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Basal Cell Carcinoma and the Hedgehog Signaling Pathway

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Nonmelanoma skin cancers are the most common type of cancer in the United States with an estimated 3.5 million cases diagnosed annually.[1] Basal cell carcinoma and squamous cell carcinoma are both nonmelanoma skin cancers, of which basal cell carcinoma is diagnosed four to five times more frequently than squamous cell carcinoma.[2] Basal cell carcinoma is rarely lethal; however, it can be significantly disfiguring. There have been multiple risk factors identified for the development of basal cell carcinoma; the major cause is exposure to ultraviolet radiation.[3] Most cases of basal cell carcinoma are detected early and are treated with surgical resection.[2] Until the recent approval by the U.S. Food and Drug Administration (FDA) of vismodegib, there was no standard therapy recommendation for patients with basal cell carcinoma and regional or distant metastases; although varied, the median survival for these patients was 8 months.[4,5] Because of the dismal prognosis for patients with locally advanced unresectable and metastatic basal cell carcinoma, coupled with the limited number of available treatment options, many patients are encouraged to participate in clinical trials. Current clinical trials are exploring hedgehog pathway inhibition for the treatment of basal cell carcinoma.

The hedgehog pathway was first discovered in *Drosophila* by Christiane Nüsslein-Volhard and Eric Weischaus in the early 1980s; their research received a Nobel Prize in 1995.[6] Under physiologic conditions, the hedgehog pathway has a large role in normal embryonic development. It is responsible for determination of cell fate as well as cell growth, survival, and differentiation.[7] Although discovered and researched most frequently in *Drosophila,* the hedgehog pathway is a highly conserved pathway, playing a large role in human development during embryogenesis.[8] In adults, the hedgehog pathway is inactive in most cells.

Normal hedgehog signaling is activated through the binding of one of the hedgehog ligands to patched homologue 1 (PTCH1), a 12-transmembrane receptor. PTCH1 inhibits the activity of smoothened homologue (SMO), a 7-transmembrane G-protein coupled-like receptor. The binding of the hedgehog ligand to PTCH1 prevents PTCH1 from inhibiting SMO, leading to downstream activation of the hedgehog pathway. SMO signaling leads to activation of transcription factors encoded by GLI family zinc finger (GLI). This activation of transcription factors ultimately leads to transcription and translation of the hedgehog target genes.[7-9]

Because of the involvement of the hedgehog pathway in cell growth and survival, it was postulated that

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activation of this pathway in adult tissues could play a role in the development of cancer. Research has shown activation of the hedgehog pathway in several different types of malignancies, including basal cell carcinoma, medulloblastoma, multiple myeloma, and breast cancer.[10] The primary mechanism for hedgehog pathway activation in most solid and hematologic malignancies is through a ligand-dependent mechanism.[11,12] This ligand-dependent activation can occur through either an autocrine mechanism, where the cancer cells secrete hedgehog ligand and respond to it, or through a paracrine mechanism, where cancer cells or other cells within the tumor microenvironment secrete hedgehog ligand but different cells respond to it.[11,12] However, in basal cell carcinoma, the primary mechanism through which the hedgehog pathway is activated is ligand independent. Most basal cell carcinomas have loss of function mutations in PTCH1 or gain of function mutations in SMO that lead to constitutively activated hedgehog pathway signaling.[13,14]

Approximately 90% of sporadic basal cell carcinomas have loss of function mutations in PTCH1 and about 10% have gain of function mutations in SMO, leading to activated hedgehog signaling through ligand-independent mechanisms.[15] This finding has prompted research in the area of inhibiting the hedgehog pathway to treat this type of malignancy. Several hedgehog pathway inhibitors are currently undergoing clinical trials in multiple different types of solid and hematologic malignancies. Most evidence for hedgehog pathway inhibition has shown benefit in cell line and animal models, but clinical trial evidence of benefit to humans has been limited. To date, only one hedgehog pathway inhibitor has been approved for the treatment of locally advanced and metastatic basal cell carcinoma.

Vismodegib (Erivedge™) is a selective small-molecule inhibitor of the hedgehog pathway that works as an SMO inhibitor.[16] Downstream activation of hedgehog target genes is blocked through the binding of vismodegib to SMO. Vismodegib was approved through an FDA priority review in January 2012 for the treatment of locally advanced (not amenable to surgery or radiation) and metastatic basal cell carcinoma based on data from phase 1 and 2 clinical trials.[16] In an open-label, multicenter, two-stage phase 1 clinical trial, 68 patients with multiple types of solid tumors refractory to standard therapy were enrolled; of these, 33 patients had locally advanced or metastatic basal cell carcinoma.[17] The overall response rate was 50% for patients with metastatic disease and 60% for patients with locally advanced tumors.[17] In the phase 2 clinical trial Erivance BCC, 104 patients with locally advanced or metastatic basal cell carcinoma were enrolled.[18] The objective response rate was 30% for patients with metastatic disease and 43% for patients with locally advanced disease.[18] The median progression-free survival was 9.5 months for the entire cohort.[18] In both of these clinical trials, the most common adverse events were muscle spasms, fatigue, hyponatremia, dysguesia, anorexia, nausea, diarrhea, and alopecia.[17,18] Vismodegib was approved at a dose of 150 mg PO (capsule) once daily.[16]

The hedgehog pathway has been shown to contribute to the development of cancer through both ligand-dependent and ligand-independent mechanisms. The approval of vismodegib has opened the possibility for use of hedgehog pathway inhibitors not only in the treatment of basal cell carcinoma, but also in many other solid and hematologic malignancies. There are additional hedgehog pathway inhibitors currently in clinical development, most of which are in the early phases of clinical trials. Although vismodegib appears to be beneficial in the treatment of basal cell carcinoma with current clinical trial data, it will be imperative to assess long-term outcomes with this new drug to ensure continued safety and efficacy. Although there is still much to learn about the hedgehog pathway and its role in the development of cancer, hedgehog pathway inhibitors have the potential to benefit patients across a wide spectrum of malignancies.

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Nominations for HOPA Membership Awards Now Being Accepted

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The HOPA Nominations & Awards Committee is now accepting nominations for the 2013 Membership Awards Program. Learn more and nominate a qualified candidate today at www.hoparx.org. The deadline for nominations is October 7, 2013.

Regorafenib (Stivarga): Extended Indication for Gastrointestinal Stromal Tumors (GIST)

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Gastrointestinal stromal tumors (GIST) are the most common neoplasms affecting the gastrointestinal tract and predominately originate in the stomach lining. GIST have an estimated incidence of 3,000 new cases identified per year and generally occur in adults aged 66 to 69 years.[1] Surgical resection remains first-line treatment for primary localized GIST, while metastatic and locally advanced tumors are more complex. During the past decade, increased identification of the molecular components of GIST has improved treatment options for unresectable and metastatic GIST and significantly increased survival for patients.[2]

More than 80% of GIST are identified to have an overexpression of the proto-oncogene KIT (c-KIT), which is believed to cause gain-of-function mutations. Tumors positive for the KIT proto-oncogene express a protein called CD117, which is a cell surface marker detectable by immunohistochemistry (IHC) and can assist in tumor diagnosis. KIT-negative GIST (5%–10%) may contain activating mutations in another receptor kinase: platelet-derived growth factor receptor alpha (PDGFRA). Those with neither mutation are considered wild-type and occur in 10%–15% of GIST.[3] In general, mutations of the KIT gene involve primarily exons 11 and 9, whereas mutations in PDGFRA involve exon 18.[1,2] Increased understanding of the molecular and genetic components of GIST has provided molecular targeted therapies that have revolutionized systemic therapy options for advanced disease.

The first orally active tyrosine kinase inhibitor (TKI) approved for the treatment of metastatic or advanced GIST was imatinib (Gleevac®) in 2002. A potent inhibitor of KIT and PDGFRA pathways, it provided a median progression-free survival (PFS) of 24 to 26 months and median overall survival (OS) of 5 years in advanced GIST patients. Disease progression occurred in 50% of patients treated within 2 years of therapy.[1,2] Dose escalation from 400 mg to 800 mg per day assisted with disease stabilization in approximately 30% of patients treated. Almost 10%–15% of GIST tumors are inherently resistant; however, the majority of acquired resistance is due to secondary mutations in the KIT gene or KIT amplification.[4] Despite risk of resistance, imatinib remains the primary treatment option for unresectable or metastatic disease.[1,3]

An alternative TKI, sunitinib (Sutent®), was approved in 2006 for patients intolerant to imatinib or imatinib-refractory and is given as 50 mg daily every 4 out of 6 weeks. Similar to imatinib, sunitinib is a multitargeted TKI with an affinity for KIT; vascular endothelial growth factor receptors 1, 2, and 3 (VEGFR 1-3); and PDGFRA. It possesses both antitumor and anti-angiogenic properties and is a more potent inhibitor of KIT.[2] Clinical benefit was identified in mutations involving exons 9 (58%) and 11 (34%) as well as wild-type mutations (56%). During a phase 3 placebo-controlled trial, sunitinib demonstrated a PFS of 24 weeks versus 6 weeks with placebo and an OS of 73 months versus 65 months, respectively.[4] It is thought that resistance to sunitinib may occur by a similar mutational pathway seen in imatinib-resistant GIST.

