Hematology/Oncology Pharmacy Association

HOPA News

Volume 12, Issue 4, 2015

Staged and Confused: Sequencing of Therapy in Metastatic Castration-Resistant Prostate Cancer

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Prostate cancer is the most prevalent cancer among North American men and accounts for the second highest number of deaths from any type of cancer.[1] In 2015, there is estimated to be a total of 220,800 new prostate cancer cases diagnosed, resulting in nearly 30,000 deaths in the United States. Prostate cancer is associated with significant morbidity and mortality, which increases as the disease progresses. After prostate cancer becomes metastatic, the estimated 5-year overall survival (OS) is approximately 31%, down from 100% with early-stage disease.[2]

The cornerstone of treatment is androgen deprivation therapy (ADT).[2] Androgens, including testosterone, are taken up by cells within the prostate and bind to the androgen receptor (AR) to promote function and growth. Activation of the AR can promote the growth of both normal and cancerous prostate cells, allowing androgens to play a role in the development and progression of prostate cancer.[3,4] For this reason, many treatment regimens for prostate cancer target the AR signaling pathway.

ADT can be surgical or medical; the most common medical approach is treatment with a gonadotropin-releasing hormone (GnRH) modulator, such as leuprolide, goserelin, or degarelix.[2,5] These agents suppress luteinizing hormone production and, thereby, the synthesis of testicular androgens through stimulation or inhibition of GnRH.

Although the majority of prostate cancer initially responds to ADT, cancer cells can become resistant to treatment and survive and grow under low levels of circulating testosterone.[2,4,5] This is defined as *castration-resistant disease*. Castration-resistant disease is still driven by AR signaling; therefore, ADT should be continued indefinitely and other chemohormonal therapies should be initiated.

The focus of this review will be on treatment options and data behind sequencing strategies for metastatic castration-resistant prostate cancer (mCRPC).

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Send administrative correspondence or letters to the editor to HOPA, 8735 W. Higgins Road, Suite 300, Chicago, IL 60631, fax 847.375.6497, or e-mail info@hoparx.org. *HOPA News* is published by the Hematology/Oncology Pharmacy Association.

Treatment Options for Metastatic Castration-Resistant Prostate Cancer

Docetaxel (DOC), a microtubule stabilizer, became the standard treatment for mCRPC with the TAX327 trial, which was the first trial to demonstrate an OS benefit with chemotherapy in mCRPC.[6] After its initial approval in 2004, there were several years without any new agents approved for mCRPC. Recently, several agents with novel mechanisms have gained approval for use in mCRPC treatment (**Table 1**).

Cabazitaxel (CAB) is an intravenous agent with a similar mechanism of action as DOC, however it has antitumor activity in mCRPC refractory to DOC therapy.[7] In 2010, TROPIC became the first trial to demonstrate an OS benefit in the post-DOC setting, comparing CAB combined with prednisone to mitoxantrone combined with prednisone. CAB, in combination with prednisone, received U.S. Food and Drug Administration (FDA) approval for use following DOC and, to date, CAB carries only that indication. Abiraterone (ABI) and enzalutamide (ENZ) are both oral agents that inhibit androgen synthesis via different mechanisms. ABI binds and inhibits CYP17A1, a critical component in both the testicular and extragonadal androgen synthesis pathways, while ENZ binds to the AR and serves as a potent androgen antagonist, preventing ligand-bound AR translocation into the nucleus.[8–11] ABI was the first of these two agents to gain FDA approval for mCRPC following DOC therapy with COUGAR 301, in which it was compared to placebo with prednisone.[8] ENZ was studied in a similar manner and first gained approval following DOC treatment with the results of the AFFIRM trial in 2012.[10] Later in 2012, COUGAR 302 became the first trial to trigger regulatory approval of an additional first-line agent, ABI, in mCRPC.[9] As of late 2014, with the release of results from the PREVAIL trial, ENZ also carries the indication for first-line treatment of mCRPC.[11] Sipuleucel-T and radium-223 were approved for mCRPC in 2010 and 2013, respectively.[12,13] These agents have very unique mechanisms, and their use is limited to a small subset of patients.

Table 1. Novel Chemohormonal Therapy Options Currently Available for mCRPC

Agent	Mechanism	FDA Approval Study	Place in Therapy
Cabazitaxel (Jevtana®)	Microtubule stabilizer	TROPIC[7] vs mitoxantrone (+prednisone)	2010: Postdocetaxel (+prednisone)
Abiraterone (Zytiga®)	CYP17A1 inhibitor	COUGAR 301[8] vs placebo (+prednisone)	2011: Postdocetaxel (+prednisone)
		COUGAR 302[9] vs placebo (+prednisone)	2012: Predocetaxel (+prednisone)
Enzalutamide (Xtandi®)	Androgen-receptor inhibitor	AFFIRM[10] vs placebo	2012: Postdocetaxel
		PREVAIL[11] vs placebo	2014: Predocetaxel
Sipuleucel-T (Provenge®)	Autologous cellular immunotherapy	IMPACT[12] vs placebo	2010: Asymptomatic or minimally symptomatic
Radium-223 (Xofigo®)	Targeted α-emitter, Ca2+ mimetic	ALSYMPCA[13] vs placebo	2013: Symptomatic bone metastasis

The Confusion

With the increase in approved agents during the past 5 years, there is much uncertainty about the optimal treatment sequence. Prostate cancer is a progressive disease during which many patients will endure multiple lines of therapy, requiring practitioners to make informed clinical decisions when selecting treatment regimens. Further investigation of suspected resistance mechanisms also is warranted because they have yet to be fully characterized. For these reasons, it is important to search for the appropriate sequences in which to use these therapies when treating patients with mCRPC.

The National Comprehensive Cancer Network (NCCN), American Urological Association (AUA), and American Society of Clinical Oncology (ASCO) have recently updated their guidelines.[2,5,14] Although these resources recommend the use of the aforementioned therapies, they do not provide guidance in terms of sequencing agents other than suggesting that

clinicians consider the previous treatments, presence or absence of visceral metastases, symptoms, patient preference, and potential side effects when selecting therapies.[5,14] The ASCO guidelines highlight the importance of continuous ADT, while outlining the available first-line chemohormonal therapies.[2] Unfortunately, the guideline fails to provide guidance about which agent to initiate after the patient progresses past any first-line, or even second-line treatment. Practitioners are left with scarce data from retrospective studies to guide treatment decisions.

Therapy Sequencing

All published studies regarding therapy sequencing in mCRPC are retrospective, single-arm studies (**Table 2**).[15–22] Patients included in these studies had progressive mCRPC with similar baseline characteristics, including: median ages of 65–72 years, Gleason scores 6–9, and Eastern Cooperative Oncology Group performance status scores of 0–2.

