses should be taken within 30 minutes of a meal; the absolute bioavailability is 37% under fed conditions. Alectinib has a large volume of distribution of 4,016 L and concentrations within the cerebrospinal fluid approximate concentrations in the plasma. Alectinib is metabolized by CYP3A4 to its major active metabolite M4, which is also metabolized by CYP3A4. Alectinib is not a substrate of P-glycoprotein, but M4 is a substrate. However no clinically meaningful effect on alectinib or M4 was observed when administered with strong CYP3A4 inhibitors and inducers. Alectinib does not seem to meaningfully affect other drugs metabolized by the CYP system or transported by a variety of transporters. Dose adjustments are not recommended for patients with mild or moderate renal impairment, or mild hepatic impairment. The safety of alectinib has not been studied in patients with severe renal impairment or moderate or severe hepatic impairment.³

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Daratumumab (Darzalex®)

Class¹: CD-38 directed monoclonal antibody

Indication¹: Used to treat multiple myeloma in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Dose¹: 16 mg/kg administered intravenously on the following schedule: weekly for weeks 1–8, every 2 weeks for weeks 9–24, then every 4 weeks from week 25 until disease progression

Dose modifications¹: None. Infusion rate adjustments are required for infusion-related reaction based on grade severity.

Common adverse effects¹: (> 20%—any grade): infusion reactions (48%), fatigue (39%), nausea (27%), back pain (23%), pyrexia (21%), cough (21%), upper respiratory tract infection (20%)

Serious adverse reactions¹: Pneumonia (6%), general physical health deterioration (3%), pyrexia (3%)

Warnings and Precautions¹: Interrupt daratumumab infusions for any grade infusion reaction and treat as necessary. Resume at half previous rate and descalate dose as tolerated. Discontinue daratumumab after three instances of grade 3 infusion reaction or in instance of life-threatening reaction. Pre- and post-infusion medications recommended with each dose. Type and screen patients prior to starting daratumumab, as daratumumab can bind to CD-38 on red blood cells and mask detection of antibodies or result in positive Coombs test.

Drug interactions¹: No drug interaction studies performed. See above warning about interaction with laboratory testing.

The Introduction of Monoclonal Antibodies in Multiple Myeloma: Targeting CD-38 with Daratumumab

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Multiple myeloma (MM) is characterized by malignant plasma cells accumulating in the bone marrow along with pathogenic antibody production, which leads to the characteristic bone, renal, hematologic, and infectious complications seen in this disease.²⁻⁴ The estimated lifetime risk of developing MM is 0.7%, with an expected 30,330 new cases in 2016 in the United States, with 12,650 expected deaths from disease.² Historically MM was responsive to conventional

chemotherapy agents, but responses were transient.⁴ Advances in treatment with proteasome inhibitors, immunomodulatory agents, and autologous stem cell transplant have improved survival.³⁻⁵ However, most patients will relapse and die from refractory disease. Patients who are refractory to multiple treatment lines, including proteasome inhibitors and immunomodulatory agents, have a median overall survival (OS) of 9 months.^{4,5} Treatment improvements in the relapsed setting would involve a novel target with clinical efficacy, little toxicity, good tolerability, and few off-target effects. Monoclonal antibodies offer a unique treatment option in MM, with targets such as SLAMF7 (CS1) and CD38 on cell surfaces.⁴ CD38 is present on normal lymphoid and myeloid cells, but is uniformly expressed in high levels on myeloma cells.⁵ Daratumumab is a human IgG1-kappa monoclonal antibody which binds to a unique CD38 epitope, thereby inducing target cell killing of CD38-expressing tumor cells via multiple mechanisms.⁵

Daratumumab was granted accelerated U.S. Food and Drug Administration approval for the treatment of MM in patients who have had at least three prior lines of therapy and are refractory to both a proteasome inhibitor or an immunomodulatory agent.¹ This approval is based on results of a phase 1/2 and a phase 2 clinical trial.^{4,5} These clinical trials are ongoing to confirm the clinical benefit of daratumumab in MM.

Lokhorst, et al⁵ conducted the phase 1/2 trial which included two parts: dose escalation and dose expansion to determine a primary endpoint of safety, along with secondary endpoints of efficacy and pharmacokinetics. The dose escalation included 10 cohorts of patients that received doses of 0.005–24 mg/kg daratumumab. Using a 1+3 design for the two lower cohorts and a 3+3 design for the remaining cohorts, no maximum tolerated dose was determined. Even though the maximum dose of 24 mg/kg was tolerated well, no clinical benefit over 16 mg/kg was demonstrated.

In part two of this trial⁵, 72 patients were randomized to five treatment groups: three receiving 8 mg/kg (30 patients) and two receiving 16 mg/kg (42 patients). Patients in all treatment cohorts were heavily pretreated: the median number of prior therapies was four in both dosing cohorts. Patients were refractory to drugs including bortezomib, carfilzomib, thalidomide, pomalidomide, and lenalidomide; 76% of patients had undergone autologous stem cell transplant. The main differences among these five treatment cohorts were variations of how the daratumumab was supplied (volume of diluent) and rate of administration. The primary endpoint of safety was impacted mostly by the rate of infusion reaction, with a rate of 71% of patients, which ranged from grades 1 or 2, though one patient experienced a grade 3 reaction. However, treatment was not discontinued based on these reactions. It also was noted that a more dilute solution infused over a longer duration (cohort C) had a lower incidence of infusion-related reactions, implying that the infusion rate is important in preventing and managing said reactions. The overall response rate (ORR) of the 16 mg/kg cohort was 26% compared to 10% in the 8 mg/kg cohort. Quality of

response, determined by a 50% reduction in M protein level or free light chains, also was higher in the 16 mg/kg cohort (46%) compared to the 8 mg/kg cohort (15%). In addition, bone marrow plasma-cell levels were improved in eight patients and remained stable in five patients of the 15 responders in the 16 mg/kg cohort. The estimated median time to response was 0.9 months, while a median duration of response was not met in the 16 mg/kg cohort, with 65% of responding patients remaining progression-free at 12 months. Higher response rates also were seen in patients who had up to three prior lines of therapy (56%) as compared to more heavily treated patients (23%).

Pharmacokinetic (PK) studies⁵ demonstrated a mean half-life of 9 ± 4.3 days after the first 16 mg/kg dose, which increased to 10.6 ± 9 days after repeated doses. Trough concentrations were assessed to compare with predicted troughs for target saturation. The 16 mg/kg cohort had trough concentrations similar to predicted, whereas trough concentrations were lower than predicted in the 8 mg/kg cohort, making 16 mg/kg the lowest tested dose with consistent PK results.