Regorafenib (Stivarga®), approved in February 2013, offers a new therapeutic option for patients with unresectable or metastatic GIST who failed primary and secondary therapies with imatinib and sunitinib.[5] In addition to inhibition of KIT, VEGFR 1-3, and PDGFR, regorafenib offers added benefit from mutational resistance in KIT and PDGRFA kinases. It displayed initial benefit in imatinib- and sunitinib-refractory patients during a phase 2 trial of 33 patients with prior disease progression on imatinib and sunitinib failure. Patients completed at least two cycles (28 days per cycle with 21 days of daily treatment followed by 7 days off) of regorafenib 160 mg daily to be accessed. Clinical benefit was achieved in 78% of patients, of which four patients achieved a partial response (PR) and 22 patients exhibited stable disease (SD) lasting longer than 16 weeks. Regorafenib demonstrated a median PFS of 10 months in these patients.[6]

Recently, the GIST-Regorafenib in Progressive Disease (GRID) trial demonstrated clinical benefit in a phase 3 randomized, double-blind, placebo-controlled, cross-over study of 199 metastatic or unresectable GIST patients. A 2:1 randomization was conducted, resulting in 133 patients receiving regorafenib 160 mg daily and 66 patients receiving placebo. Both patient groups received best supportive care (excluding additional antineoplastic therapy) concurrently during the 28-day cycle of 21 days on and 7 days off treatment. The primary endpoint was PFS; patients receiving placebo whose disease progressed could cross-over to receive open-label regorafenib. Patients treated with regorafenib had a median PFS of 4.8 months compared with 0.9 months for the placebo group (hazard ration [HR] 0.27, 95% confidence interval [CI]: 0.19-0.39; $p < .0001$). Patients in the placebo group who crossed over to open-label regorafenib ($n = 56$) demonstrated a PFS of 5 months after initial disease progression.[7]

A secondary endpoint of OS showed no significant difference between placebo (26%) and regorafenib (22%; HR 0.77, 95% CI: 0.42-1.41; $p = .199$). Of note, OS evaluation included placebo patients who switched to open-label regorafenib. An additional secondary endpoint of disease control rate, measured as at least a PR or complete response (CR) plus standard deviation of <12 weeks, was shown in six regorafenib patients and one placebo patient. Adverse events related to regorafenib therapy included hand-foot skin reaction (56%), hypertension (49%), and diarrhea (40%).[7] Discontinued therapy due to adverse events occurred in eight patients in the regorafenib group (6%) compared with five patients (8%) in the placebo group, although drug modifications occurred more frequently in the regorafenib group. As a third-line agent for refractory GIST patients, regorafenib significantly improves PFS in patients who previously failed other TKI therapy and offers additional benefit over placebo with relatively manageable adverse effects.[7,8]

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Summary of NCCN 2013 Oncology Pharmacy Best Practices Webinar Series

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In April, the National Comprehensive Cancer Network® (NCCN) hosted an Oncology Pharmacy Best Practices webinar series designed to meet the educational needs of pharmacists. The NCCN acknowledges the important role pharmacists play in the clinical decision-making process both in the care of patients and the drug-use policy process. The five webinars hosted by the NCCN focused on emerging data and current trends relating to formulary management, reimbursement, legislative issues, and therapeutic management challenges increasingly encountered by today's oncology pharmacist.

Mark Smith, a partner of Liberty Partners Group, LLC, was the first speaker in the series. He provided participants an overview of legislation aimed at addressing the all-too-familiar problem of drug shortages as well as regulatory issues surrounding biosimilars and their incorporation into clinical practice. Historical data on drug shortages were presented in conjunction with federal efforts to mitigate or prevent medication shortages. The positive impact of these policies was detailed along with some remaining challenges. With respect to biosimilars, Smith highlighted federal legislation and regulations affecting this relatively new class of medications. The session ended with a detailed discussion on the U.S. Food and Drug Administration (FDA) draft guidance on scientific considerations in determining biosimilarity to a reference product.

The next installment in the webinar series was a review of new and emerging oncology drugs and biologics facilitated by two of our HOPA colleagues—Hillary Prescott, PharmD BCOP, University of Texas MD Anderson Cancer Center; and Bradley Burton, PharmD BCOP CACP, Johns Hopkins Hospital. Prescott focused on bosutinib (second-generation tyrosine kinase inhibitor), ponatinib (third-generation tyrosine kinase inhibitor), and omacetaxine mepesuccinate (a first-in-class cephalotaxine), all of which were approved by the FDA in late 2012 for the treatment of chronic myelogenous leukemia. Clinical data, toxicities, dosing modifications, and important drug-drug interactions for each agent were outlined. Prescott concluded by noting each medication's place in therapy within the NCCN Guidelines® *Chronic Myelogenous Leukemia* (Version 4.2013). The focus of the webinar shifted to recently approved oncologic drugs for the treatment of solid tumors. Burton provided his clinical expertise on pertuzumab, ziv-aflibercept, and vismodegib, drugs with FDA-approved indications for metastatic breast cancer, metastatic colorectal cancer, and basal cell carcinoma, respectively. Therapeutic targets, clinical efficacy, and safety data were summarized for these three newly marketed targeted agents.

Rebecca Johnson, MD, Seattle Children's Hospital, was the host for the program dedicated to pharmacy implications for managing adolescent and young adult (AYA) patients with cancer, a topic that continues to garner national interest. Johnson introduced the subject by reviewing the epidemiology of cancers in this patient group, a population defined by the National Cancer Institute as being between the ages of 15 and 39 years. The unique medical and psychosocial issues of AYA patients were mentioned before the focus of the discussion turned to comparisons of AYA patient outcomes according to tumor type, treatment protocol, and location of medical service delivery. To end the session, Johnson summarized the NCCN Guidelines® *Adolescent and Young Adult (AYA) Oncology* (Version 1.2012), emphasizing patient care aspects such as dosing recommendations, toxicity management, promotion of medication adherence, and follow-up recommendations for survivors, all of which are outcomes pharmacists can positively impact.

Implications of obesity in oncology care continue to be a topic of interest as evidenced by recent traffic on the HOPA Listserv. This subject was the focus of the fourth webinar, presented by Jennifer Griggs, MD MPH, University of Michigan Comprehensive Cancer Center. Griggs identified the leading theories regarding the relationship between cancer and obesity and then summarized outcome data in

obese cancer patients, recognizing several factors that have contributed to disparities in outcomes among this patient population. Much of the presentation was devoted to analyzing chemotherapy prescribing patterns in obese patients and their influence on survival as well as the development of therapy-related toxicities. The activity ended with Griggs reviewing the recommendations listed in the recently published American Society of Clinical Oncology (ASCO) clinical practice guidelines on appropriate chemotherapy dosing for obese adult patients with cancer.[1] In addition, Griggs noted there are several clinical tools and resources available in an electronic format (www.asco.org/guidelines/wbd), which accompany these guidelines, to further aid healthcare practitioners in addressing the clinical conundrum of chemotherapy dosing in obese adult patients.

The final installment of this webinar series focused on trends in oncology reimbursement and was presented by Pamela Germain, MBA, Roswell Park Cancer Institute; and Ranae Dahlberg, BSN RN, UnitedHealthcare. Germain opened the session discussing the current landscape of reimbursement strategies for oncology drug products in both inpatient and outpatient healthcare facilities. She then noted several forces influencing changes to reimbursement structures, warning of the approach of a perfect storm as the forces of an aging population, rising healthcare costs, an increasing federal deficit, and a growing shortage of healthcare professionals in oncology care converge. Next, Dahlberg illustrated a few examples of cost-savings strategies within her organization, including adherence to evidence to drive coverage of high-cost medications (such as bevacizumab) and using analytics to identify gaps in care and new methods for contracting. At the end of the program, participants were offered several helpful hints to maximize the chance for successful reimbursement within their workplace settings.

Want to learn more about these topics? Visit NCCN's website portal dedicated to this series (http://education.nccn.org/oncology-pharmacy) where you can view the recorded presentations and download the handouts. Each of the five activities is ACPE accredited for continuing pharmacy education credit (0.5–1 hour of credit/session). This webinar series, supported by an educational grant from Amgen, is available free of charge through May 10, 2014.

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Recalls, Withdrawals, and Safety Alerts from the FDA

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Lowlite Investments d/b/a Olympia Pharmacy (Lowlite) announced a voluntary multistate recall of all sterile drug products compounded by the pharmacy with a use-by date of September 25, 2013, or earlier. The recall is being initiated due to concerns associated with prior quality control procedures that impacted sterility assurance.