Third-Line ENZ (DOC → ABI → ENZ)

There are three published retrospective studies reviewing the use of third-line ENZ in patients with progressive mCRPC after previous treatment with DOC and ABI.[17–19] Although less robust than in the second-line setting, these studies have revealed a response to third-line ENZ.[17–19] Prostate-specific antigen (PSA) responses, defined by the Prostate Cancer Clinical Trials Working Group as a ≥50% decline from baseline PSA, were less than those seen with second-line ENZ therapy in the AFFIRM trial.[10] In AFFIRM, 54% of patients experienced a PSA response with ENZ, whereas 17%–45.7% of patients had the same response to third-line ENZ.[10,17–19]

The lower PSA response rates were thought to be due to cross-resistance between ABI and ENZ.[17–19] Response to previous therapy was not found to be predictive of response to ENZ. For example, of the 16 (45.7%) patients in the study by Schrader and colleagues with a PSA response to ENZ, 43.8% previously had a PSA response to ABI and 13.8% did not.[17]

Third-Line ABI (DOC → ENZ → ABI)

One study by Noonan and colleagues investigated the third-line use of ABI for progressive mCRPC after previous treatment with DOC and ENZ.[20] In contrast to the ENZ studies, the primary endpoint was a PSA response of ≥30% from baseline, with only three (11%) patients meeting that endpoint. In addition, only 4% of patients had a ≥50% PSA decline with third-line ABI, which was less than the 29.5% of patients who had the same response from second-line ABI in COUGAR 301.[8] The poor responses seen in the study by Noonan and colleagues[20] and the minimal, but apparent, responses seen with the previous studies may suggest that second-line ABI followed by third-line ENZ may be the more favorable treatment sequence. These data must be confirmed with larger, randomized sequencing studies.

Third-Fourth-Line CAB (DOC → ABI [→ENZ] → CAB)

There are two published studies reviewing the third-line use of CAB after DOC and ABI therapy.[21,22] Sella and colleagues investigated third-line CAB after previous treatment with DOC and ABI.[21] The duration of CAB therapy was comparable to the TROPIC study, which evaluated second-line CAB therapy.[7] PSA responses of ≥50% were similar between both studies, with 31.5% of patients in Sella and colleagues and 39.2% of patients in TROPIC achieving this response. Despite similar PSA responses, the median OS in Sella and colleagues' study (8.2 months, 95% CI: 3.34–13.05) was shorter than in the TROPIC trial (15.1 months, 95% CI, 14.1–16.3).

Nakouzi and coleauges cumulatively investigated third- and fourth-line CAB after previous treatment with DOC, ABI, and ENZ.[22] Although dosage and duration were not specified, this study included six (7.6%) patients who received ENZ before fourth-line CAB. Similar to the aforementioned study, the duration of CAB therapy in Nakouzi et al. was comparable to that in TROPIC.[7] PSA responses of ≥50% were seen in 35% of patients, and median OS was shorter in Nakouzi and colleauges' study (10.9 months, 95% CI: 8–14) than in TROPIC (15.1 months, 95% CI: 14.1–16.3). However, median progression-free survival of 4.4 months (95% CI: 3.5–5.2) in Nakouzi and colleagues' was longer than the 2.8 months (95% CI: 2.4–3.0) seen in the TROPIC study.

Although the results of Sella and colleagues and Nakouzi and colleagues do not adequately address CAB in the third- and fourth-line setting due to the limited number of patients, these data suggest that CAB retains activity after prior treatment exposure. The optimal place in therapy for CAB requires further investigation.

Future Directions

Several sequences and combinations have not yet been addressed in the literature. Studies continue to investigate therapies in mCRPC, including the active phase 3 trial (NCT01949337) of ENZ monotherapy against the combination of ENZ, ABI, and prednisone in recurrent mCRPC.[23] Along with new combinations and sequencing strategies being investigated, there also are a few new agents in the pipeline for treatment of mCRPC. Oral agents cabozantinib and tasquinimod and subcutaneous vaccine PROSTVAC-V/F are being studied in phase 3 clinical trials for use in mCRPC.[24] Cabozantinib is a tyrosine kinase inhibitor that targets met proto-oncogene and vascular endothelial growth factor receptor 2 and is FDA-approved for use in medullary thyroid carcinoma.[25] It is being studied for third-line use in mCRPC after failure of DOC and either ABI or ENZ.[24,25] Tasquinimod binds and inhibits S100A9, a calcium-binding protein implicated in prostate cancer, while PROSTVAC-V/F contains transgenes for PSA as the target tumor antigen.[24] Both agents are being studied for first-line use in mCRPC against placebo. The potential approval of new agents for this indication will certainly add more confusion for providers when initiating treatment and sequencing subsequent therapies.

Conclusions

Prostate cancer is a progressive and potentially deadly disease. Chemohormonal therapies result in improved survival for patients with mCRPC, but there is limited evidence for guiding treatment decisions after patients progress beyond first- or even second-line therapy. At this time, there is insufficient evidence to designate the optimal sequence or combination of therapies in mCRPC. Current data regarding sequencing are from retrospective, single-arm studies and offer limited guidance in the third- and later-line settings.[17–22] There is likely some cross-resistance between agents, which may be lessened when using ABI before ENZ.[20] CAB appears to retain some activity in the third-line setting after treatment with DOC and ABI.[21,22] When

Table 2. Therapy Sequencing Studies

	Sample Size	Median DOC Duration, cycles (range)	Median ABI Duration, cycles (range)	Median ENZ Duration, cycles (range)	Median CAB Duration, cycles (range)	PSA Response, No. of Patients (%) [95% CI]	Median OS*, months (95% CI)	Median PFS*, months (95% CI)
Third-Line ENZ (DOC → ABI → ENZ)								
Schrader et al.[17]	35	8 (4–12)	9 (2–19)	4.9 (2.4–7.4)	N/A	>50% decline 16 (45.7)	N/A	4 (2–6)
Thomsen et al.[18]	24	8 (1–14)	6 (2–14)	4 (1–8.5)	N/A	>50% decline 4 (17) >30% decline 11 (46) [24–67]	4.8 (3–8.4)	N/A
Badrising et al.[19]	61	8 (6–10)	6.1 (3–8.6)	3.5 (2.6–4.7)	N/A	>50% decline 13 (21) >30% decline 28 (46)	7.4 (>6.7)	2.8 (2.6–3.7)
AFFIRM[10†]	800	U/A	N/A	8.3	N/A	>50% decline 395 (54)	18.4 (>17.3)	8.3 (5.8–8.3)
Third-Line ABI (DOC → ENZ → ABI)								
Noonan et al.[20]	27	10 (3–18)	3 (0.2–12.1)	9.6 (1.4–22.2)	N/A	>30% decline 3 (11) >50% decline 1 (4)	11.7 (6.6–16.8)	3.6 (2.5–4.7)
COUGAR 30[18†]	797	N/A	7.4 (0.2–25.6)	N/A	N/A	>50% decline 235 (29.5)	15.8 (14.8–17)	8.5 (8.3–11.1)
Third/Fourth-Line CAB (DOC → ABI [→ ENZ] → CAB)								
Sella et al.[21]	24	U/A	U/A	N/A	4 (1–13)	>50% decline 6 (31.5) [11.8–54.2]	8.2 (3.34–13.05)	N/A
Nakouzi et al.[22]	79	8 (4–12)	4.8 (1–55)	U/A	6 (1–15)	>50% decline 28 (35) [25–47] >30% decline 48 (62) [51–73]	10.9 (8–14)	4.4 (3.5–5.2)
TROPIC[7*]	378	U/A	N/A	N/A	6 (3–10)	>50% decline 129 (39.2) [33.9–44.5]	15.1 (14.1–16.3)	2.8 (2.4–3)