Lonial, et al⁴ conducted a multicenter, open label, phase 2 trial in multiple countries looking at a primary endpoint of ORR, which includes partial response (PR), very good PR, complete response (CR), and stringent CR, in patients refractory to multiple lines of therapy. Duration of response, progression free survival (PFS), overall survival (OS), and clinical benefit rate (minimal response plus ORR) were all assessed as secondary endpoints. The study had two parts, and part one had two stages. The first stage compared 8 mg/kg given intravenously (IV) every 3 weeks to 16 mg/kg weekly for 8 weeks, followed by every other week for 16 weeks, followed by every 4 weeks through duration of treatment. An interim analysis determined the 8 mg/kg dose did not meet criteria for expansion with an ORR of 11.1%. In stage two of part one, 25 additional patients were recruited to the 16 mg/kg arm, including three patients from the 8 mg/kg arm that crossed over as it was deemed beneficial by their investigator. A second interim analysis completed part one and led into part two of the trial, which enrolled an additional 65 patients into the 16 mg/kg arm, giving a total of 106 patients studied at this dose. Patients who received treatment were highly refractory to previous therapy, having had a median number of five previous treatments, including proteasome inhibitors and immunomodulatory agents. Ninety of the 106 patients discontinued therapy, owing to disease progression, symptoms related to disease progression, and adverse events unrelated to treatment. Overall, 31 of the 106 patients responded to daratumumab 16 mg/kg (ORR 29.2%), showing a clinical benefit in 36% of patients. Median time to response was 1 month, with a median duration of response of 7.4 months. Eight of the 31 responders experienced an improved response over time with continued treatment. Median PFS was 3.7 months and median OS was not reached in patients who responded to therapy.

The most common adverse reaction in all patients treated with daratumumab was infusion related reactions.^{1,4,5} Reactions were most prevalent with the first infusion (46%), and incidence decreased with second (5%) and third (4%) infusions.¹ Some reactions were delayed up to 4 hours after the infusion was completed when pre-infusion

medications were given. In the event of a grade 1 or 2 reaction, the infusion should be stopped, reaction managed, and infusion restarted as tolerated at half the previous rate.¹ Further escalation may resume as the patient tolerates it.¹ If a patient experiences a grade 3 infusion reaction, stop the infusion and treat the reaction.¹ Consider restarting if reaction improves to grade 2 or lower at half the previous rate.¹ Permanently discontinue daratumumab if the patient has experienced three grade 3 or higher infusion reactions.¹ Pre-infusion medications should include a corticosteroid (100 mg methylprednisolone equivalent), acetaminophen (650–1000 mg), and diphenhydramine (25–50 mg or equivalent) to lessen the chance of infusion reaction.^{1,4} Post-infusion oral corticosteroids (20 mg methylprednisolone equivalent) are recommended on days 1 and 2 after the infusion for all patients.^{1,4} Patients with obstructive pulmonary history may benefit from short- or long-acting bronchodilators and inhaled corticosteroids initially as prophylactic therapy to prevent any respiratory complications from infusion reactions.¹ These may be discontinued after the fourth infusion if the patient does not experience severe reactions.¹

Other common adverse reactions include fatigue (39%), nausea (27%), back pain (23%), pyrexia (21%), cough (21%), and upper respiratory tract infection (20%).¹ Serious adverse reactions occurred in 33% of patients, the most frequent being pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).¹ Laboratory abnormalities noted (all grade; grade 3): lymphopenia (72%; 30%), neutropenia (70%; 17%), thrombocytopenia (48%; 10%), and anemia (45%; 19%).¹ Additionally, because of binding to CD38 on red blood cells, daratumumab interferes with compatibility testing, including antibody screening and cross matching.¹ For this reason, type and cross-match should be completed prior to starting patients on daratumumab therapy.¹

Dartumumab is supplied as a 20-mg/mL solution.¹ The appropriate volume of diluent should be removed from the infusion bag equal to the dose volume to be added. The first dose should be further diluted in 1000 mL 0.9% sodium chloride, with subsequent infusions being diluted in 500 mL 0.9% sodium chloride. Daratumumab infusion should be protected from light and infused with an in-line, 0.22 or 0.2 micrometer pore size filter. The infusion should be completed within 15 hours of start of the infusion. The first infusion should start at a rate of 50 mL/hour. It can be increased by 50 mL/hour increments every hour to a maximum rate of 200 mL/hour. Dose escalation of each subsequent infusion can be considered if patients do not experience grade 1 infusion reactions within the first 3 hours of the previous administration. If tolerated, the second infusion will run at the same rate as the first infusion, and the third infusion can start at a rate of 100 mL/hour if there were no grade 1 infusion reactions with rates greater than or equal to 100 mL/hour in the first two infusions. On average, the first infusion will last 7 hours, second infusion 4.6 hours, and subsequent infusions 3.4 hours.¹ Patients should receive pre- and post-infusion medications as outlined above.^{1,4,5} Patients also should be instructed on monitoring for infusion reaction symptoms at home, as some can occur in the delayed setting.

With improved survival demonstrated in relapsed/refractory MM, daratumumab is being investigated further within this disease.⁵ Current trials include combination regimens with daratumumab as either front-line or in the refractory setting. Daratumumab is also being investigated to treat certain lymphoma cell types in the refractory setting: mantle cell, follicular cell, and diffuse large B-cell. The future uses of this monoclonal antibody are still under investigation, but current results demonstrate disease response with good safety and tolerability.

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Elotuzumab (Empliciti®)

Class: SLAMF-7 Monoclonal Antibody

Indication: Multiple myeloma

Dose: 10 mg/kg intravenous infusion weekly on days 1, 8, 15, and 22 of a 28-day cycle for two cycles; 10 mg/kg once every 2 weeks on subsequent cycles

Dose modifications: Interrupt the infusion for Grade ≥ 2 infusion-related reactions. The infusion may be resumed at a slower rate when symptoms have improved to \leq Grade 1.

Common adverse effects: Fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy

Serious adverse effects: Infusion reactions, infections, secondary primary malignancies, hepatotoxicity

Drug interactions: None known; no formal drug interaction studies have been conducted.