To date, Lowlite has received no reports of injury or illness associated with the use of their sterile products. This voluntary recall is being conducted as a precautionary measure to ensure the sterility of their sterile products, and is being conducted with the full knowledge of the U.S. Food and Drug Administration (FDA; www.fda.gov/Safety/Recalls/ucm354450.htm).

For a list of recalled products, visit www.fda.gov/downloads/Safety/Recalls/UCM354451.pdf.

SynchroMed Implantable Infusion Pump Priming Bolus

Medtronic has issued an Urgent Medical Device Correction notification that provides physicians with important safety information and patient management recommendations regarding the SynchroMed Implantable Infusion System priming bolus function.

The priming bolus function is used to quickly move a drug from the SynchroMed pump reservoir to the catheter tip to initiate intrathecal drug delivery therapy while a patient remains under medical supervision. Medtronic has found that any time the priming bolus is used with a SynchroMed pump, drug mixes with the sterile water or cerebrospinal fluid already in the catheter, resulting in the unintended delivery of the drug prior to the end of the programmed bolus, as well as dilution of some of the drug remaining in the catheter at the end of the bolus. This can contribute to an increased risk of adverse events involving drug overdose or underdose following an initial system implant or revision.

Medtronic recommends healthcare professionals continue using the priming bolus procedure to ensure therapy is initiated while a patient is under medical supervision. Recommendations are being provided for performing a priming bolus, monitoring patients postimplant, and educating patients and caregivers. Medtronic continues to investigate factors related to this issue to determine appropriate product updates. The FDA has classified this notification as a Class I recall.

SynchroMed Implantable Infusion Pump Shorting

Medtronic has issued an Urgent Medical Device Correction notification to inform physicians about the potential for an electrical short within the SynchroMed pump.

An electrical short could lead to pump motor stall and a subsequent loss of or reduction in therapy, which can result in the return of underlying symptoms or withdrawal symptoms. The SynchroMed II pump is equipped with alarms designed to alert the patient in the event of a motor stall.

Medtronic encourages patients to contact their physicians immediately if they experience a return of symptoms or hear a device alarm.

The cumulative failure rate due to this issue is less than 1% at 7 years postimplant. Because of the estimated low occurrence rate, the alarm safety feature, and the risks associated with replacement surgery, Medtronic is not recommending removal of the devices unless a patient's pump shows signs of a malfunction. Medtronic is in the process of developing design updates to mitigate this issue. The FDA has classified this notification as a Class I recall.

SC Intrathecal Catheter Product Removal

Medtronic has redesigned its Sutureless Connector (SC) Catheter to reduce the potential for *occlusion,* which is the blockage or cessation of drug flow due to misalignment at the point where the catheter connects to an implantable pump. As a result, the company has initiated a voluntary removal of unused products manufactured before the catheter design change. To reduce the risk for occlusion, Medtronic strongly recommends that customers discontinue the use of all SC Catheter models 8709SC, 8731SC, 8596SC, and 8578 manufactured prior to the design change. These products are identified by a "use-by" date prior to August 25, 2014. The FDA has classified this notification as a Class I recall.

SynchroMed Implantable Infusion Pump Refill Procedure Safety Update

Medtronic is distributing a revised Clinician Refill Reference Card with information about the pump refill procedure for the SynchroMed Implantable Infusion System. The revised reference card reflects new product labeling approved by the FDA to help healthcare professionals reduce the potential for a pocket fill during the SynchroMed pump refill procedure. A *pocket fill* is the inadvertent injection during a refill procedure of all or some of the prescribed drug into the patient's subcutaneous tissue, which includes the pump pocket (area under the skin where the pump is placed), instead of into the pump. This is a continuation of a 2011 notification that was previously classified as a Class I recall.

For additional information on safety recalls, please visit www.fda.gov/Safety/Recalls/ucm359069.htm.

Hematology/Oncology Approvals and Safety Notifications

- **May 14, 2013:** FDA approved erlotinib (Tarceva, Astellas Pharma Inc.) for the first-line treatment of metastatic non-small cell lung cancer (NSCLC) patients whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. This indication for erlotinib is being approved concurrently with the cobas® EGFR Mutation Test, a companion diagnostic test for patient selection (www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm352317.htm).
- **May 15, 2013:** FDA approved radium Ra 223 dichloride (Xofigo Injection, Bayer HealthCare Pharmaceuticals Inc.) for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease. Xofigo is an alpha-particle-emitting radiotherapeutic drug that mimics calcium and forms complexes with hydroxyapatite at areas of increased bone turnover, such as bone metastases (www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm352393.htm).
- **May 29, 2013:** FDA approved dabrafenib (Tafinlar capsule, GlaxoSmithKline, LLC) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test (www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm354477.htm).
- **May 29, 2013:** FDA approved trametinib (Mekinist tablet, GlaxoSmithKline, LLC) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test (www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm354478.htm).
- **June 5, 2013:** FDA approved lenalidomide capsules (Revlimid, Celgene Corporation) for the treatment of patients with mantle cell lymphoma whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm355438.htm).
- **June 13, 2013:** FDA approved denosumab (Xgeva injection, for subcutaneous use, Amgen Inc.) for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity (www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm356667.htm).
- **July 12, 2013:** FDA approved afatinib (Gilotrif tablets, Boehringer Ingelheim Pharmaceuticals, Inc.) for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. The safety and efficacy of afatinib have not been established in patients whose tumors have other EGFR mutations. Concurrent with this action, FDA approved the therascreen EGFR RGQ PCR Kit (Qiagen) for detection of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm360574.htm).

For a full list of hematology/oncology approval and safety notifications, please visit www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm.

ISMP Medication Safety Alert!

- **May 2, 2013 (Volume 18, Issue 9):** Computer listings for generic doxorubicin liposomal injection should be verified because some computer systems are listing the medication without identifying it as the liposomal product (www.ismp.org/newsletters/acutecare/issues/20130502.pdf).
- **May 16, 2013 (Volume 198, Issue 10):** Because of name confusion with PAZOPanib (Votrient) and PONATinib (Iclusiq), computer systems should be updated to list the dose strengths and dosing information, as well as use tall man lettering for these agents (www.ismp.org/newsletters/acutecare/issues/20130516.pdf).
- **May 30, 2013 (Volume 18, Issue 11):** Pfizer's doxorubicin 200 mg/100 ml vial is labeled as "multidose," but contains no preservatives. The company states that the stopper can

be punctured multiple times when preparing several bags as long as they are being prepared at the same time. The vial should not be saved for future use once the stopper has been punctured (www.ismp.org/newsletters/acutecare/issues/20130530.pdf).

- **June 13, 2013 (Volume 18, Issue 12):** A reminder was issued for Cathflo® Activase®: final reconstituted solution must be filtered with a 5-micron filter upon withdrawal from the container (www.ismp.org/newsletters/acutecare/issues/20130613.pdf).
- **June 27, 2013 (Volume 18, Issue 13):** Mix-ups have occurred between leucovorin and LEVOleucovorin (Fusilev®). The dose of LEVOleucovorin is half the dose of leucovorin, which can result in incorrect dosing. Tall man lettering of LEVOleucovorin is recommended (www.ismp.org/newsletters/acutecare/issues/20130627.pdf).
- **July 11, 2013 (Volume 18, Issue 14):** The syringe pull-back method of verifying IV admixtures is unreliable when preparing admixtures that contain multiple additives. There is a potential for interchange for vials or syringes (www.ismp.org/newsletters/acutecare/issues/20130711.pdf).

Changes in Safety Labeling

- **April 2013:** None
- **May 2013:** www.fda.gov/Safety/MedWatch/SafetyInformation/ucm355680.htm
  - Gemcitabine: Precautions updated to include capillary leak syndrome
  - Ipilimumab: Precautions updated to include autoimmune central neuropathy (encephalitis), neurosensory hypoacusis, myositis, polymyositis, ocular myositis, and sarcoidosis
  - Rituximab: Precautions updated to include severe mucocutaneous reactions
- **June 2013:** www.fda.gov/Safety/MedWatch/SafetyInformation/ucm359843.htm
  - Docetaxel: Postmarketing events updated to include respiratory—dyspnea, acute pulmonary edema, acute respiratory distress syndrome/pneumonitis, interstitial lung disease, interstitial pneumonia, respiratory failure, and pulmonary fibrosis have rarely been reported and may be associated with fatal outcome. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.
  - Goserelin acetate: Postmarketing events updated to include acne and mood swings
  - Lapatinib: Warning and precautions, patient counseling information updated to include diarrhea
  - Nilotinib: Postmarketing events updated to include additional information regarding concomitant acid suppression medication
  - Paclitaxel protein-bound (Abraxane®): Adverse reactions updated to include sepsis and neutropenic sepsis
  - Sorafenib: Adverse reactions updated to include hypokalemia

Board Update

Niesha Griffith, RPh MS FASHP, HOPA President

It has been a busy summer for the HOPA Board, as well as many of our committee and task force members. We are excited to have welcomed a new executive director, planned our first fall meeting, launched three new health policy task forces, completed our Scope of Hematology/Oncology Pharmacy Practice document, and invited five applicants to submit full proposals for funding consideration by the HOPA Foundation. With the help of Jeremy Scott and Erin Morton, our government relations staff from Drinker Biddle & Reath (DBR), and Jordan Wildermuth, our health policy and advocacy manager, we continue to be actively involved in issues critical to our profession and our patients. Following our summer board meeting, a group of past and current HOPA leaders met to discuss ways to build leadership development into the HOPA organizational structure and educational program planning. Last but certainly not least, we are actively planning for our Annual Conference in New Orleans, including a 10th Anniversary Gala celebration!