** Reflective of treatment with third-line agent*

†Second-line therapy study ABI = abiraterone, CAB = cabazitaxel,

CI = confidence interval, DOC = docetaxel, ENZ = enzalutamide, N/A = not applicable, U/A = unavailable.

making treatment decisions, providers must take clinical trial evidence along with patient factors and agent-specific characteristics into consideration. In addition, the identification of appropriate predictors for response to these agents is still needed for clinical trials. Prospective, head-to-head trial comparisons addressing cross-resistance and therapy sequencing are needed to make definitive, evidence-based recommendations for patients with mCRPC.

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Ensuring Healthcare Worker Safety When Handling Hazardous Drugs: The Joint Position Statement from the Oncology Nursing Society, the American Society of Clinical Oncology, and the Hematology/Oncology Pharmacy Association

On March 10, 2015, HOPA, ONS, and ASCO announced the release of a joint position statement, "Ensuring Healthcare Worker Safety When Handling Hazardous Drugs." The intent of this document is to ensure that there are policies and procedures in place to safeguard healthcare workers as well as their patients and minimize exposure risk when handling hazardous drugs.

Hazardous drugs (HDs) are chemicals that demonstrate one or more of the following characteristics: carcinogenicity, genotoxicity, teratogenicity, reproductive toxicity, or organ toxicity.[1] Healthcare workers (HCWs) are potentially exposed to HDs in the workplace during drug preparation, administration, and disposal and when handling patients' excreta following treatment with these drugs. More than 100 studies since 1994 have documented evidence of contamination of the work environment with HDs, which increases the potential for exposure of nurses, pharmacists, and other HCWs when these agents are handled without appropriate precautions. More than 50 studies have demonstrated the presence of HDs in the urine of HCWs, indicating actual exposure. Occupational exposure to HDs has been associated with acute symptoms such as nasal sores and hair loss, adverse reproductive outcomes such as infertility and miscarriages, genetic changes such as DNA damage, and an increased occurrence of cancer.[2]
The Occupational Safety and Health Administration[3] acknowledged the occupational risks of HDs and issued recommendations for their safe handling nearly 30 years ago. Updated guidelines from NIOSH and professional societies subsequently have been published.[4-6] All guidelines address the need for HD-related policies and procedures, education and training, and safe handling precautions in organizations where HDs are present. Safe handling precautions include the use of safety equipment, safe work practices, and personal protective equipment (PPE). When used consistently, recommended precautions can reduce occupational HD exposure[1].

Occupational HD exposure can be minimized by a comprehensive HD safe-handling program based on a hierarchy of controls.[7] When a hazard cannot be eliminated, engineering controls are recommended to control exposure. Biological safety cabinets and compounding aseptic containment isolators are primary engineering controls, and closed-system transfer devices are supplemental engineering controls, both of which reduce HD exposure. Administrative controls are the next level of protection and include safe handling policies and procedures, hazard communication, education, and medical surveillance of those who are potentially exposed. Finally, PPE that has been tested for use with HDs provides barrier protection for workers. PPE includes gowns, gloves, eye and face shields, and respirator protection, depending on the HD handling activities.

Nurses and pharmacists usually work as employees rather than independent practitioners in hospitals, clinics, and offices; therefore, employers and employees share the responsibility for HD safe handling. It is the position of the Oncology Nursing Society, the American Society of Clinical Oncology, and the Hematology/Oncology Pharmacy Association that

- Organizations in which HDs are present will establish evidence-based policies and procedures for safe handling that comply with regulatory requirements.
- Organizations in which HDs are prepared and administered will provide and maintain primary engineering controls and evaluate the utility of supplemental engineering controls, such as closed-system transfer devices, to reduce worker exposure.
- Organizations in which HDs are present will ensure that appropriate PPE is available to all staff to minimize exposure.
- Organizations in which HDs are present will provide education and training specific to each worker's role for staff who are potentially exposed. Education and training will include the risks of exposure, including the reproductive and developmental effects, the recommended precautions for specific handling activities, safe handling of contaminated patient excreta, proper disposal of contaminated waste, and how to handle acute exposure.
- Organizations in which HDs are present will protect the right of staff who are trying to conceive, pregnant, or breast feeding to engage in alternative duty that does not require HD handling.
- Organizations in which HDs are present will ensure that patients who receive these drugs and their caregivers receive education about safe handling to minimize unintended exposure.
- Organizations will ensure that HD waste is disposed of according to regulatory guidelines and in a manner that protects staff and the environment.
- Our professional societies will continue to explore evidence-based strategies for mitigation of risk associated with handling HDs and share recommendations with our respective members.

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Highlights from the 2015 HOPA Preconference Session Radiation for the Oncology Pharmacist

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One of the featured preconference sessions at HOPA's 11th annual conference was Radiation for the Oncology Pharmacist, which provided a wonderful overview of how to select the appropriate candidate for radiation therapy after a cancer diagnosis, specifically in the breast and prostate cancer populations. Education was also provided on the different preventive and treatment regimens a pharmacist can recommend to help a patient manage specific radiation-induced toxicities.

The goal of radiation treatment is to destroy cancer cells while preserving the integrity of normal tissues within and immediately adjacent to the radiation treatment field. The two major categories of radiation therapy are external beam radiation, which delivers radiation by a machine outside of the body, and brachytherapy, which delivers radiation by radioactive material placed in the body near or within the tumor itself. Advances in radiation therapy now allow for better visualization of the patient's anatomy to more clearly focus the radiation, improved manipulation of necessary doses, less of an exit dose with proton therapy, and more precise alignment of the patient for daily treatments. The presentation by radiation oncologist Dr. Karen E. Hoffman included multiple images to help the audience to truly envision what a patient would experience throughout his or her time in radiation therapy—from the first day of stimulation, through daily visits, to follow-up care after radiation is complete.

In breast cancer patients, radiation therapy can be utilized after breast-conserving surgery and is administered over the whole breast. Radiation therapy is also used in select women who have clinically significant risks of recurrence after a mastectomy. Radiation therapy can improve both local cancer control and breast cancer survival. Radiation therapy is a treatment option for the majority of men with localized prostate cancer. Dr. Hoffman said dose-escalated radiation therapy improves prostate cancer control compared with standard-dose radiation. The addition of androgen deprivation therapy to external beam radiation therapy improves prostate cancer survival for men whose cancer has unfavorable prognostic factors.