Elotuzumab for Relapsed or Refractory Multiple Myeloma

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Multiple myeloma is a plasma cell malignancy with approximately 30,000 new cases diagnosed in the United States in 2015.¹ Multiple myeloma has an incidence rate that is increasing by about 1% per year and accounts for 1.6% of all new cancer cases.² Multiple myeloma is not considered curable; however, survival has improved significantly with the advent of novel therapies. Newer agents such as bortezomib and lenalidomide, as well as hematopoietic stem cell transplant, have extended the median survival to 45–60 months.³

The majority of identified risk factors for multiple myeloma are non-modifiable, including age, gender, and race.² Various staging systems have been referenced in the literature, the most common of which is the International Staging System (ISS). Prognostic features such as serum beta-2 microglobulin and albumin are utilized in combination with cytogenetic information to risk stratify patients.¹

Standard initial treatment for patients with multiple myeloma often is determined based upon his or her eligibility for an autologous stem cell transplant. For those who are transplant-eligible, therapy typically consists of a combination of agents, including bortezomib, dexamethasone, and lenalidomide or thalidomide while non-transplant candidates may receive melphalan-based therapies. Overall response rates (ORR) to initial treatment can range from 78%–94% with progression free survival (PFS) reported at 27–36 months. Depending on time to relapse, patients may be re-treated with the same medications used in the first-line setting, or with alternative agents such as carfilzomib, ixazomib, liposomal doxorubicin, daratumumab, pomalidomide, or combination chemotherapy.⁴

New therapeutic targets continue to be investigated in an effort to further improve long-term outcomes in patients with multiple

myeloma. One such agent, elotuzumab, is a humanized recombinant IgG kappa monoclonal antibody against signaling lymphocytic activation molecule family member 7 (SLAMF7)—a glycoprotein expressed on the surface of myeloma, natural killer, and plasma cells.^{5,6} This glycoprotein has been found on more than 90% of bone marrow samples obtained from patients with myeloma.⁷ Elotuzumab leads to targeted lysis of myeloma cells expressing SLAMF7 via antibody-dependent, cell-mediated cytotoxicity and direct activation of natural killer cells. It has also been shown to synergistically increase the activation of natural killer cells when used in combination with lenalidomide.^{5,7}

Elotuzumab was approved by the U.S. Food and Drug Administration (FDA) on November 30, 2015, based on data from the ELOQUENT-2 study, a phase 3, randomized trial of 646 patients with previously treated multiple myeloma.^{6,8} Enrolled between June 2011 and November 2012, eligible patients were 18 years old with confirmed multiple myeloma who had received one to three prior therapies (previous lenalidomide was permitted), but had progressed following the most recent treatment. Additionally, the patient's disease burden had to be measurable and their creatinine clearance had to be ≥ 30 mL/min. Patients were excluded if their absolute neutrophil count (ANC) was $< 1,000$ or platelets were $< 75,000$. Study participants had a median age of 66 years (20% of whom were over the age of 75), 43% had ISS stage one disease, and 32% had del(17p). Slightly less than half of patients enrolled had received one prior line of therapy, with a median of two previous treatments among all participants, 70% of whom had received bortezomib.⁸

Patients in the control arm received lenalidomide 25 mg by mouth daily for 21 days of a 28-day cycle and dexamethasone 40 mg by mouth daily on days 1, 8, 15, and 22. Those randomized to elotuzumab received 10 mg/kg on days 1, 8, 15, and 22 for cycles one and two and the same dose on days 1 and 15 only for cycles three and beyond.⁸ On the days elotuzumab was administered, patients were given dexamethasone 8 mg intravenously (IV) and 28 mg by mouth. Prophylaxis for thromboembolism was required as were the pre-medications as stated in the prescribing information. The primary endpoints were PFS and ORR with overall survival as a secondary endpoint.⁸

The median follow-up was 24.5 months and baseline characteristics were similar between the two groups. The study met early stopping criteria based on superior PFS and ORR in the elotuzumab group compared to the control arm. Of the 646 patients evaluated, PFS at 1 and 2 years was 68% and 41% for those who received elotuzumab compared to 57% and 27% in the control group. In the elotuzumab arm, median PFS was 19.4 months compared to 14.9 months for those receiving lenalidomide and dexamethasone alone (hazard ratio [HR] = 0.7; 95% confidence interval [CI]: 0.57–0.85; $p < .001$). ORR for the elotuzumab and control groups were 79% and 66%, respectively (odds ratio [OR] = 1.9; 95% CI: 1.4–2.8; $p < .001$). Responses appeared to be durable at 21 months with elotuzumab as compared to 17 months with lenalidomide and dexamethasone alone. Complete response (CR) rates were reported as 4% in the elotuzumab group versus 7% in the

control group; however, it should be noted that because elotuzumab is a humanized IgG kappa antibody, it interferes with the immunofixation and serum protein electrophoresis assays, potentially underestimating the CR rates in this group. Overall survival data has not yet matured.^{5,8}

More than half of patients experienced serious adverse events, including approximately a third who had grade 3 or 4 neutropenia (34% in the elotuzumab group versus 44% in the control arm).⁸ Secondary primary malignancies have been reported in up to 11% of patients who received elotuzumab with lenalidomide and dexamethasone.⁷ There also was a significantly higher rate of herpes zoster infection in the elotuzumab group, likely attributable to the higher rates of grades 3 and 4 lymphopenia (77% versus 49%).⁵ Other adverse events that occurred more commonly in the elotuzumab group included fatigue (47%), pyrexia (37%), nasopharyngitis (25%), diarrhea (47%), constipation (36%), and cough (31%). Infusion reactions were reported in 10% of patients in the elotuzumab group, all of which were grade 1 or 2.⁸

The safety of elotuzumab has not been established in pediatric patients. Reproductive studies also have not been performed with elotuzumab; however, a risk for fetal harm does exist as monoclonal antibodies are known to cross the placenta, particularly during the third trimester. Additionally, lenalidomide is a known teratogen, therefore this therapy is contraindicated in women who are pregnant and should be avoided in those who are breastfeeding.⁵ Safety has been relatively well established in patients with renal impairment, including those with a creatinine clearance < 30 mL/min or with end-stage renal disease receiving hemodialysis. Average serum concentrations of elotuzumab were similar in these patient populations compared to those with normal renal function. Additionally, no changes in glomerular filtration rate were noted with the addition of elotuzumab. Serum concentrations of the drug did not differ before as compared to after dialysis.⁹

Elotuzumab is supplied as a 300- or 400-mg single-use lyophilized vial, which is reconstituted to a final concentration of 25 mg/mL. It is approved in combination with dexamethasone and lenalidomide 25 mg by mouth daily on days 1–21 of a 28-day cycle. Patients should receive dexamethasone 28 mg by mouth 3–24 hours prior to each elotuzumab dose. Additionally, 8 mg of IV dexamethasone should be given 45–90 minutes prior to elotuzumab administration. Starting with cycle 3, dexamethasone 40 mg by mouth should be given on days 8 and 22 of each cycle. Additional pre-medications include an antihistamine such as diphenhydramine 25–50 mg IV or by mouth (PO), an H2 blocker such as ranitidine 50 mg IV or 150 mg PO, and acetaminophen 650–1,000 mg PO, 45–90 minutes prior to elotuzumab. The recommended initial infusion rate is 0.5 mL/min for 30 minutes, which gradually can be escalated to a maximum rate of 2 mL/min based on tolerability; however, the infusion should be complete within 24 hours of drug reconstitution. This rate can be further escalated to 5 mL/min starting with cycle 4. The infusion of elotuzumab may be paused for grade 2 or higher reactions and resumed at a rate of 0.5 mL/min once symptoms have resolved to grade 1. Patients should be counseled on the risk of infections, including herpes zoster, infusion reactions, hepatotoxicity, and second primary malignancy.⁵