An Enthusiastic Welcome and a Fond Farewell

We'd like to extend a welcome to Suzanne Simons, HOPA's new executive director. Suzanne comes to us with more than 25 years of association management experience and has a passion for leveraging her strategic leadership to advance healthcare practices and improve patient outcomes through collaboration, education, and empowerment. She recognizes the importance of bringing people together around a common cause to achieve mission objectives, and knows the value of cultivating and nurturing vital relationships. Suzanne sees great opportunity in HOPA's future and is looking forward to building on its solid foundation as it embraces the next phase of its development.

We would also like to thank Karen Nason for her service to HOPA. During her tenure as executive director, Karen helped HOPA navigate the transition to a new management company. She helped the association establish the HOPA Foundation and the Industry Relations Council. HOPA experienced steady growth with Karen at the helm—membership increased by approximately 17% from 2010 to 2013. Under her direction, the policies and procedures manual, critical to the everyday operations of the organization, was developed. Additionally, HOPA hired DBR, a government relations firm, to assist us in realizing our health policy and advocacy goals. Karen also led HOPA through the strategic planning process in 2010 and 2012. We are grateful for her dedication and hard work on behalf of our members.

Fall Oncology Pharmacy Practice Management Program

We are excited about the launch of our newest educational offering, the fall Oncology Pharmacy Practice Management Program. Registration has exceeded our expectations; 140 people have already signed up to attend the 1-day event in Chicago. The program will cover justification for clinical services, cost-containment, CPOE and Smart Pumps, maximizing reimbursement, and regulatory compliance, all topics of interest among oncology pharmacists. We have sold out our table-top exhibit space and exceeded our budget in obtaining commercial support funding.

Health Policy Updates

Three new workgroups have begun work on emerging issues in health policy related to hematology/oncology pharmacy, including provider status for pharmacists, access to pain management for cancer patients, and counterfeit drug prevention. Both the pain management and the counterfeit drug prevention workgroups will be publishing issue briefs for distribution to policy makers, while the provider status group will be providing background and recommendations to the Health Policy Committee on the pursuance of provider status for pharmacists.

HOPA submitted comments to the Center for Medicare & Medicaid Services (CMS) on the CY 2014 Physician Fee Schedule and the CY 2014 Hospital Outpatient Prospective Payment System. HOPA also signed on to the Cancer Leadership Council's letter of support for H.R. 2477, the Planning Actively for Cancer Treatment Act and sent separate letters to the sponsors, Rep. Lois Capps (D-CA) and Rep. Charles Boustany, Jr. (R-LA), stating the importance of the inclusion of hematology/oncology pharmacists in the development of cancer treatment plans. HOPA signed on to the Cancer Leadership Council's comments on the FDA's draft guidance for industry regarding four programs that are part of the effort to expedite review of drugs for unmet medical needs. Specifically, the draft guidance document provides important advice by describing the four programs—fast track, priority review, accelerated approval, and breakthrough therapy designation—in a single document and explaining the relationships among them.

Finally, HOPA member Sarah Hudson-DiSalle, RPh PharmD, attended the Patient Equal Access Coalition's (PEAC) lobby day in Washington, DC to educate Senators on the issue of oral chemotherapy parity and its impact on our patients. Sarah and Erin Morton from DBR met with the offices of Senators Tim Scott (R-SC), Pat Roberts (R-KS), Rob Portman (R-OH), Marco Rubio (R-FL), and the Senate HELP Committee Ranking Member Mike Enzi (R-WY). The goal of the lobby day was to try to secure a Republican who would cosponsor a Senate companion bill to H.R. 1801, the Cancer Drug Coverage Parity Act.

Scope of Hematology/Oncology Pharmacy Practice

We are excited to announce that the ***Scope of Hematology/Oncology Pharmacy Practice*** is in the final stages of the publication process. We plan to post the document onto the HOPA website in October to share it with the membership. We will support the release with a promotional campaign directed at trade publications, associations of interest, and consumer press. In addition, Task Force

Chair Laura Michaud, PharmD BCOP FASHP, and Lisa Holle, PharmD BCOP, will be submitting a summary of the work for publication. We would like to thank Laura and Lisa, along with the other contributors and reviewers, for all of their hard work on this very important document. Thanks to their efforts, HOPA has a foundational document that outlines the unique knowledge, skills, and abilities of oncology pharmacists to facilitate the provision of high-quality, team-based care of patients with cancer.

HOPA Foundation Grants

The HOPA Foundation Board reviewed 27 letters of intent and invited five applicants to submit full proposals. HOPA Foundation grant proposals were due on Monday, September 16. Final awards will be announced in November.

Leadership Task Force

On August 3, 2013, a task force of HOPA past and future leaders and key HOPA staff members met to explore recommendations to ensure ongoing and capable leadership for the association and to assist in developing leadership skills within the profession. Specifically, the purpose of the task force was to

- identify recommended changes to HOPA's Board and committee leadership structure and process
- determine how HOPA can assist in building leadership within the profession.

Recommendations from the task force will be submitted to the board at the November meeting and shared with the membership once approved.

10th Anniversary Gala

A task force has been assembled to start planning a 10th Anniversary Gala, to be held Friday, March 28, 2014, during the annual conference (March 26–29) in New Orleans, LA. The gala will highlight HOPA's accomplishments during its first 10 years, acknowledging HOPA's founders, past leaders, supporters, and industry partners, as well as highlight future direction and initiatives for the organization. This event will be hosted at The Chicory (located in the historic warehouse district, across the street from the conference hotel) and promises to be an opportunity for celebration, remembrance, networking, and most importantly, a good time! Stay tuned for additional details from the task force as we get closer to the date.

I want to thank all the HOPA members and staff for their hard work and for helping to make all of these great endeavors possible. Having committed volunteers has made HOPA the successful organization it is today and will be vital to our future growth and development.

HOPA Welcomes Suzanne Simons as Executive Director

HOPA is thrilled to welcome Suzanne Simons as our new executive director. She brings more than 25 years of successful association management experience in the healthcare sector. Most recently, she worked as an independent healthcare communications and public relations consultant with a client base that included companies from the pharmaceutical industry, public relations, and healthcare publishing with an emphasis on strategic counsel for development, disease awareness, and advocacy relations. Prior to consulting, Suzanne worked for the National Headache Foundation (NHF) of Chicago in various roles, most recently as the executive director of strategic projects where she served a leading role in helping to forge the NHF as a major health education and advocacy organization. She has also been the recipient of several awards including three Telly Awards, a Founders Award, and multiple awards for NHF's publications and programs.

Ado-Trastuzumab Emtansine (Kadcyla™)

Class: Antibody-drug conjugate; anti-HER2 and microtubule inhibitor
Indication: Metastatic, HER2-positive breast cancer patients who have previously been treated with trastuzumab and a taxane, separately or in combination
Dose: 3.6 mg/kg given as an intravenous infusion once every 21 days until disease progression or unacceptable toxicity
Dose modifications: Doses may be modified, held, or permanently discontinued based on toxicity: infusion-related reactions, hepatotoxicity, left ventricular cardiac dysfunction, peripheral neuropathy, thrombocytopenia, pulmonary toxicity. Do not re-escalate dose after implementing any dose reduction.
Common adverse effects: Thrombocytopenia, nausea, fatigue, musculoskeletal pain, headache, constipation, and increased transaminases
Serious adverse effects: Hepatotoxicity including liver failure and death, thrombocytopenia, cardiotoxicity, extravasation reactions, anaphylaxis, peripheral neuropathy, pulmonary toxicity, embryo-fetal toxicity
Drug interactions: Major substrate of CYP3A4; avoid concomitant use of strong CYP3A4 inhibitors.