The development of radiation-induced toxicity depends on multiple factors, including the area of the body treated, dose given per day, total dose given, patient's performance status, and concomitant therapy. Acute toxicity can occur hours to weeks after radiation exposure and lasts up to 3 months after receiving therapy. Primary acute toxicities include radiation dermatitis, otitis externa, serous otitis media, osteoradionecrosis, xerostomia, thick saliva, dysgeusia, mucositis, nausea/vomiting, diarrhea, proctitis, acute cystitis, and pneumonitis. Chronic toxicities usually present 6 or more months after a course of radiation. Potential chronic toxicities include oropharynx issues, cardiac toxicity, pulmonary fibrosis, radiation necrosis, cognition issues, infertility, and development of a secondary malignancy. Each of these toxicities can negatively affect a patient's quality of life and potentially duration of life. Pharmacologic strategies are available to manage many acute radiation toxicities and some chronic radiation toxicities. It is essential for pharmacists to be involved in educating patients who are receiving radiation therapy about the potential side effects and risks of treatment as well as assisting providers in management strategies to prevent and treat these radiation-induced toxicities.

Two Residents' Perspectives on the HOPA 11th Annual Conference

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The 11th Annual HOPA Conference was held in Austin, TX, this past March and provided learning opportunities for all attendees—from students to residents to seasoned clinical pharmacists. Two second-year oncology pharmacy residents from the University of Colorado describe their experiences.

Jennifer Grabowski, PharmD

Because this year was my first time attending the HOPA clinical conference, I wasn't sure what to expect. I knew it would provide great networking opportunities and educational experiences, but aside from that, I was going in with an open mind. I was pleasantly surprised to find a relaxed, yet professional, atmosphere at the conference. The presentations were educational and enjoyable, and the career fair was less intimidating than I had imagined. It was also great to connect with old classmates and hear about their accomplishments during their residency year. The city of Austin was as unique as it claims to be and just as exciting to explore. I consider this HOPA conference to be my first of many.

I do have some advice for future residents or students who will be going to the HOPA annual conference for the first time:

1. Download the handouts ahead of time. And, if you're technologically challenged like me, print them off to be able to take notes during the conference. Much of the information is not available on the slides, and keeping notes can help you remember the key concepts.
2. Take advantage of the career fair. Not only is it a great tool for launching or expanding your career, it also helps you explore a variety of clinical opportunities you may not have otherwise been interested in or even considered. Even if the positions listed don't seem to interest you on paper, speaking with the representatives will help you gain a better understanding of the opportunities available and may change your opinion of working in various environments.
3. Check out the research posters. Support your coresidents nationwide by appreciating their work. Chances are they are investigating clinical issues you may come across in your future practice.
4. Be prepared to hand out your CV. The networking opportunities are everywhere and not only limited to the career fair. You will likely meet somebody who knows somebody who knows somebody who will be beneficial to your future and help to expand your network of colleagues.
5. Enjoy the city. Austin was a beautiful city to explore, rich in music, food, and Texas culture. Although we may be there for "business," take some time and enjoy the atmosphere of whatever city the conference happens to be in that year.
6. Don't forget to turn in your clickers at the end of the conference! If you forget, they know who you are and they will find you.
7. Most importantly, learn lots and have fun!

Joseph Kaiser, PharmD

The HOPA conference was an extremely valuable and rewarding experience. As a PGY2 oncology pharmacy resident, my initial intent for attending this conference was to present my research project. However, this event turned out to be so much more. The educational sessions provided me with cutting-edge information that can't be found from some of the other nationally recognized oncology organizations, such as National Comprehensive Cancer Network or American Society of Clinical Oncologists. These discussions were focused on the practical pharmaceutical aspects of cancer care. I gained a great wealth of insight and clinical knowledge that will benefit me and my patients as I move forward in my career. My only regret was that I could not attend all of the sessions.

Besides the vast amount of educational opportunities available, this conference opened my eyes to the fact that oncology pharmacy is a relatively small and tight-knit community. The networking opportunities were endless, and I was able to make contacts that I will be able to count on for shared knowledge and expertise, ultimately bettering the services I offer to the healthcare team I will be working with and improving the treatment of our patients.

I would recommend attending the HOPA annual conference to not only PGY2 oncology pharmacy residents, but to PGY1 residents and students alike. Anyone who has an interest in oncology pharmacy stands to gain from attending this conference. HOPA offers very reasonable registration rates for residents and students, as well as the opportunity to apply for a travel grant, helping to make attendance affordable to those who have limited resources. Considering this and the networking and educational opportunities, the HOPA annual conference is a tremendous value and well worth the cost. I am very much looking forward to the HOPA 12th Annual Conference. See you there!

The Resident's Cubicle: Advice to Those Embarking on a New Oncology Career

Brandi Anders, PharmD
Hematology/Oncology Clinical Pharmacist
Wake Forest Baptist Health
Winston-Salem, NC

This time of the year marks new beginnings for individuals in many different aspects of oncology pharmacy. You may have made it through the first few months of your oncology pharmacy residency and you are wondering, "What have I gotten myself into?" Or, maybe you have finished a PGY2 oncology residency and have just started a new position as an oncology clinical pharmacist and you question if you are really ready for this challenge. Whatever situation you may find yourself in, the new and unknown can be a scary place. I have found that the best way to face these challenges is with the help and advice of those who have been there—those who came, saw, and conquered. For this edition of The Resident's Cubicle, I have compiled advice from several of my colleagues and mentors who have helped me along my path to becoming an oncology clinical pharmacist. I hope that their wisdom will offer support to you as well.

It is an exciting time as the field of oncology is growing immensely! Begin your PGY2 with an open mind to all oncology specialties. Please also understand that 1 year of training will not make you an oncology expert. The goal of this program is to provide you with the essential tools necessary to pursue any oncology specialty area, with the understanding that oncology specialization requires years of experience.

Erin Bailey, PharmD BCOP
GYN/GU Oncology Clinical Pharmacist
Huntsman Cancer Institute, University of Utah
Salt Lake City, UT
PGY2 Oncology Residency: Huntsman Cancer Institute—University of Utah

My advice to new oncology clinical pharmacists just starting their careers would be to continue to seek mentorship from seasoned oncology clinical pharmacists and to not be afraid to ask your colleagues questions as you set up your practice. One of the great things about practicing in oncology pharmacy is the great community of pharmacists who are always willing to share innovative ideas and advice. There are some great e-mail discussion and Google groups out there. I would recommend joining HOPA Central if you haven't already!