As multiple myeloma is increasingly treated as a chronic disease, more therapies are needed to prolong the time until disease progression, particularly for those patients who have demonstrated a poor response to immunomodulatory therapy or proteasome inhibitors. Elotuzumab, in combination with lenalidomide and dexamethasone, has been demonstrated to improve PFS in those patients who have received one to three prior therapies for multiple myeloma. It is important to note that elotuzumab does not provide activity against myeloma when used as monotherapy.^{9,10} Based on the results of the ELOQUENT-2 study, elotuzumab is currently listed as a category 1 recommendation for previously treated patients.⁴ Adverse effects, including infusion reactions, neutropenia, and infection, can be severe and require regular monitoring. Further studies plan to investigate the safety and efficacy of elotuzumab in its currently approved regimen, as well as in combination with other agents such as bortezomib, thalidomide, and pomalidomide.¹¹ Combinations with bortezomib have been promising to date and the toxicity profiles appear tolerable.¹⁰ Maintenance therapy with elotuzumab following autologous transplant or in the first-line setting also is being evaluated in an attempt to improve outcomes in these patients.^{10,11} Without the addition of tremendous toxicity, elotuzumab has provided a significant improvement in the outcomes of patients with previously treated multiple myeloma.

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Ixazomib (Ninlaro™)

Class: Proteasome Inhibitor

Indication: Relapsed or refractory multiple myeloma in combination with lenalidomide and dexamethasone

Dose: 4 mg by mouth once weekly on days 1, 8, and 15 of a 28-day treatment cycle

Dose modifications: First dose reduction to 3 mg for absolute neutrophil count (ANC) nadir below $0.5 \times 10^9/L$ or platelet count less than $30 \times 10^9/L$, and any grade 2 or 3 rash despite withholding lenalidomide and second dose reduction to 2.3 mg. Starting dose of 3 mg in patients with moderate or severe hepatic impairment, severe renal impairment ($CrCl < 30 mL/min$) or end-stage renal disease requiring dialysis

Common adverse effects: Diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain

Serious adverse effects: Thrombocytopenia and diarrhea

Drug interactions: Strong CYP3A inducers such as rifampin, phenytoin, carbamazepine, and St. John's Wort should be avoided.

Ixazomib for Relapsed and Refractory Multiple Myeloma

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Multiple myeloma (MM) is a plasma cell malignancy characterized by genetics and epigenetics aberrations that lead to bone destruction, hypercalcemia, cytopenia, renal dysfunction, hyperviscosity, and peripheral neuropathy. It is the second most common hematological malignancy after non-Hodgkin's lymphoma and represents 1.6% of all new cancer cases in the United States. Approximately 96,000 people are living with, or in remission from MM in the United States. It is an incurable but treatable malignancy in which the 5-year survival rate was nearly 50% of patients in 2011 due to novel immunomodulatory agents and proteasome inhibitors such as lenalidomide and bortezomib.¹ However, even patients who achieve a high quality and prolonged duration of response with initial therapy will ultimately relapse despite these novel agents. In a recent analysis of 286 relapsed MM patients, it takes approximately 3 years from time of diagnosis to time to relapse.² According to the International Myeloma Working Group (IMWG), treatment options are limited in patients who relapse and refractory to lenalidomide and bortezomib.³

In November 2015, the first oral proteasome inhibitor, ixazomib (Ninlaro™), was approved for the treatment of relapsed or refractory multiple myeloma.⁴ The approval was based on the Tourmaline-MM1

study (NCT01564537), a phase 3 double-blinded multicenter study in which adult patients with relapsed or refractory MM were randomized to either receive ixazomib 4-mg capsules on days 1, 8, and 15 or matching placebo in combination with lenalidomide 25 mg daily on day 1 through 21 and dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle until disease progression (DP) or unacceptable toxicity, whichever occurred first. A total of 722 patients who had received one to three prior therapies were included with few restrictions on specific prior treatments. However, patients were excluded if at any time their disease was refractory to lenalidomide or a proteasome inhibitor. Refractory disease was defined as DP on treatment or progression within 60 days after the last dose of a given therapy while relapsed disease was defined as DP after 60 days from the last dose of a given therapy. Approximately 60% of the patients had at least one line of prior therapy and 30% of the patients were naive to proteasome inhibitor. The primary outcome measure was progression-free survival (PFS), which was defined as the time from randomization to the time of first documentation of DP or death of any cause. DP was assessed by an independent review committee using the IMWG response criteria, which required one of the following: increase of $\geq 25\%$ nadir in serum M-protein (absolute increase of ≥ 0.5 g/dL); urine M-protein (absolute increase of ≥ 200 mg/24 hours); in patients without measurable serum and urine M-protein levels the difference between involved and uninvolved free light chain levels (absolute increase of > 10 mg/dL); development of new or increase in the size of existing bone lesions or soft tissue plasmacytomas; development of hypercalcemia (corrected calcium > 11.5 mg/dL) attributed solely to plasma cell proliferative disease.

The data from the first analysis showed a significant improvement in PFS with ixazomib compared to placebo (20.6 months versus 14.7 months, $p = .012$). The overall survival (OS) was not established at the time due to immaturity of the data, but the overall response rate (ORR), defined as the percentage of patients with complete response including stringent complete response, very good partial response, and partial response, was 78.3% in the ixazomib arm and 71.5% in the placebo arm. Furthermore, the PFS in patients with high-risk cytogenetic features which were those with $del(17)$, translocation $t(4:14)$ or $t(14:16)$ was 21.4 months who received ixazomib versus 9.7 months who received matching placebo. The duration of response was 20.5 months for those who received ixazomib and 15 months for those who received matching placebo.⁵

The most frequently reported adverse reactions ($\geq 20\%$) in the ixazomib arm and greater than the placebo arm were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Serious adverse reactions reported in $\geq 2\%$ of patients included thrombocytopenia and diarrhea.⁵

The fetal risk with ixazomib cannot be ruled out and women should avoid becoming pregnant while being treated with ixazomib. It is

unknown whether ixazomib or its active metabolite are present in human milk and therefore, women should stop nursing while taking ixazomib.⁶