Ado-Trastuzumab for the Treatment of Relapsed HER2-Positive Breast Cancer

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Breast cancer is the most common malignancy in females, affecting approximately 235,000 women in the United States annually.[1] It is estimated that more than 40,000 U.S. women will die from metastatic breast cancer in 2013.[1] Systemic treatment decisions are based not only on stage of disease at diagnosis and patient symptoms, but also take into consideration predictive factors including hormone receptor and HER2 status. The HER2 oncogene is overexpressed in approximately 20% of breast cancer diagnoses and it predicts a worse prognosis when amplified.[2] Currently, there are three agents available that target the HER2 oncogene: trastuzumab, lapatinib, and pertuzumab. The combination of these agents with cytotoxic chemotherapy is the current standard of care in the treatment of HER2-positive advanced breast cancers. It has also been shown that continuing HER2 oncogene inhibition once progressing on an anti-HER2 therapy leads to improved outcomes compared to discontinuation of anti-HER2 therapy.[3] Recently, a novel antibody-drug conjugate, ado-trastuzumab emtansine (T-DM1), was approved for the treatment of metastatic, HER2-positive breast cancer patients who have previously been treated with trastuzumab and a taxane, separately or in combination. This drug consists of two components. The first component, trastuzumab (T), is linked to an antimictrotubule agent, emtansine (DM1), through a stable nonreducible thioether link. The antibody-drug complex is internalized into HER2-overexpressing cells, and DM1 is released following proteolytic degradation inside the cell.[4] The targeted delivery of T-DM1 ultimately leads to apoptosis of malignant cells with minimal exposure to normal cells.

The safety and efficacy of T-DM1 was evaluated in a pivotal international phase 3 trial, EMILIA, which included 991 patients with HER2-positive unresectable, locally advanced, or metastatic breast cancer who had previously been treated with trastuzumab and a taxane.[5] Patients who had progressed during treatment for metastatic disease or who had recurrent disease within 6 months of adjuvant therapy were randomized in a 1:1 ratio to receive T-DM1 at a dose of 3.6 mg/kg intravenously every 21 days or lapatinib 1,250 mg orally daily plus capecitabine 1,000 mg/m^2 orally twice daily on days 1 through 14 of a 21-day cycle. Treatment continued until disease progression or unacceptable adverse events developed. Dose modifications for toxicities were allowed. Patients were stratified by location, number of prior chemotherapy regimens for advanced disease, and the presence of visceral disease. All patients were HER2 positive as confirmed by either immunohistochemical status (3+) or fluorescence in situ hybridization (amplification ratio ≥2), an Eastern Cooperative Oncology Group performance status of 0 or 1, and a left ventricular ejection fraction of 50% or more. Patients were excluded if they had received prior T-DM1, lapatinib or capecitabine treatment, grade 3 or higher peripheral neuropathy, symptomatic or recently treated central nervous system metastases, or significant cardiac disease history (symptomatic congestive heart failure, serious arrhythmia, history of myocardial infarction, or unstable angina within the previous 6 months). The primary endpoints of the study were progression-free survival (PFS) determined by independent review, overall survival (OS), and safety. Additional endpoints included objective response rates, time to symptom progression, and investigator-assessed PFS. Results of the study demonstrated a median PFS of 9.6 months in the T-DM1-treated arm compared with 6.4 months in lapatinib plus capecitabine–treated patients (stratified hazard ratio [HR] = 0.650, 95% confidence interval [CI]: 0.55–0.77; $p < .0001$). Subgroup analyses indicated this benefit across most subgroups with a few exceptions where the results were less well defined. PFS was not statistically different in patients 65 years of age or older or in patients with nonvisceral or nonmeasurable disease. Additionally, T-DM1-treated patients 75 years of age or older had a decreased PFS compared with the lapatinib-plus-capecitabine group. This subgroup of the population was small, accounting for only 2.5% of enrolled patients ($n = 25$). A 5.8-month improvement in median OS was demonstrated in T-DM1-treated patients compared with the lapatinib-plus-capecitabine group (30.9 months versus 25.1 months; $p < .001$). T-DM1 was found to be superior to lapatinib plus capecitabine in all secondary endpoints as well. Grade 3 or 4 adverse events rates were higher with the lapatinib-plus-capecitabine group than with T-DM1 (57% versus 41%) with elevated transaminases and thrombocytopenia most common in the T-DM1 arm. Additional adverse effects included a higher incidence of anemia, thrombocytopenia, elevated

transaminases, and fatigue seen with T-DM1 and a higher incidence of diarrhea, vomiting, nausea, mucositis, and hand-foot syndrome in the lapatinib-plus-capecitabine group. Rates of cardiac dysfunction were similar between groups and were low. The stratified HR for death from any cause with T-DM1 versus lapatinib plus capecitabine was 0.62 (95% CI: 0.48–0.81; p = .0005).

Additional adverse effect information outlined in the product's prescribing information is derived from safety results obtained from a total of 884 patients treated with T-DM1. These data were obtained from the phase 3 EMILIA trial, compiled with data from five additional studies (three phase 2 trials, one phase 1 trial, and one QTc study).[5-10] The most common (frequency ≥25%) adverse drug reactions seen in patients from this pooled data included fatigue, nausea, musculoskeletal pain, headache, thrombocytopenia, increased transaminases, and constipation. Warnings and precautions are also included for the following serious adverse events: hepatotoxicity including liver failure and death, thrombocytopenia, cardiotoxicity, extravasation reactions, anaphylaxis, peripheral neuropathy, pulmonary toxicity, and embryofetal toxicity.

T-DM1 is supplied in 100-mg and 160-mg single-use vials and is dosed at 3.6 mg/kg as an intravenous infusion every 3 weeks until disease progression or unacceptable toxicity.[11] Unlike trastuzumab, T-DM1 does not require a loading dose. T-DM1 cannot be substituted for trastuzumab. Doses greater than 3.6 mg/kg should not be administered. T-DM1 should be reconstituted in 5 mL of sterile water for injection (SWFI) for the 100-mg vial and 8 mL of SWFI for the 160-mg vial. Do not use dextrose (5%) solution. The reconstituted vial is stable for up to 4 hours in a refrigerator (2°C to 8°C). The vial should not be shaken or frozen. Though possible, infusion-related reactions are rare (1.4%) and no recommendations for premedications exist. The initial infusion should be administered through an in-line nonprotein adsorptive polyethersulfone filter (0.22 micron) over 90 minutes followed by a 90-minute observation for reactions. Subsequent infusions may be administered at an increased rate over 30 minutes if the first dose is well tolerated. A 30-minute observation is recommended following each subsequent administration. The infusion rate should be decreased or the dose temporarily held if a patient develops an infusion-related reaction. Permanently discontinue T-DM1 if a life-threatening or anaphylactic reaction occurs.

No dose modifications are recommended for mild to moderate renal impairment.[11] Dose modifications for hepatic and severe renal impairment (CrCl <30 ml/min) have not been fully investigated. However, multiple dose modifications and reductions for serious toxicities exist for T-DM1. When indicated, dose reductions should be downward in a stepwise fashion using 0.6-mg/kg increments. If a reduced dose is necessary, dose re-escalations should not be performed. If more than two dose reductions are indicated, T-DM1 should be discontinued. Serum transaminases, bilirubin, and platelets should be monitored prior to each dose of T-DM1 and dose modifications made if indicated. T-DM1 should be held for grade 3 increases in serum transaminases and resumed at one dose level reduction after transaminases have resolved to ≤ grade 2. Grade 4 elevations in serum transaminases require permanent discontinuation of T-DM1. T-DM1 dosage should also be delayed or modified for hyperbilirubinemia. If grade 2 or 3 hyperbilirubinemia occurs, future doses should be held until the total bilirubin level recovers to ≤1.5 x upper limit of normal (ULN). T-DM1 may be resumed at the same dose level with initial grade 2 toxicity and should be reduced one dose level with initial grade 3 toxicity. Discontinue T-DM1 permanently for grade 4 hyperbilirubinemia, if serum transaminases >3 x ULN, and concomitant total bilirubin >2 x ULN or if patient is diagnosed with nodular regenerative hyperplasia (NRH). In the event of grade 3 or 4 thrombocytopenia, hold future doses until platelets recover to ≥75,000 cells/mm^3 and then resume at the same dose level (initial grade 3) or reduce dose one level (initial grade 4). Specific dose modifications also exist for left ventricular cardiac dysfunction. Left ventricular ejection fraction (LVEF) should be monitored at baseline and every 3 months while on therapy. T-DM1 has not been studied in patients with LVEF <50% at baseline assessment. T-DM1 does not need to be held, but a repeat LVEF assessment within 3 weeks should be performed for any LVEF reduction of 40% to ≤45% and <10% point decline from baseline. If LVEF is 40% to ≤45% and ≥10% point decline from baseline or LVEF is <40%, hold T-DM1, reassess LVEF within 3 weeks, and permanently discontinue if LVEF has not improved or has declined further. Additionally, T-DM1 should be permanently discontinued in patients with symptomatic congestive heart failure, interstitial lung disease, or pneumonitis. Hold treatment in patients with severe to life-threatening peripheral neuropathy (grades ≥3) until symptoms resolve to grades ≤2. If there is more than one indication for a dose adjustment, the most conservative approach should be taken.

Though no formal drug-drug interactions studies have been conducted, T-DM1 undergoes hepatic metabolism via the CYP3A4 and CYP3A5 enzyme systems and has the potential for drug-drug interactions.[11] Concomitant use of strong CYP3A4 inhibitors should be avoided while on T-DM1 because of the potential increase in concentration and toxicity related to the cytotoxic DM1 component. If unavoidable, patients should be monitored more frequently for the development of T-DM1-related adverse events.