Megan Bodge, PharmD
Inpatient Oncology (Solid Tumor) Clinical Pharmacist
West Virginia University Healthcare
Morgantown, WV
PGY2 Oncology Residency: Vanderbilt University Medical Center

Learn something from every patient encounter. It could be asking the patient to describe a drug toxicity or looking up the evidence to support a chemo regimen that was given in the past. Every patient offers a unique case study to learn about cancer and chemotherapy. There's so much to learn that you don't want to miss an opportunity for patient-centered learning.

John Bossaer, PharmD BCPS BCOP
Associate Professor, Department of Pharmacy Practice
East Tennessee State University Bill Gatton College of Pharmacy
Johnson City, TN
PGY2 Oncology Residency: Medical University of South Carolina

I would tell a new PGY2 oncology resident to enter the year with an open mind. Oncology is such a diverse and vastly different realm of practice than any other area of clinical pharmacy. The things that were really important during your PGY1 year might be ancillary in the field of oncology. Keep an open mind about what you like and what you don't like, and search for the area of oncology that really interests you. There are countless subfields of oncology that you may like and others that you don't, but entering the year with an open mind will help you find what is right for you.

David Eplin, PharmD BCOP
Outpatient BMT Clinical Specialist
Nashville VA Medical Center
Nashville, TN
PGY2 Oncology Residency: University of Pittsburgh Medical Center

It will definitely be overwhelming with all the new information that you will have to learn with all the novel agents and mechanisms that are currently being studied in the world of oncology. And the expectations from your preceptors and medical staff will far surpass what you have experienced so far as a PGY1 and as a student. But it will all be worth it in the end. There will be rotations that you may love and experiences that you may dislike, but learn from everyone and everything because you will never have a time like this to dedicate all of your energy into your training. Keep in contact with all of your peers and network with others in your field because you never know when you might need to collaborate and reach out to them!

Maho Hibino, PharmD BCOP
Clinical Oncology Pharmacist
Wake Forest Baptist Health
Winston-Salem, NC
PGY2 Oncology Residency: University of Washington Medicine

I found it beneficial to maintain charts that were easy to update each rotation. For example, I kept a chart including landmark trials with included patient populations and results to reference throughout the year. I also kept an ongoing chart with chemotherapeutic agents and their unique attributes to also reference as I progressed through my year. These allowed me to both retrieve information quickly as well as review key points.

Jordan Hill, PharmD
Clinical Pharmacist
West Virginia University Healthcare
Morgantown, WV
PGY2 Oncology Residency: The James Cancer Hospital at The Ohio State University

Try not to feel overwhelmed with all of the new topics and medications you will be learning about. Remember that most of your counterparts doing other PGY2s (such as internal medicine or critical care) are honing skills and knowledge they learned as PGY1s. As an oncology PGY2, you will be learning about disease states and medications you may have never seen or heard of before. Your learning curve will be vastly different than your counterparts, and that is OK. Do your best to take advantage of all the learning opportunities presented to you and then things will start to piece together.

Daphne O'Hara, PharmD BCOP
Stem Cell Transplant Clinical Pharmacist
University of Miami, Miller School of Medicine
PGY2 Oncology Residency: Indiana University Health System

Begin developing your medical library early in residency. Pull supporting primary literature for each regimen, review guidelines to learn staging and treatment algorithms, and utilize your drug resources to better understand adverse effects/mechanisms of action. These drug information skills and organization will help you to develop your oncology foundation.

Laura Beth Parsons, PharmD
Oncology Clinical Pharmacist
University of Louisville, James Graham Brown Cancer Center, Jewish Medical Center Northeast
Louisville, KY
PGY2 Oncology Residency: University of Louisville/James Graham Brown Cancer Center/KentuckyOne Health

I love being a hematology/oncology pharmacist because of the unique relationship that we get to have with our patients. I was encouraged by coresidents and some preceptors not to get too close to my patients or let their outcomes have an impact on my personal life. I strongly feel that I love my job and what I get to do because I *do* let their outcomes and personal stories affect my personal life. My advice is to get to know, love, and truly cherish your patients and their families. You have been given a unique opportunity to help people during one of the most difficult and vulnerable times in their lives. I have become a better person and pharmacist just because of the people I get to take care of every single day. Your patients need you, but there will be some days you may need them even more.

Morgan Pendleton, PharmD BCOP
Pediatric and Adult Hematology/Oncology Clinical Pharmacist
Wake Forest Baptist Health
Winston-Salem, NC
PGY2 Oncology Residency: Wake Forest Baptist Health

Treasure the moments you are able to help make a difference for your patients—even the smallest gestures can mean so much to them—and tuck those memories away for when things get difficult. Oncology is full of sad times that weigh on your heart, but being able to remember all the good that you do and those patients who are able to thrive really helps to pull you through the tough times.

Alex Shillingburg, PharmD, BCOP
Bone Marrow Transplant Clinical Specialist
West Virginia University Healthcare
Morgantown, WV
PGY2 Oncology Residency: West Virginia University Healthcare

Always remember that as a resident you don't have to know everything. Take this time to learn as much as possible. Read a lot and take advantage of your preceptors' knowledge. Right now, you're surrounded by oncology pharmacist mentors with a wealth of experience. Ask questions and pick their brains while you still can!

Christan Thomas, PharmD BCOP
Assistant Clinical Professor, St John's University College of Pharmacy
Lymphoma/Multiple Myeloma Clinical Pharmacist, Weill Cornell Medical Center
New York, NY
PGY2 Oncology Residency: NewYork-Presbyterian Hospital

So, what can new residents and practitioners do to avoid becoming overwhelmed and succeed in this new endeavor? Sage advice I have received includes the following: learn to manage your time wisely, prioritize and reprioritize regularly, and make a plan and stick to it. Work hard and keep yourself motivated, but also remember to take some time for yourself. Do things you enjoy on a regular basis. Spend time with family and friends, take a walk, watch a movie, or read a book. Anything that makes you happy and gives you time to unwind is important. Don't procrastinate. Try to stay ahead of projects and deadlines to avoid stress. Reach out to and seek advice from preceptors and mentors, and don't be afraid to ask questions. Remember your passion for your patients and your practice. There is a reason that you chose the field of oncology; remember that reason!

Board Update: A Year of Introspection and External Connections

Scott Soefje, PharmD MBA BCOP FCCP, HOPA President

Introspection

As professional organizations grow and mature, it is necessary to stop and self-assess to determine if everything is going well and if the organization is moving in the right direction. This year is one of those times for HOPA. We have started a systematic review of all aspects of HOPA. I would like to explain what we are looking at and then talk about several of the organizations that we have connected with in the past few months.

Earlier this year, we completed negotiations on a new contract with Association Management Center (AMC). We feel this contract has measurable outcomes, meets the needs of HOPA, and provides fair compensation for AMC. We also have completed a review of our health policy advisors and, through a request for proposal, elected to stay with the District Policy Group. We will be negotiating a new contract with them at the end of the year.

The AMC staff completed a review of HOPA policies and procedures and we have updated and modified the policies to match our current initiatives. We also asked each committee to review their policies and submit any updates and changes by the end of the year. Our goal is to begin the next committee year (which starts in June 2016) with a complete and updated set of policies and procedures.