Ixazomib is a second-generation boronate proteasome inhibitor and represents the first oral agent PI to be evaluated in MM clinical trials. Its improved pharmacokinetic profiles compared to the first-generation boronate proteasome inhibitor, bortezomib (Velcade) makes it an attractive agent in the treatment of patients with MM. Following oral administration of ixazomib capsules, the active compound MLN2238 was rapidly absorbed with time to peak concentration of 1 hour and the systemic exposure was found to be similar with intravenous administration.⁶ Similar to bortezomib, ixazomib disrupts the ubiquitin-proteasome signaling pathway by inhibiting the chymotrypsin-like proteolytic ($\beta 5$) site of the 20S proteasome, and at higher concentrations inhibit the caspase-like ($\beta 1$) and trypsin-like ($\beta 2$) proteolytic sites.^{6,7} In addition, it exerts a time-dependent reversible proteasome inhibition similar to bortezomib but the dissociation half-life ($t_{1/2}$) is about six times faster than that of bortezomib (18 minutes versus 110 minutes).⁷ At steady state, the terminal $t_{1/2}$ of ixazomib is 9.5 days. It has a larger volume of distribution at a steady state of 20.2 L/kg compared to bortezomib of 4.3 L/kg, which leads to greater drug distribution from blood to tissue compartments and significant anti-tumor activity. At clinically relevant concentrations, CYP450 isoenzymes showed no specific CYP450 contributes to ixazomib's metabolism. At higher concentrations, ixazomib was metabolized primarily by the CYP3A4 and CYP1A2 isoforms. Approximately 60% of ixazomib is excreted in urine and 22% in feces with unchanged ixazomib accounting for less than 5% of the administered dose recovered in urine. Based on population pharmacokinetics analysis, the PK of ixazomib was similar between patients with normal hepatic function and in patients with mild hepatic impairment (T Bili \leq ULN and AST $>$ ULN or T Bili $>$ 1 to 1.5 x ULN and any AST).⁶ However, in patients with moderate or severe hepatic impairment, the mean AUC increased by 20% compared to those with normal hepatic function and hence, the recommended dose is reduced from 4 mg to 3 mg in this population. Similar dose reduction is to be made in patients with severe renal impairment (CrCl $<$ 30 mL/min) or those with end-stage renal disease requiring dialysis. It is non-dialyzable and can therefore be administered regardless to the timing of dialysis.⁶

Ixazomib is available in three different gelatin capsule strengths: 4 mg, 3 mg, and 2.3 mg and the capsules are either supplied in one single blister pack or three single packs in a carton. An ixazomib capsule should be swallowed whole once a week for the first 3 weeks on a 4-week cycle on an empty stomach as it has been shown to have a lower AUC and C_{max} when taken with high-fat meal. Ixazomib

should not be taken with dexamethasone as it has to be taken with food. If the patient misses a dose, advise them to take the missed dose as long as the next scheduled dose is \geq 72 hours away; otherwise, skip dose if it is within 72 hours of the next scheduled dose. Advise patients to keep the capsules in the original packaging and not to remove the capsule from the packaging until just prior to taking it.⁶ In cases when the patient vomits after taking the capsule, advise him or her not to repeat the dose but resume dosing at the time of the next scheduled dose. Follow safe practices in handling ixazomib capsules in case of capsule breakage by avoiding direct contact of the capsule contents with the skin and eyes. If there are no available medicine take-back programs or Drug Enforcement Agency authorized collectors, place any unused capsules in a sealable bag with used coffee grounds or pet litter when disposing in the trash.⁸

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Marizomib

Class: Proteasome inhibitor

Indication: Orphan drug for the treatment of malignant glioma

Dose: Recommended phase 2 dose as a single agent is 0.7 or 0.8 mg/m² IV over 10 minutes on days 1, 8, and 15 of a 28-day cycle

Dose modifications: Unknown

Common adverse effects: Fatigue, insomnia, nausea, vomiting, diarrhea, dizziness, headache, dysgeusia, anorexia, and infusion site pain

Serious adverse effects: Lymphopenia and anemia have been reported. At doses above the recommended phase 2 dose, hallucinations, dizziness, and unsteady gait have been reported.

Drug interactions: Unknown

Orphan Drug Status for Marizomib for Malignant Glioma

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Malignant primary brain tumors are relatively rare, comprising 1.4% of all new cancer diagnoses.¹ Gliomas account for approximately one-third of all primary brain lesions and are classified based on histology as grades 1 through 4. Malignant gliomas are grade 3 or 4 lesions and include glioblastoma multiforme (GBM), the most common and aggressive of these tumors.² The primary treatment for GBM is surgical resection; however, the majority of resected patients will experience recurrence of their disease. Adjuvant therapy for patients < 70 years old with good performance status includes a combination of temozolomide and radiation therapy. Patients > 70 years old or frail patients may receive temozolomide alone.³ Despite standard treatment, median overall survival for GBM is approximately 14 months and less than 10% of patients are alive 5 years after diagnosis.⁴

A novel strategy for the treatment of malignant glioma is proteasome inhibition. Proteasomes are responsible for the degradation of proteins that are damaged or no longer in use. Blockade of this function leads to accumulation of toxic proteins, resulting in cell death. Proteasome inhibition has considerably less effect in normal cells than in malignant cells, where it also is thought to stabilize tumor inhibitory factors.⁵ The proteasome pathway is already a validated therapeutic target in the treatment of multiple myeloma. Unfortunately, a phase 2 trial of bortezomib, a proteasome inhibitor approved for the treatment of multiple myeloma, in combination with the histone deacetylase inhibitor vorinostat, failed to prevent progression in patients with recurrent GBM.⁶ Marizomib is a second generation proteasome inhibitor derived from the marine bacterium *Salinospora tropica*. An intravenous (IV) formulation of marizomib has been administered in phase one trials and an oral formulation has been developed that has not yet entered clinical

testing. Preclinical models of GBM indicate that marizomib induces proteasome inhibition and death in glioblastoma cells.⁵

Marizomib possesses several characteristics that make it attractive for use in the setting of malignant glioma, in contrast to bortezomib. Marizomib possesses a more lipophilic structure than bortezomib, allowing for penetration of the blood-brain barrier. Marizomib binds the protease irreversibly and demonstrates a more potent blockade than bortezomib, a reversible inhibitor. While peripheral neuropathy and myelosuppression, particularly thrombocytopenia, are dose-limiting toxicities of bortezomib, marizomib has little effect on neural cells and does not appear to cause neurotoxicity. Additionally, marizomib use has not been commonly associated with myelosuppression.⁵