Pregnant women and women of childbearing age should be counseled regarding the risks of T-DM1 to the fetus. The individual components of T-DM1, trastuzumab and DM1, have both been associated with or suspected to cause fetal harm that could result in death.[11] Counsel patients to use contraception during treatment and for 6 months following the last dose of T-DM1.[11] Nursing mothers should be advised to either discontinue nursing or discontinue therapy because IgG has been found in maternal milk and may lead to unnecessary risk to the baby in patients treated with T-DM1. The benefit-to-risk ratio for administering T-DM1 must be taken into consideration in both pregnant and nursing mothers.

T-DM1 is a novel treatment option recently approved for the treatment of patients with HER2-positive advanced breast cancer who have been previously been treated with trastuzumab and a taxane. The NCCN Breast Cancer Guidelines have recently been updated to include T-DM1 as the preferred regimen for trastuzumab-exposed

HER2-positive disease.[12] T-DM1 currently is being investigated in the neoadjuvant and adjuvant breast cancer settings as well as for additional indications including first-line therapy in metastatic breast cancer. MARIANNE is a randomized, three-arm trial comparing T-DM1 alone and T-DM1 plus pertuzumab with trastuzumab plus a taxane in patients with HER2-positive progressive or recurrent locally advanced or previously untreated metastatic breast cancer. A second ongoing phase 3 trial, TH3RESA, is comparing T-DM1 to physician's choice of treatment as a third-line option for metastatic breast cancer. The results of these trials may lead to an increased role for T-DM1 in the management of breast cancer.

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Dabrafenib (Tafinlar®)

Class: ATP-competitive BRAF kinase inhibitor
Indication: Treatment of unresectable or metastatic melanoma with BRAF V600E mutation
Dose: 150 mg orally twice daily; 1 hour before or 2 hours after meals
Dose modifications: Dose reductions may be considered based on side effects. No data exist to guide dose adjustments in patients with renal or hepatic insufficiencies; however, dose adjustments are not recommended for mild to moderate renal dysfunction or mild hepatic dysfunction. Refer to the package insert for specific dose changes.

Dose Modifications Based on Side Effects[8]

Dose Reductions	Dose and Schedule
First dose reduction	100 mg orally twice daily
Second dose reduction	75 mg orally twice daily
Third dose reduction	50 mg orally twice daily
Unable to tolerate 50 mg twice daily	Discontinue dabrafenib

Common adverse effects: Hyperkeratosis, alopecia, palmar-plantar erythrodysesthia (PPES), rash, headache, pyrexia, arthralgia, and papilloma
Serious adverse effects: New primary cutaneous malignancies, febrile drug reaction, hemolytic anemia in G6PD deficiency, hyperglycemia, uveitis, and iritis
Drug interactions: Dabrafenib is a substrate of CYP3A4, CYP2C8, and P-glycoprotein. It is recommended to avoid strong inhibitors and inducers of these enzymes. Medications that alter gastric pH may decrease the bioavailability of this medication.

Dabrafenib for the Treatment of Metastatic Melanoma

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In 2013 an estimated 76,960 individuals will be diagnosed with melanoma and approximately 9,480 deaths will occur from this disease.[1] Nearly 50% of melanomas are caused by an oncogenic mutation of BRAF, which causes activation of the mitogen-activated kinase (MAPK) pathway.[2,3] Until recently, therapies used to treat melanoma included cytotoxic medications (e.g., interferon, dacarbazine, temozolomide, carboplatin, paclitaxel), imatinib, and high-dose interleukin. These agents have been associated with limited efficacy in patients with nonresectable, metastatic disease in whom the 5-year survival rate is only 10%.[4]

In 2011 the U.S. Food and Drug Administration (FDA) approved the first selective BRAF inhibitor, vemurafenib, which specifically targets the BRAF V600E mutation. This medication was found to have a response rate of 48%, whereas the response rate for dacarbazine was only 5%.[3] In May 2013 dabrafenib became the second selective BRAF inhibitor to be approved by the FDA. This medication also targets the BRAF V600E mutation and was shown to inhibit mediators for the MAPK pathway within 24 hours of the first dose.

The phase 1 BREAK-1 study comprised 184 patients, including 156 patients with metastatic melanoma.[5] During this trial, it was standard practice to identify the BRAF V600 mutation before treatment was initiated because patients found to have wild-type BRAF did not respond to the treatment. Thirty-six melanoma patients with BRAF V600 mutation and no brain metastases received 150 mg orally every 12 hours. Of those patients, 25 (69%; 95% CI: 51.9–83.7) achieved a partial or complete response with a mean duration of response of 6.2 months (95% CI: 4.2–7.7). Median progression-free survival (PFS) was similar between patients with BRAF V600E (n = 21) versus BRAF V600K (n = 4) mutations (5.5 months [95% CI: 3.5–9.5] versus 5.6 months [95% CI: 3.9–10.8]). Ten patients with metastatic brain lesions also were given 150 mg orally every 12 hours. Of these patients, nine experienced shrinking of their metastases and four achieved complete resolution of their lesions. PFS in these patients was 4.2 months (95% CI: 3.3–5.3), and all 10 patients were alive after 5 months. These findings were groundbreaking in the treatment of metastatic melanoma because less than 10% of brain lesions are known to respond to systemic therapy.[6]

In the phase 2 BREAK-MB trial, Long and colleagues looked specifically at the use of dabrafenib for the treatment of BRAF V600E/K mutant melanoma with brain metastases regardless of previous treatments.[6] The trial's findings confirmed that administering dabrafenib 150 mg orally every 12 hours was an effective treatment for this patient population. Intracranial responses with BRAF V600E were 39% (n = 29) in patients who had not received any previous local treatment for brain metastases and 30.8% (n = 20) in patients who had disease progression in the brain after surgery, whole-brain radiotherapy, or stereotactic radiosurgery.

A second phase 2 trial of dabrafenib (BREAK-2) was a single-treatment-arm study evaluating the efficacy of dabrafenib 150 mg orally every 12 hours in patients with BRAF V600E/K mutations only.[3,7] Ninety-two patients were included; 76 patients with BRAF V600E and 16 patients with BRAF V600K. The response rate was 60% in the BRAF V600E group compared with 13% in the BRAF V600K group. The mean PFS was also longer in the BRAF V600E group verses the BRAF V600K group (27 weeks versus 20 weeks). Results of the mature data from this trial are pending. In the phase 3 trial (BREAK-3), 250 patients with untreated stage IV or unresectable stage III BRAF V600E mutatant melanoma were randomized to receive either dabrafenib (n = 187) or dacarbazine (n = 63).[8] Median PFS was 5.1 months in the dabrafenib group versus 2.7 months for the dacarbazine group (95% CI: 0.18–0.51; p < .0001). An independent review confirmed the investigator-assessed results for PFS.

The most common adverse events seen during the trials were hyperkeratosis, alopecia, palmar-plantar erythrodysesthia (PPES), rash, headache, pyrexia, arthralgia, and papilloma.[9] Some of the more

serious adverse events included pyrexia, PPES, new primary cutaneous malignancies, febrile drug reaction, hemolytic anemia in patients with G6PD deficiency, and hyperglycemia. Due to the risk of developing new cancers, including cutaneous squamous cell carcinoma, patients should be counseled to monitor for new warts, skin sores, or changes in the size or color of moles. They should also be evaluated every 2 months for new cancerous lesions. Dabrafenib is mostly excreted through the feces unchanged but does undergo some hepatic and renal metabolism. Dabrafenib is a substrate of CYP3A4, CYP2C8, and P-glycoprotein. It is recommended to avoid strong inhibitors and inducers of these enzymes. Medications that alter gastric pH (antacids, PPIs, H2RAs) may also decrease the bioavailability of this medication.

Dabrafenib is orally administered and available as either 50-mg or 75-mg capsules.[9] This medication should be taken at least 1 hour prior to meals or 2 hours after food has been consumed. Capsules should not be opened, crushed, or broken. Patients who miss a dose can take it up to 6 hours from the previously scheduled dose. Patients should be reminded that this medication can cause fetal harm. It is recommended that patients use nonhormonal contraception during therapy because dabrafenib could decrease the efficacy of oral contraceptives.

As this medication establishes its role in the treatment of BRAF V600 melanoma, it will be important to evaluate the studies comparing the efficacy of similar drugs (i.e., vemurafenib). Currently no head-to-head trials have been performed to evaluate the superiority of the FDA-approved, ATP-competitive BRAF kinase inhibitors. Additional studies are being performed to determine dabrafenib's effect on brain metastases. Further investigations are being conducted with drafrenib in combination with trametinib.[10] Preliminary trials have shown that dabrafenib 150 mg every 12 hours plus trametinib 2 mg daily have improved outcomes compared with monotherapy with PFS of 9.4 months (0.39; 95% CI: 0.25–0.65) to 5.8 months, respectively. Fewer events of cutaneous squamous cell carcinoma also were seen with 10 events (19%) in the monotherapy group verses 4 events (7%) in the combination group. As more mature data become available, the prognosis of patients who develop aggressive or advanced melanoma with BRAF V600E mutations may improve.