The board completed a self-assessment using a tool provided by BoardSource. We identified gaps, changed some of our board orientation process to fill those gaps, and started an action plan to finish addressing the areas we felt needed the most attention. This is an ongoing evaluation process. As part of this process, we have developed a twice yearly review of the HOPA Executive Director (ED) that addresses board feedback and the progress made toward goals that the ED develops at the beginning of the year. We finalize the evaluation process by providing annual feedback to the ED on the effectiveness of the AMC staff. We feel this total review process creates an environment of continuous improvement in which we learn from mistakes and capitalize on successes.

As many people have realized, the committee structure at HOPA has become unwieldy. With the addition of BCOP recertification, we added fix to six new committees and task forces to meet the needs of the proposal that we submitted. Charges originally given to one committee have moved to another to meet current needs; we have overlapping charges in some cases, and overall the committee structure is losing its effectiveness. Our plan is to develop a task force (yes, another one) to develop a new committee structure to meet our current needs. The task force will start in early 2016 and make a recommendation to the board for implementation in the 2017 committee year. It sounds like a long time, but we want to get this right and not rush the process. Stay tuned for updates on committee structure.

We also will be reviewing our bylaws. There are several items, such as certain committees, that may no longer be necessary for our organization. As we develop new ways to do things, we will update the bylaws to reflect our roles and obligations. This review also will occur in 2016 and requires a membership vote.

The last introspection area to discuss is that HOPA has started the process of revitalizing our website and updating our brand. We plan to introduce our new brand and website shortly after the 2016 annual meeting. We will be modernizing the look and feel of the HOPA brand, and the website will be more user friendly and reflect state-of-the-art Web design features. A small part of this was the move to the HOPA Central messaging platform, which has been successful and offers tremendous opportunities as we grow.

External Connections

From the comments above, you might think HOPA is cloistered in a room somewhere redeveloping our organization. That is far from reality. This year has been a banner year for us in making external contacts. In some cases, organizations sought us out, and in others, we did the reaching out to make the connection.

We had great meetings with the Association of Community Cancer Centers (ACCC), European Society of Oncology Pharmacists, and the Advanced Practice Society for Hematology and Oncology. As a result, we are looking to develop collaborative educational meetings that each organization can share. ACCC helped market our Pharmacy Practice Management Program and endorsed our Investigational Drug Service standards. The United Oncology Pharmacy Organization, a global organization of oncology pharmacy associations, invited HOPA to join. We deferred this membership for now because of our commitment to BCOP education; however, we will continue conversations with our international colleagues. We started a dialog with the Livestrong Foundation because they have several surveys and patient advocacy initiatives that we think would alignwith HOPA's goals.

Two new groups, the National Community Oncology Dispensing Association (NCODA) and the Community Oncology Pharmacy Association (COPA), a subgroup of the Community Oncology Alliance (COA), met with HOPA to discuss issues around oral chemotherapy. These groups are working to maintain control of the oral medications in the community setting. HOPA is working with both groups to ensure that patients have access to oral chemotherapy. COPA helped promote our Practice Management Program and NCODA has asked us to join their advisory board.

A unique opportunity to develop joint educational material with the American Society of Pediatric Hematology/Oncology and the Association of Pediatric Hematology/Oncology Nurses has arisen. Grant funding will allow these three organizations to develop educational materials focusing on pediatric hematology/oncology

patients. We have asked two of our members, Susannah Koontz and Brooke Bernhardt, to represent HOPA in developing this material.

HOPA was one of two pharmacy organizations at the table for the American Society of Clinical Oncology and Oncology Nursing Society (ONS) update and revision of the handling hazardous drugs guidelines. This was a unique opportunity to give the pharmacy perspective on chemotherapy ordering, mixing, handling, and administration. We are working with ONS on several initiatives and have asked them to endorse our IDS standards.

Through our relationship with the Joint Commission of Pharmacy Practitioners (JCPP), we partnered with the Academy of Managed Care Pharmacy (AMCP) to conduct a survey of a random sample of our membership and of AMCP's membership regarding the naming convention for biosimilars. The survey is complete and will be published shortly. We are considering joining Pharmacy Workforce Coalition, which will give us the opportunity to participate in their workforce surveys. Through JCPP, we are meeting with the American Association of Colleges of Pharmacy to discuss the current quantity of oncology education in pharmacy schools. Finally, we have meetings in November in Washington, DC, with the American Pharmacy Association and American Society of Health-Systems Pharmacy where we plan to discuss the role and impact of the hematology/oncology pharmacist.

As you can see, we have been very busy expanding our recognition and working to find areas where we can collaborate with other organizations. These discussions have been mutually beneficial and set HOPA up as the voice of the hematology/oncology pharmacist. We plan to continue these collaborations and seek others that benefit HOPA and its membership.

Recalls and Safety Alerts from the FDA

Jennifer Kwon, PharmD BCOP
Clinical Pharmacist Specialist, Hematology/Oncology
VA Medical Center
West Palm Beach, FL

Recalls

Carboplatin, Cytarabine, Gemcitabine, and Methotrexate

Mylan has issued a voluntary recall of select lots of injectable products including gemcitabine, carboplatin, methotrexate, and cytarabine. This is because of the presence of visible particles observed during a routine quality testing. There have been no adverse events reported related to this recall.

http://www.fda.gov/Safety/Recalls/ucm450140.htm

Fluorouracil Injection (Adrucil)

Teva Parenteral Medicines issued a voluntary recall of eight lots of fluorouracil injection (5 g/100 mL) due to the potential presence of silicone rubber pieces from a filter diaphragm and fluorouracil crystals. There have been no adverse events reported.
http://www.fda.gov/Safety/Recalls/ucm445584.htm.

Prescription Center Pharmacy Recall in North Carolina

The North Carolina Board of Pharmacy has ordered a recall for all nonsterile and sterile products compounded, repackaged, and distributed by Prescription Center Pharmacy in Fayetteville, NC, during the time period between September 10, 2014 and March 10, 2015. Prescription Center Pharmacy distributed products in all 50 states and Canada during the time period of the recall. The recall was mandated because the pharmacy was unable to ensure sterility, stability, and potency for their products. Furthermore, the North Carolina Board of Pharmacy has ordered the Prescription Center Pharmacy to close. There have been no adverse events reported from the recalled products.
http://www.fda.gov/Safety/Recalls/ucm441046.htm

Safety Alerts

Bevacizumab (Avastin)

An embryo-fetal toxicity section has been added to the warnings and precautions for bevacizumab. Animal studies resulted in congenital malformations with the administration of bevacizumab to pregnant rabbits. These animal models also have linked angiogenesis and vascular endothelial growth factor (VEGF) and VEGF Receptor 2 to essential aspects of female reproduction, embryo-fetal development, and postnatal development. Pregnant women should be aware of the potential risk to a fetus and be counseled on using effective contraception during treatment and for 6 months after completion of therapy with bevacizumab.