The IV formulation of marizomib has been given as a single agent and in combination with other agents to patients with both solid tumors and hematologic malignancies in phase one trials. Depending on the study, the maximum tolerated dose and recommended phase 2 dose for marizomib as a single agent is 0.7 or 0.8 mg/m² IV over 10 minutes on days 1, 8, and 15 of a 28-day cycle. The most common adverse events were fatigue (36%–70%), nausea (21%–70%), diarrhea (31%), injection site pain (24%–29%), dizziness (24%), and vomiting (21%–43%). Lymphopenia, anemia, dysgeusia, insomnia, anorexia and headache also have been reported. At doses above the maximum tolerated dose, transient visual hallucinations have been described, as well as dizziness and unsteady gait.^{7–9}

In November 2015, the U.S. Food and Drug Administration granted orphan drug status for marizomib for the treatment of malignant glioma. The drug can be obtained only through enrollment in a clinical trial. A phase 1 study of marizomib in combination with bevacizumab in malignant gliomas is currently enrolling patients with recurrent or progressive disease who have not received prior bevacizumab. Marizomib also has been designated as an orphan drug in multiple myeloma and is currently undergoing phase 1 testing in the relapsed refractory setting of this disease, in combination with pomalidomide and dexamethasone.¹⁰

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Necitumumab (Portrazza™)

Class: IgG1 human monoclonal antibody which is an epidermal growth factor receptor (EGFR) antagonist that *in vitro* leads to EGFR internalization, degradation, and antibody-dependent cellular cytotoxicity (ADCC) in cells expressing EGFR

Indication:

- First-line treatment of patients with metastatic squamous non-small cell lung cancer in combination with gemcitabine and cisplatin
- Not indicated for the treatment of non-squamous non-small cell lung cancer

Dose: Max 800 mg intravenous (IV) over 60 minutes on days 1 and 8 of each 3-week cycle prior to gemcitabine and cisplatin

Premedication:

- For first Grade 1/2 infusion-related reaction: diphenhydramine prior to future doses
- For second Grade 1/2 reaction: diphenhydramine, acetaminophen, and dexamethasone prior to future doses
- Correct electrolytes prior to infusion (magnesium, calcium, phosphorus, and potassium)

Dose modifications:

Infusion-related reactions (IRR)

- Grade 1: Reduce the infusion rate by 50%
- Grade 2: Hold infusion until resolution or Grade 1 and continue at 50% rate
- Grade 3 or 4: Permanently discontinue

Dermatologic toxicity

- Grade 3 rash or acneiform rash: Hold until Grade \leq 2, then resume at reduced dose of 400 mg for one cycle. May increase to 600 mg and 800 mg subsequently if symptoms are controlled.
- Permanently discontinue for Grade 3 rash or acneiform rash that does not resolve within 6 weeks, skin indurations/fibrosis, or rash that worsens at 400 mg dose.
- Grade 4: permanently discontinue

Warnings/Precautions: Increased risk of cardiopulmonary arrest (3%) and venous and arterial thromboembolic events (9% and 5%), hypomagnesemia (83%), dermatologic toxicities (79%), infusion-related reactions (1.5%), embryo-fetal toxicity: effective contraception during and 3 months after chemotherapy

Common adverse effects: Rash and dermatitis acneiform, nausea, and vomiting

Drug interactions: Increased AUC and C_{max} of gemcitabine by 22% and 63% respectively

Necitumumab: Monoclonal Antibody Human EGFR Receptor Antagonist

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Lung cancer is the most common cancer worldwide in men and second to breast cancer in women. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases and out of those, about 40% are adenocarcinomas and 25% squamous cell carcinomas. There will be an estimated 50,000 cases of squamous NSCLC cases in the United States in 2015 with approximately one-third diagnosed as stage IV disease.²⁻⁴ Metastatic squamous NSCLC is a difficult-to-treat form of lung cancer with few treatment options. The 5-year survival rate for patients with metastatic disease is less than 5%.⁵

Therapy goals for advanced NSCLC are, in most cases, survival prolongation and maintaining quality of life. Since cure is usually not achievable, there are multiple chemotherapy regimen options and no current standard of care. Patient characteristics play a significant role in choosing the most appropriate regimen. In the absence of mutations, usual therapy options are platinum-based, two-drug combinations that can be combined with bevacizumab in non-squamous histology, but not in squamous histology. Therapy continues for four to six cycles, followed by maintenance therapy for patients with stable disease.⁶ One of the cornerstones of NSCLC treatment is the ability to use mutation-guided chemotherapy. Therefore, for all patients with adenocarcinoma NSCLC, epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) status are strongly recommended. In EGFR positive status, for an effective therapy, Kirsten RAS (KRAS) status is also recommended. In contrast, in squamous type, because of a low probability of genetic mutation, genetic mutation studies currently are not recommended. Due to the newer drugs targeting genetic mutations in cell lines, adenocarcinoma NSCLC has received more attention within the last few years as most of the new drugs were developed for this indication. In contrast, treatments for squamous NSCLC did not show much progress during the last decade and platinum-based combinations seem to be the mainstay for chemotherapy options. Category 1 chemotherapy regimens contain a combination of two agents: cisplatin or carboplatin with gemcitabine, etoposide, docetaxel, paclitaxel, albumin-bound paclitaxel, or vinorelbine. Non-platinum regimens include gemcitabine combinations with paclitaxel or vinorelbine. Single agent therapy options are irinotecan, paclitaxel or vinorelbine.⁶

The approval of necitumumab as an add-on therapy to a platinum-combination is potentially the first step in aiming at specific targets in squamous NSCLC. Necitumumab is a monoclonal antibody against epidermal growth factor receptor (EGFR), a receptor that is expressed in higher concentrations in squamous NSCLC. Interestingly, it is not approved for non-squamous NSCLC and colorectal cancer, although both of these diseases share an increased expression of EGFR similar to squamous NSCLC. In fact, necitumumab does not show efficacy as an add-on to all platinum combinations. In particular, it did not show efficacy in combination with cisplatin and pemetrexed and there are only a limited number of regimens where adding necitumumab improves survival.^{7,9}

The U.S. Food and Drug Administration granted orphan drug designation to necitumumab in 2015. Orphan drug status is based on the drug demonstrating potential for the diagnosis or treatment of rare diseases or conditions.