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Ponatinib (Iclusig™)

Class: Pan-Bcr/Abl tyrosine kinase inhibitor
Indication: Ponatinib is approved for patients with leukemias (chronic and acute) harboring the Philadelphia chromosome who are resistant/intolerant to other tyrosine kinase inhibitors or with the T315I mutation.
Dose: 45 mg orally once daily with or without food; supplied as 15-mg and 45-mg tablets
Dose modifications: Ponatinib dosing should be modified for hematologic toxicity not related to leukemia (neutropenia, thrombocytopenia) by withholding the dose. The same dose should be resumed upon recovery without dose reduction on the first occurrence. Doses should be withheld on the second and third occurrence until recovery with a 15-mg dose reduction each time when dosing is resumed.

Ponatinib dosing should be modified for nonhematologic toxicities, primarily hepatotoxicity and pancreatitis. If elevation of liver transaminases of ≥ grade 2 (>3 x upper limit of normal [ULN]) occurs, the dose of ponatinib should be held (permanently if hyperbilirubinemia >2 x ULN occurs in conjunction with transaminitis). The dose may be resumed with a 15-mg dose reduction when liver transaminases return to < grade 2. If a patient experiences > grade 2 increase in serum lipase or pancreatitis, the dose of ponatinib should be held. After toxicity has returned to < grade 2, then the patient can be restarted on ponatinib with a 15-mg dose reduction.

The dose of ponatinib should be reduced to 30 mg daily when given with strong CYP3A inhibitors.
Black box warning: Arterial thrombosis and hepatotoxicity
Common adverse effects (≥20%): Rash, fatigue, fever, arthralgia/myalgia, elevations in aspartate aminotransferase/alanine aminiotransferase, myelosuppression, hypertension, and abdominal pain
Serious adverse effects (<6%): Arterial ischemic event (MI), congestive heart failure, hypertension, cardiac arrhythmias, hemorrhage, pancreatitis, hepatotoxicity, venous thromboembolism, gastrointestinal perforation, tumor lysis syndrome, fluid retention, stroke, and myelosuppression
Drug interactions: Strong CYP3A inhibitors, strong CYP 3A4 inducers, antacids, histamine 2 blockers, and proton pump inhibitors
Patient education: A medication guide included with the package insert is intended to be discussed with patients and provided to them upon medication dispensing.

Ponatinib Approved for Treatment of TKI-Resistant or Intolerant Leukemia (CML and Ph+ ALL)

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The treatment options for chronic myeloid leukemia (CML) have increased drastically during the past decade. The approval of imatinib in 2002 for first-line therapy of CML shifted treatment from interferon-α and stem cell transplant to chronic administration of an oral tablet. Long-term follow-up of the IRIS study has shown that imatinib prevents progression to accelerated or blast phase with long-term suppression of the Philadelphia-chromosome positive (Ph+) clone for 93% of newly diagnosed CML patients.[1] Nearly two-thirds of patients remained on treatment after 6 years of follow-up.

Nilotinib, dasatinib, and bosutinib, second-generation Bcr-Abl tyrosine kinase inhibitors (TKIs), are more potent than imatinib and have activity on multiple Bcr-Abl-mutated kinases, which confer imatinib resistance.[2] Randomized, phase 3, front-line data have revealed each of these options to be at least as effective as imatinib with a propensity to meet treatment endpoints at a faster rate.[3-5] Despite these advances, a subset of patients remain treatment resistant or intolerant, particularity those with the Bcr-Abl mutation T315I.

Unfortunately, treatment resistance is common. It is estimated that 20%–30% of patients treated with imatinib will develop resistance.[6] Although multiple mechanisms of treatment resistance exist, the most common reason for imatinib resistance is genetic mutation within the Philadelphia chromosome. More than 100 point mutations at the Abl binding site have been identified,[6] with the most common point mutation resulting from a substitution of isoleucine for threonine at position 315 (T315I).[7] Through the effects of steric hindrance and reduced hydrogen bond formation, the T315I mutation confers resistance to most Bcr-Abl TKIs.[8] Because it blocks entry of Bcr-Abl TKIs to their site of action, it is considered to be the gatekeeper mutation.

Ponatinib targets the active site of the native and mutated Bcr-Abl tyrosine kinase, specifically the T315I gatekeeper mutation. The structure of ponatinib was designed to form an ethynyl bond between the methylphenyl and purine groups, which allows it access to its binding site on Abl without steric hindrance from isoleucine. Ponatinib also does not rely on a hydrogen bond with threonine at position 315. Otherwise, ponatinib binds to the active site in a similar fashion as imatinib or nilotinib.

Data

The PACE study, a phase 2 clinical trial designed to evaluate efficacy and safety of ponatinib, began in September 2010 and completed enrollment in September 2011. The results were presented at the American Society of Hematology Annual Meeting in December 2012.[9] Four hundred forty-four patients with chronic phase CML (n = 267), accelerated phase CML (n = 83), or blast phase CML/acute lymphoblastic

leukemia (ALL; *n* = 94) were evaluated for efficacy and safety. Patients were required to be resistant or intolerant to dasatinib or nilotinib or have the T315I mutation. The median number of prior therapies was three with 96%, 84%, and 65% of patients with previous exposure to imatinib, dasatinib, and nilotinib, respectively. Eighty-eight percent were resistant and 12% were intolerant to previous treatment. Sixty-six percent of patients had a Bcr-Abl mutation with 29% of the overall population having the T315I mutation. The primary objective was major cytogenetic response (MCyR) in patients with chronic phase CML and complete hematologic response (CHR) in patients with accelerated phase CML, blast phase CML, or ALL.

Of the patients with chronic phase CML, 55% achieved MCyR and 46% achieved a complete cytogenetic response. Seventy percent of patients with a T315I mutation achieved MCyR. Major molecular response (ratio of Bcr-Abl to Abl <0.1% of the international standard) was achieved by 32% of patients. The responses appear to be durable, with 91% remaining in response at 1 year. Of the patients with accelerated phase CML or blast phase CML/ALL, CHR was achieved in 57% and 34%, respectively, which was durable at 1 year. MCyRs were also achieved in patients with advanced disease (accelerated phase CML [30%], blast phase CML [18%], and ALL [60%]).[10] Patient characteristics that affected response included the number of previous therapies, time since diagnosis, and age. The most common reasons for withdrawal from study were disease progression (18%) and intolerance (12%). The most common serious adverse effect was pancreatitis, which occurred early in therapy and was managed with dose reduction. These results compare favorably to similar studies with dasatinib[11,12] and nilotinib,[13,14] which were conducted with a patient population that was less treatment resistant.

The results of this phase 2 study prompted the U.S. Food and Drug Administration (FDA) to grant accelerated approval of ponatinib for patients with CML in any phase or Philadelphia chromosome (+) ALL with demonstrated resistance or intolerance to previous TKI therapy on December 14, 2012.

Adverse Effects

Black box warnings for ponatinib include arterial thrombosis (myocardial infarction, stroke, etc.) and hepatotoxicity/liver failure. The most common adverse effects reported with ponatinib are rash, fever, fatigue, arthralgia/myalgia, transaminitis, myelosuppression, hypertension, and abdominal pain. Serious adverse events (all of which occurred in fewer than 5% of patients) included an arterial ischemic event, congestive heart failure, hypertension, cardiac arrhythmias, hemorrhage, pancreatitis, hepatic failure, venous thromboembolism, arterial clots, pneumonia, neutropenic fever, gastrointestinal perforation, tumor lysis syndrome, and myelosuppression. Ponatinib poses a theoretical risk of delayed wound healing. All side effects have been seen previously with currently available Bcr-Abl TKIs.

Dose

The dose of ponatinib is 45 mg orally once daily taken with or without food.

Important Pharmacokinetic/Drug-Drug Interactions

The half-life of ponatinib is 22 hours, allowing for once daily dosing. Ponatinib is primarily a substrate for CYP3A4/5. Administration of ponatinib with ketoconazole to healthy volunteers resulted in an increase in the AUC and CPmax by 78% and 47%, respectively.[15] The dose of ponatinib should be reduced to 30 mg daily if given in conjunction with a strong CYP3A inhibitor. Though no formal evaluation has been completed, administration of ponatinib with either a strong CYP3A inducer or medications that raise the gastric pH will likely decrease ponatinib bioavailability.