The package labeling on use in specific populations has been updated to include the animal data in pregnancy and a section on females and males of reproductive potential.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm287610.htm

Capecitabine (Xeloda)

Patients with certain homozygous or compound heterozygous mutations in the dihydropyrimidine dehydrogenase deficiency (DPD) gene that result in absence of DPD activity are at increased risk for capecitabine toxicity; acute early-onset, severe, life-threatening, or fatal (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity also may be at increased risk for toxicity. These findings were based on postmarketing reports. Capecitabine should be held or discontinued based on clinical assessment of the patient and observed toxicities. There is no capecitabine dose shown to be safe for patients with absence of DPD activity and there is

insufficient data to recommend a specific dose in patients with partial DPD activity.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm422806.htm

Carfilzomib (Kyprolis)

The warnings and precautions section of the prescribing information for carfilzomib has been updated to include thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) and posterior reversible encephalopathy syndrome (PRES). Therapy should be interrupted if TTP/HUS is suspected and the syndromes should be managed appropriately. The safety of starting carfilzomib therapy after a TTP/HUS diagnosis is unknown. Though rare, there have been reports of PRES with carfilzomib use. Symptoms of PRES include seizure, headaches, lethargy, confusion, blindness, altered consciousness, hypertension, and other visual or neurological disturbances. Therapy should be discontinued if PRES is suspected.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm441458.htm

Cetuximab (Erbitux)

The updated warnings and precautions section now includes information about increased tumor progression and increased mortality in patients with RAS-mutant metastatic colorectal cancer. Cetuximab is not indicated for the treatment of patients with colorectal cancer having mutations in the exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-RAS or N-RAS. Subset analyses of RAS-mutant and wild-type populations across several randomized clinical trials showed cetuximab given to patients with RAS mutations had no clinical benefit with treatment-related toxicity. Reports of Stevens-Johnson syndrome, toxic epidermal necrolysis, and life-threatening and fatal bullous mucocutaneous disease have been made with cetuximab use. These dermatologic toxicities are now included in the warnings and precautions section of the product labeling.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm289979.htm

Ferumoxytol (Faraheme)

The new labeling for ferumoxytol includes a boxed warning regarding the risk of serious and potentially fatal hypersensitivity reactions. Ferumoxytol should only be administered when personnel and therapies are immediately available to treat anaphylaxis and other hypersensitivity reactions. Patient should be observed for signs and symptoms of hypersensitivity for at least 30 minutes following the infusion. Blood pressure and pulse should also be monitored during and after the infusion. Hypersensitivity reactions have occurred in patients that previously tolerated ferumoxytol. A contraindication also has been added for patients with a history of allergic reaction to any intravenous iron product. The warnings and precautions section for ferumoxytol has been updated to caution use in elderly patients (>65 years of age) or patients with multiple comorbidities, as these patients may have more severe outcomes if they experience a serious hypersensitivity reaction.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm235636.htm

Interferon alfa-2b (Intron A)

The warnings and precautions section for interferon alfa-2b has been updated to include the risk of gastrointestinal disorders, neuropsychiatric disorders, and hepatic monitoring parameters. There is an increased risk of hepatic decompensation in patients with cirrhosis. Patients who develop liver function abnormalities during treatment should be monitored closely. Liver function tests (serum bilirubin, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase) should be monitored at 2, 8, and 12 weeks after starting interferon alfa-2b, then every 6 months afterwards. Interferon alfa-2b should be discontinued for severe (grade 3) hepatic damage or hepatic decompensation (Child-Pugh score > 6; class B and C). In patients who experience worsening psychiatric symptoms or those who develop suicidal ideation or aggressive behavior towards others, interferon alfa-2b should be discontinued and patients should be monitored closely with psychiatric interventions as appropriate.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm311115.htm

Panitumumab (Vectibix)

The updated warnings and precautions address the lack of benefit of panitumumab in patients with metastatic colorectal cancer with RAS-mutations; specifically somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of KRAS or NRAS. Results from a retrospective subset analyses across several randomized clinical trials showed no clinical benefit in patients with tumors having the RAS mutations, and exposed those patients to anti-EGFR-related adverse reactions. In study 3 of the package insert, the subgroup analysis demonstrated the overall survival was shorter in patients with metastatic colorectal cancers with RAS mutations who received panitumumab and FOLFOX versus FOLFOX alone.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm319207.htm

Pazopanib (Votrient)

The updated warnings and precautions section for pazopanib includes the increased risk for hepatotoxicity in patients >65 years. Liver function tests should be monitored regularly while on pazopanib therapy. There have been reports of retinal detachment and this has been added in the postmarketing section under adverse reactions.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm303649.htm

Pertuzumab (Perjeta)

The package labeling for pertuzumab has been updated with additional information on embryo-fetal toxicity. If a patient becomes pregnant while receiving pertuzumab or within 7 months following the last dose of this drug in combination with trastuzumab, the patient should be informed of the potential hazard to the fetus. Female patients of reproductive potential should be counseled on avoiding becoming pregnant while receiving pertuzumab therapy or within 7 months after completion of pertuzumab therapy in combination with trastuzumab. Women who may be exposed to pertuzumab during pregnancy or become pregnant within 7 months after the last dose of pertuzumab should enroll in the Mother Pregnancy Registry by contacting

800.690.6720. If a patient becomes pregnant while receiving treatment with pertuzumab or within 7 months following the last dose of this drug, immediately report the exposure to the Genentech Adverse Event Line at 888.835.2555.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm450065.htm

Pomalidomide (Pomalyst)

The risk of venous and arterial thromboembolism has been added to the black box warnings and the warnings and precautions section of the package labeling for pomalidomide. There is an increased risk of both arterial and venous thromboembolic events in patients with multiple myeloma receiving pomalidomide with dexamethasone. Due to the increased risk of thrombotic events, modifiable risk factors should be minimized and antithrombotic prophylaxis should be administered. Several updates have been made to the warnings and precautions section of the package insert for pomalidomide, including the risk for hematologic toxicity, hepatotoxocity, hypersensitivity reactions, dizziness and confusion, neuropathy, and tumor lysis syndrome. The most frequently reported grade 3/4 adverse reaction was neutropenia, followed by anemia and thrombocytopenia in patients receiving pomalidomide in combination with dexamethasone. Cases of hepatic failure have been reported in patients receiving pomalidomide. Liver function tests should be monitored at least monthly and pomalidomide therapy should be stopped if elevation in liver enzymes is present. Angioedema and severe dermatologic reactions have occurred with pomalidomide use. The medication should be permanently discontinued for any severe dermatologic reactions. Patients receiving both pomalidomide and dexamethasone may experience dizziness and a confused state. Patients should be instructed to avoid situations where dizziness or confusion may be a problem and not to take other medications that may cause overlapping symptoms. Neuropathy and tumor lysis may also occur in patients treated with pomalidomide. Appropriate monitoring and precautions should be taken for patients at risk for tumor lysis syndrome.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm446484.htm