The SQUIRE Trial was the basis for necitumumab's approval which was an open-label, randomized, multi-center phase 3 trial which compared first-line treatment of metastatic squamous NSCLC using necitumumab in combination with gemcitabine and cisplatin versus gemcitabine and cisplatin alone.⁸ The trial enrolled 1,093 patients with stage IV squamous NSCLC and they were allowed to receive a maximum of six cycles in both treatment arms with overall survival (OS) being the primary endpoint. Patients that demonstrated at least stable disease on the necitumumab arm were able to receive additional cycles of single agent necitumumab until disease progression or unacceptable toxicity. Ninety-one percent had a baseline performance status (PS) 0–1, and 9% had PS 2. Of the patients enrolled, 91% had metastatic disease at two or more sites. The combination necitumumab arm showed a statistically significant improvement in OS, with a median OS of 11.5 months (95% confidence interval (CI): 10.4–12.6), as compared to the gemcitabine plus cisplatin alone arm of 9.9 months (95% CI: 8.9–11.1). The progression-free survival (PFS) in the necitumumab combination arm was 5.7 months (95% CI: 5.6–6.0) and for the gemcitabine plus cisplatin arm was 5.5 months (95% CI: 4.8–5.6; $p = .02$). There was no difference in overall response rate (ORR) with the necitumumab combination arm at 31% (95% CI: 27–35) and the gemcitabine and cisplatin arm at 29% (95% CI: 25–33; $p = .40$). Side effects in the trial included cardiopulmonary arrest or sudden death which occurred in 15 (3%) of 538 patients treated with the necitumumab combination arm as compared to three (0.6%) of 541 patients treated with gemcitabine and cisplatin alone. The adverse reactions most commonly observed in the necitumumab-treated patients were rash (44% versus 6%), vomiting (29% versus 25%), diarrhea (16% versus 11%), dermatitis acneiform (15% versus 0.6%), and hypomagnesaemia (83% versus 70%). The most common severe (grade 3 or higher) adverse events in the necitumumab-treated arm were venous thromboembolic events (5%; including pulmonary embolism), rash (4%), and vomiting (3%).⁸

Necitumumab currently is not recommended in non-squamous NSCLC patients and the results of the INSPIRE trial confirmed this.⁹ The INSPIRE trial randomized 633 patients with advanced

non-squamous NSCLC to receive either first-line chemotherapy with cisplatin 75 mg/m² and pemetrexed 500 mg/m² on day 1 of a 3-week cycle for a maximum of six cycles along with the addition of necitumumab 800 mg on day 1 and 8 of each cycle ($n = 315$) or standard cisplatin and pemetrexed at the same doses ($n = 318$). The OS was 11.3 months (95% CI, 9.5–13.4) in the necitumumab-combination arm versus in the non-necitumumab arm was 11.5 months (95% CI, 10.1–13.1; $p = .96$). Grade 3 or higher adverse events were more prevalent in the necitumumab combination group including deaths regarded as being related to study drug which were found in 15 (5%) of the necitumumab combination arm versus 9 (3%) in the cisplatin and pemetrexed arm. Adverse events that were seen as serious were also higher in the necitumumab combination arm (51% versus 41%). Patients also experienced more grade 3–4 rash (15% versus < 1%), hypomagnesaemia (8% versus 2%), and grade 3 or higher venous thromboembolic events (8% versus 4%). Due to these results, necitumumab currently is not recommended for patients with advanced non-squamous NSCLC as first-line chemotherapy.⁹

Currently, necitumumab represents a novel therapy to treat squamous NSCLC and highlights the need for further receptor based therapies for this type of tumor. It is also currently being investigated with other combinations for squamous NSCLC, recurrent squamous NSCLC, and potentially other solid tumor types. Due to the high cost, the data and potential side effects need to be thoroughly reviewed with the patient prior to consideration as a treatment mainstay.

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Osimertinib (Tagrisso™)

Class: Tyrosine kinase inhibitor (TKI), epidermal growth factor receptor (EGFR) inhibitor

Indication: EGFR T790M mutation positive non-small cell lung cancer (NSCLC), who have progressed on or after EGFR TKI therapy

Dose: 80 mg once daily

Dose modifications: Dose can be reduced to 40 mg once daily. Osimertinib should be permanently discontinued for patients who develop interstitial lung disease (ILD) or pneumonitis, QTc interval prolongation with signs of life-threatening arrhythmia, symptomatic congestive heart failure, or asymptomatic, absolute decrease in LVEF of 10% from baseline and below 50% not resolved on up to 4 weeks holding therapy. Specific parameters for dose reductions are provided in the package information.

Common adverse effects: Diarrhea, rash, dry skin, and nail toxicity

Serious adverse effects: Interstitial lung disease/pneumonitis, QTc prolongation, and cardiomyopathy

Drug interactions: Strong CYP3A4 inhibitors and inducers may affect the concentration of osimertinib; osimertinib may affect the concentrations of drugs that are substrates of CYP3A4, BCRP, or CYP1A2 with narrow therapeutic indices

Osimertinib for EGFR T790M-Mutated NSCLC after Progression on Other EGFR TKI Therapy

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The most common sensitizing EGFR mutations found in NSCLC are deletions in exon 19 (45%) and a mutation in exon 21 (40%). These mutations more commonly are found in Asian patients versus Caucasian patients (50% versus 10%). Insertion mutations in exon 20 are associated with resistance to EGFR TKIs; however, it is rare to find these mutations *de novo*. The EGFR T790M mutation, reported in about 60% of patients, is the most common acquired resistance mutation found after progression on erlotinib, gefitinib, and afatinib, and usually occurs after anywhere from 8–16 months of therapy.¹ Osimertinib (AZD9291) is a 3rd-generation EGFR TKI targeted toward the T790M mutation, and was granted accelerated approval for the treatment of EGFR T790M mutation-positive NSCLC, as detected by a U.S. Food and Drug Administration (FDA)-approved test in those who have progressed on or after EGFR TKI therapy.

Osimertinib was approved in November 2015 based on two multicenter, single-arm, open-label clinical trials. Both studies included patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI. Patients who received two or more prior lines of therapy made up 70%

and 68% of the study population in the first and second studies, respectively. The primary outcome of objective response rate (ORR) reported in the two studies was 57% (95% confidence interval [CI]: 50%–64%) and 61% (95% CI: 54%–68%). Survival outcomes of progression-free survival and overall survival have yet to mature.² Afatinib originally was studied in hope of overcoming the T790M resistance mutation, however in the LUX-Lung 4 trial for afatinib after progression on erlotinib, gefitinib, or both, the ORR was 8.2% (95% CI: 2.7%–18.1%).³ Current National Comprehensive Cancer Network (NCCN) recommendations for progressive EGFR-positive NSCLC include switching to osimertinib, continuing erlotinib, afatinib, or gefitinib with (or without) local therapy, or switching to chemotherapy.¹

In a phase 1 dose-finding study with 253 patients receiving osimertinib, no dose-limiting toxic effects occurred at doses ranging from 20 mg–240 mg. Patients included in the trial had known EGFR TKI-sensitizing mutation (or had benefit on said TKI therapy) and had documented progression on therapy; there was no upper limit for number of prior therapies. The most common adverse effects reported were diarrhea (47%), rash (40%), nausea (22%), and decreased appetite (21%). Patients were assessed for T790M positivity and for correlated response. ORR for all patients was 51% (95% CI: 45%–58%), 61% for patients with T790M (95% CI: 52%–70%), and 21% for patients without T790M (95% CI: 12%–34%). Median progression-free survival was 8.2 months overall, 9.6 months in T790M positive patients, and 2.8 months in T790M negative patients.⁴