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Trametinib (Mekinist™)

Class: Mitogen-activated extracellular signal regulated kinase (MEK) inhibitor
Indication: Unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test
Dose: 2 mg orally once daily, taken at least 1 hour before or 2 hours after a meal
Dose modifications: Reduce, hold, or discontinue doses based on organ-specific toxicities (cutaneous, cardiac, ocular, pulmonary)
Common adverse effects: Rash, diarrhea, stomatitis, abdominal pain, lymphedema
Serious adverse effects: Cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, interstitial lung disease/pneumonitis, severe dermatologic toxicities
Drug interactions: None reported

Trametinib for the Treatment of Unresectable or Metastatic Melanoma

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Unresectable or metastatic melanoma is a very aggressive form of skin cancer that is generally considered to be extremely challenging to treat. The lack of survival benefit seen with the use of traditional systemic chemotherapies in this setting stimulated investigation of new treatment mechanisms. The improved understanding of genetics involved in the development and progression of melanoma has led to the advent of targeted therapies that provide more individualized and effective treatment for patients.[1,2] These novel therapies target components of the mitogen-activated protein (MAP) kinase signal-transduction pathway, which regulates proliferation and survival of tumor cells in many types of cancer. The activity of the MAP kinase pathway can be enhanced with the presence of BRAF mutations that subsequently activate downstream constituents, such as mitogen-activated extracellular signal regulated kinases (MEK).[1-4] MEK is the target of the recently approved agent trametinib. Trametinib is a reversible, highly selective inhibitor of MEK1/MEK2 that has been shown to improve rates of progression-free survival (PFS) and overall survival (OS) in metastatic melanoma patients with BRAF V600 mutations.[4]

Trametinib was approved by the U.S. Food and Drug Administration (FDA) in May 2013 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.[5] Trametinib's approval was largely supported by the results of a phase 3 randomized controlled trial. This international, multicenter, open-label trial consisted of 322 patients who had unresectable stage IIIC or IV melanoma with a V600E or V600K BRAF mutation. Patients could have received one previous chemotherapy or immunotherapy regimen for melanoma; however, patients were excluded if they were previously treated with a BRAF inhibitor, MEK inhibitor, or ipilimumab. Patients were randomized in a 2:1 ratio to receive trametinib 2 mg by mouth daily or intravenous chemotherapy consisting of either dacarbazine 1,000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks, selected at the discretion of the investigator. Patients were stratified according to baseline lactate dehydrogenase (normal or elevated) and whether they previously had received chemotherapy. Patients in the chemotherapy treatment group were allowed to cross over to receive trametinib after disease progression had been confirmed by an independent review. The primary endpoint was PFS, and secondary endpoints included OS, overall response rate (ORR), duration of response, and safety. The median duration of PFS was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group (hazard ration [HR], 0.45; 95% confidence interval [CI]: 0.33-0.63; $p < .001$). A subgroup analysis assessing baseline characteristics revealed no significant difference between groups in PFS for patients with a V600K mutation or those 65 years and older. Investigator-assessed response rates were 22% (2% complete response, 20% partial response) for the trametinib group and 8% (0% complete response, 8% partial response) for the chemotherapy group ($p = .01$). Data for OS and duration of response were not complete at the time of publication. In the trametinib group, adverse events led to dose interruptions in 35% of patients and dose reductions in 27% of patients. The most common adverse events reported in this group were rash, diarrhea, peripheral edema, fatigue, and dermatitis acneiform. A decreased left ventricular ejection fraction (LVEF) or ventricular dysfunction was observed in 7% of trametinib patients and ocular events occurred in 9% of patients. In the chemotherapy group, adverse events led to dose interruptions in 22% of patients and dose reductions in 10% of patients.[4]

Because of trametinib's different target of action, it has been hypothesized that trametinib could be effective for patients who fail BRAF inhibitor therapy.[2,6] An open-label, multicenter, phase 2 study was conducted to evaluate the activity of trametinib in patients with BRAF-mutated metastatic melanoma previously treated with a BRAF inhibitor. The study consisted of 97 patients who were divided into two cohorts. Cohort A was made up of 40 patients who were previously treated with a BRAF inhibitor (vemurafenib or dabrafenib), and cohort B was made up of 57 patients who were previously treated with chemotherapy or immunotherapy, but not with a BRAF inhibitor. Patients from both cohorts received trametinib 2 mg by mouth daily until disease progression or unacceptable toxicity. The primary endpoint was ORR as determined by the investigator. Secondary endpoints included PFS and OS. The median duration of treatment was 56 days for cohort A and 120 days for cohort B. There were no confirmed clinical responses among patients enrolled in cohort A at the interim analysis, thus enrollment was terminated at this time. The confirmed response rate for cohort B was 25% (2% complete response, 23% partial response). The median PFS was 1.8 months for cohort A and 4.0 months for cohort B. The median OS was 5.8 months for cohort A and had not been reached for cohort B at the time of publication.[6]

The results of this study support the conclusion that trametinib lacks clinical activity in the treatment of patients with metastatic melanoma previously treated with BRAF inhibitor therapy and therefore is not indicated for use in this population.[5,6]

Although there are no contraindications for trametinib, there are several precautions that should be addressed prior to initiation of therapy and throughout treatment.[5] Cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased LVEF) was reported in 11% of patients receiving trametinib in clinical trial experience. Due to this risk, it is recommended to assess LVEF by echocardiogram or multigated acquisition scan at baseline, 1 month after treatment initiation, and at 2–3-month intervals while on treatment. Adverse ophthalmic effects including retinal pigment epithelial detachment and retinal vein occlusion (RVO) have been reported in <1% of patients. Although these serious complications are rare, ophthalmic evaluations should be performed if patients report any visual disturbances. In clinical trials, interstitial lung disease or pneumonitis occurred in 1.8% of patients. Dermatologic toxicities have been commonly reported in trametinib patients (up to 87%), and severe skin toxicity occurred in 12% of patients. In addition to these precautions, other adverse effects reported with trametinib include diarrhea, stomatitis, lymphedema, peripheral edema, fatigue, dizziness, anemia, hypertension, bradycardia, xerostomia, hypoalbuminemia, and elevated liver enzymes.[2-6]

The recommended starting dose for trametinib is 2 mg orally once daily. There are specific dose modifications suggested based on organ-specific adverse reactions:

- Cutaneous: For a grade 2 rash, it is recommended to reduce the dose by 0.5 mg, or discontinue the medication in patients taking 1 mg daily. For an intolerable grade 2 rash that does not improve within 2 weeks following dose reduction or for a grade 3–4 rash, it is recommended to hold trametinib for up to 3 weeks. If improved within 3 weeks, resume treatment at a dose reduced by 0.5 mg, or discontinue in patients taking 1 mg daily. Trametinib should be permanently discontinued in patients with intolerable grade 2 or grade 3–4 rash that does not improve within 3 weeks, despite interruption of dosing.
- Cardiac: For an asymptomatic decrease in LVEF ≥10% from baseline to a value below lower limits of normal, it is recommended to hold trametinib for up to 4 weeks. If improved within 4 weeks, resume at a dose reduced by 0.5 mg, or discontinue in patients taking 1 mg daily. Trametinib should be permanently discontinued in patients who develop symptomatic congestive heart failure, a decrease in LVEF >20% from baseline, or a decrease in LVEF ≥10% from baseline to a value below lower limits of normal that does not improve to normal within 4 weeks following interruption of trametinib therapy.
- Ocular: For grade 2–3 RPED, it is recommended to hold therapy for up to 3 weeks. If improved within 3 weeks, resume at a dose reduced by 0.5 mg, or discontinue in patients taking 1 mg daily. If no improvement within 3 weeks, therapy should be permanently discontinued. Trametinib should be permanently discontinued in patients who develop RVO.
- Pulmonary: Permanently discontinue in patients who develop interstitial lung disease or pneumonitis.

There are no recommended dose adjustments for patients with moderate to severe hepatic or renal dysfunction because trametinib has not been studied in these populations. Trametinib is pregnancy category D and has been shown to cause fetal harm in animal studies. It is not known whether trametinib is present in human milk.[5]

Pharmacokinetic analyses have revealed that peak plasma concentrations occur 1.5 hours after oral dosing. The bioavailability of a single 2-mg oral dose is 72%. Absorption is impaired when doses are administered with a high-fat, high-calorie meal. Trametinib is 97.4% plasma protein bound and has a volume of distribution equal to 214 L. Trametinib is predominantly metabolized via deacetylation with or without mono-oxygenation and glucuronidation. The elimination half-life is 4–5 days, and it is excreted primarily in the feces (>80%).[3,5] To date, there have been no formal clinical studies conducted to evaluate drug interactions with trametinib.[5]

Trametinib is available as 0.5-mg, 1-mg, and 2-mg tablets that should be stored in a refrigerator, protected from moisture and light. Patients should be instructed to take trametinib at least 1 hour before or 2 hours after meals to avoid the possibility of subtherapeutic concentrations. Patients should be counseled on the risk of cardiomyopathy and the importance of LVEF monitoring during therapy. Patients should notify their provider if they experience visual disturbances, dyspnea, intolerable rashes, or severe diarrhea. Women of reproductive potential should use effective contraception during treatment and for 4 months after treatment completion. Lactating mothers should avoid breastfeeding while taking trametinib.[5]

Trametinib has been shown to provide significant survival benefits for patients with advanced melanoma who have otherwise limited treatment options. However, given that head-to-head trials of trametinib and other targeted agents have not been completed, its ideal place in therapy is yet to be defined.

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