Osimertinib is supplied as 80- and 40-mg tablets. Osimertinib can be taken with or without food, although the C_{max} and AUC increase by 14% and 19% respectively with a high-fat, high-calorie meal compared to fasting conditions. For patients who have difficulty swallowing solids or for those with feeding tubes, osimertinib can be prepared in liquid form by stirring the tablet in 4 tablespoons of noncarbonated water until completely dispersed. The container should then be rinsed with 4–8 ounces of water and immediately administered orally or through tube. The mean volume of distribution is 986 L and estimated elimination half-life is long at 48 hours. CYP3A4 is the primary metabolic pathway for osimertinib, making it pertinent to check for drug interactions with strong CYP3A4 inhibitors and inducers, as it is recommended that these agents be avoided. Osimertinib is also a substrate of P-glycoprotein and BCRP, however the clinical significance of this has yet to be documented. Osimertinib inhibits CYP3A4 and BCRP and induces CYP3A4 and CYP1A2 and thus may affect concentrations of medications utilizing these pathways, especially those with narrow therapeutic indices. Avoidance of these medications with osimertinib is recommended. No dedicated studies have been performed in patients with renal impairment or hepatic impairment, therefore there are no recommendations of dosing osimertinib in patients with severe renal impairment or moderate to severe hepatic impairment.⁵

There are a plethora of ongoing trials for osimertinib.^{6,7} There are studies continuing to investigate osimertinib alone and in combination with other therapies for resistant/progressive disease, as well as formal

drug interaction studies. There also are trials investigating osimertinib as adjuvant therapy for NSCLC and against chemotherapy for EGFR-progressive disease.⁷ Osimertinib is a novel, needed option for patients who have progressed after first-line EGFR therapy, whether they possess the T790M mutation or not.

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Uridine Triacetate (VISTOGARD®)

Class: Antidote

Indication: Emergency treatment following a fluorouracil or capecitabine overdose regardless of the presence of symptoms, or in patients who exhibit early-onset, severe, or life-threatening toxicity affecting the cardiac or central nervous system and/or early-onset, unusually severe adverse reactions (e.g., gastrointestinal toxicity or neutropenia) within 96 hours following the end of fluorouracil or capecitabine administration

Dose: *Adult patients:* 10 grams orally every 6 hours for 20 doses administered as soon as possible after an overdose or early-onset toxicity. Administer a full course of 20 doses as directed. If vomiting occurs within 2 hours of dose ingestion, administer another complete dose as quickly as possible, then proceed with next dose at regularly scheduled time.

Pediatric patients: 6.2 g/m² orally every 6 hours for 20 doses (max dose: 10 grams). Measure dose using a scale accurate to at least 0.1 gram, or a graduated teaspoon accurate to ¼ teaspoon.

Administration: Mix packet with 3 to 4 ounces of soft food and ingest without chewing within 30 minutes. Drink at least 4 ounces of water with each dose. Nasogastric or gastrostomy tube administration is permitted, when necessary.

Dose modifications: None

Common adverse effects: In clinical trials, the most common adverse events were vomiting (10%), nausea (5%), and diarrhea (3%).

Drug interactions: No *in vivo* data currently available. *In vitro*, drug interactions are possible as the agent is a P-gp inhibitor. Bismuth, sucralfate, and cholestyramine should be avoided as they may interfere with absorption.

Uridine Triacetate for Emergency Treatment of Fluorouracil or Capecitabine Toxicity

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Fluorouracil (5-FU), and its pro-drug capecitabine, are pyrimidine antimetabolite agents utilized in the treatment of breast and gastrointestinal malignancies, and other solid tumor cancers. These agents have a narrow therapeutic index and use is sometimes limited by severe gastrointestinal and hematologic toxicity. Factors contributing to overexposure may include errors with ambulatory infusion pump programming, miscalculations, and device malfunctions.¹ In addition, patients with genetic abnormalities such as dihydropyrimidine dehydrogenase deficiency may also be at risk for overexposure.¹ Toxicities may begin to manifest in the first 3 to 8 days following drug administration and may include nausea, vomiting, diarrhea, and anorexia, potentially followed by mucositis and gastrointestinal bleeding. These symptoms may subsequently progress to dehydration, systemic

infection, and sepsis. Ultimately, severe fluorouracil toxicity can be fatal and it has been reported that more than 1,300 deaths occur in the United States each year as a result of 5-FU exposure.²

Fluorouracil is a fluorinated analogue of uracil, a naturally occurring pyrimidine. Uridine is a pyrimidine nucleoside which is part of the same biochemical pathway as fluorouridine triphosphate (FUTP), a metabolite of fluorouracil.¹ Uridine is converted to uridine triphosphate (UTP) and can therefore be effective as an antidote by competitively inhibiting the incorporation of FUTP into RNA.¹ In recent years, uridine triacetate, an acetylated prodrug of uridine, has been made available through an orphan drug program from Wellstat Therapeutics (previously Vistonuridine®). On December 11, 2015, the U.S. Food and Drug Administration (FDA) granted approval with orphan drug designation to uridine triacetate oral granules (VISTOGARD® granules, Wellstat Therapeutics Corporation) for emergency use in adult and pediatric patients following fluorouracil or capecitabine overexposure or in the setting of severe or life-threatening adverse events within 4 days of treatment with either agent. Safety and efficacy when initiated > 96 hours following the end of fluorouracil or capecitabine administration has not been established.

FDA approval of VISTOGARD® was based on two single-arm, open-label, expanded access clinical studies, which included 135 adult and pediatric patients who had either received an overdose of 5-FU or capecitabine, or had early-onset, unusually severe or life-threatening toxicities within 96 hours after chemotherapy administration.³ The primary outcome was survival at 30 days or resumption of chemotherapy, if prior to 30 days. Results demonstrated that 97% of patients who received the medication to treat an overdose of 5-FU or capecitabine, as well as 89% of patients who were treated for early-onset or life-threatening toxicity, were still alive 30 days later when uridine triacetate was administered within 96 hours following chemotherapy administration. Thirty-three percent of patients were able to resume chemotherapy in less than 30 days. These results are in contrast to results demonstrating that 84% of patients receiving supportive care only died following fluorouracil overdose.

VISTOGARD® is an important antidote for patients who may be experiencing life-threatening toxicity following 5-FU or capecitabine administration; however, this agent should be reserved for emergency situations only as VISTOGARD® may reduce the efficacy of the chemotherapy agent previously administered.³

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