Sunitinib (Sutent)

Updates have been made to the warnings and precautions section to include the risk of thrombotic microangiopathy (TMA). Incidences of thrombotic thrombocytopenic purpura and hemolytic uremia have been reported in clinical trials and in postmarketing surveillance of patients receiving sunitinib. For patients who develop TMA, sunitinib therapy should be discontinued. Additional elements of the warnings and precautions section have been updated. "Left ventricular dysfunction" has been changed to "cardiovascular events," and "myocardial disorders" has been replaced with "myocardial ischemia, myocardial infarctions." Sunitinib should be used with caution in patients who are at risk or who have a history of these events.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm224050.htm

Trastuzumab (Herceptin)

The package labeling for trastuzumab has been updated to include information on potential embryo-fetal toxicity. Female patients of reproductive potential should be counseled on avoiding becoming pregnant while receiving trastuzumab therapy. If contraceptive methods are utilized, patients should be advised to use effective contraception during treatment and for at least 7 months after the last dose of trastuzumab. If a patient becomes pregnant while receiving trastuzumab or within 7 months following the last dose of the medication, inform the patient of the potential hazard to the fetus.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm392225.htm

Vismodegib (Erivedge)

The boxed warning for vismodegib has been edited to address the embryo-fetal toxicity of the drug. Teratogenic effects of vismodegib include severe midline defects, missing digits, and other irreversible malformations, as well as embryo-fetal death. The pregnancy status of females of reproductive potential should be verified within 7 days prior to starting vismodegib therapy. Education for using effective contraception during and after vismodegib therapy should be provided for female patients. Male patients should be counseled on the risk of vismodegib exposure through semen and to use condoms with a pregnant partner or female partner of reproductive potential.

The updated warnings and precautions section for vismodegib also addresses measures for blood donation and semen donation. Patients should not donate blood or blood products while taking vismodegib and for 7 months after the completion of therapy. Male patients should not donate semen during and for 3 months after the last dose of vismodegib.

The use in specific populations section of the package labeling now discusses pregnancy risk, lactation, and hepatic impairment. In animal reproduction studies, oral administration of vismodegib at doses lower than the recommended doses for humans led to embryotoxicity, fetotoxicity, and teratogenicity in rats. There are no available data on the use of vismodegib in pregnant females. Pregnant woman should be counseled on the potential risk to a fetus. No data are available addressing the presence of vismodegib in human milk, the effects of the drug on breastfed infants, or the effects of the drug on milk production. Due to the potential for serious adverse reactions in breastfed infants from vismodegib, nursing women should be instructed not to breastfeed while on vismodegib therapy. In patients with hepatic impairment, there are no dose adjustments required for vismodegib.

An additional section, females and males of reproductive potential, has been added to the package labeling for the drug. Both female and male patients need to be counseled on vismodegib causing fetal harm and to use effective contraception measures or condoms during sexual intercourse. Vismodegib can potentially cause infertility as amenorrhea can occur in females, and the reversibility of amenorrhea is unknown at this time.
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm450147.htm

New Drugs and Drug Updates: Changes in Labeling, Indications, and Dosage Forms (March 1, 2015–May 31, 2015)

Bonnie A. Labdi, PharmD
Clinical Pharmacy Specialist–Hematology/Oncology
Memorial Hermann Cancer Center
Houston, TX

Xeloda® (Capecitabine)

On March 2, the U.S. Food and Drug Administration (FDA) approved changes in the labeling. Toxic encephalopathy was added to the adverse events section of the label.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/020896Orig1s036ltr.pdf

Opdivo® (Nivolumab)

On March 4, the FDA approved the new drug, nivolumab. It is indicated for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after treatment with platinum-based therapy. For more detailed information on this new drug, please see "Drug Update—Nivolumab" on page 23 of this newsletter.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125527Orig1s000ltr.pdf

Rapamune® (Sirolimus)

On March 6, the FDA approved changes in the labeling. Diabetes mellitus was added to the metabolic/nutritional subsection of the adverse events section of the label. In addition, in the postmarketing experience section of the label, posterior reversible encephalopathy syndrome was added under the nervous system subsection. These changes also were reflected in the medication guide.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/021083Orig1s056,021110Orig1s074ltr.pdf

Zarxio® (Filgrastim-Sndz)

On March 6, the FDA approved the biologics license application for this new product.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125553Orig1s000ltr.pdf

Levoleucovorin Calcium

On March 9, the FDA approved the abbreviated new drug approval for this product.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/203563Orig1s000ltr.pdf

Treanda® (Bendamustine)

On March 10, the FDA approved a labeling revision concerning the incompatibility of the liquid formulation and certain closed system transfer devices.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/022249Orig1s019ltr.pdf

Erbitux® (Cetuximab)

On March 11, the FDA approved a labeling revision concerning the risk of skin and subcutaneous tissue disorders.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125084Orig1s263ltr.pdf

Vectibix® (Panitumumab)

On March 11, the FDA approved several labeling revisions pertaining to indications and usage, dosage and administration, warnings and precautions, and clinical pharmacology.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125147Orig1s200ltr.pdf

Yervoy® (Ipilimumab)

On March 19, the FDA approved a modification to the clinical pharmacology section of the label.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125377Orig1s072ltr.pdf

Xeloda® (Capecitabine)

On March 19, the FDA approved the removal of dipyrimidine dehydrogenase (DPD) deficiency from the contraindications section of the label. The presence of DPD deficiency was updated in the warnings and precautions section of the label.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/020896Orig1s037ltr.pdf

Zytiga® (Abiraterone Acetate)

On March 20, the FDA approved changes in labeling. The final results of study COU-AA-302 were incorporated into the clinical studies section of the label.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/202379Orig1s016ltr.pdf

Xalkori® (Crizotinib)

On March 20, the FDA approved the addition of QTc prolongation and heart rate effects to the pharmacodynamics section of the labeling.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/202570Orig1s013ltr.pdf

Kyprolis® (Carfilzomib)

On March 27, the FDA approved additional information regarding thrombocytopenic thrombotic purpura/hemolytic uremic syndrome and posterior reversible encephalopathy syndrome to the warnings and precautions section of the labeling.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/202714Orig1s008ltr.pdf

Neupogen® (Filgrastim)

On March 30, the FDA approved a new, additional indication for filgrastim. The drug is now indicated to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome).
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/103353Orig1s5183ltr.pdf

Tykerb® (Lapatinib)

On March 31, the FDA approved a revision to the prescribing information which lists the carcinogenic potential of the drug.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/022059Orig1s020ltr.pdf

Votrient® (Pazopanib)

On March 31, the FDA approved a revision that lists the increased risk for hepatotoxicity in patients >65 years. It also includes the addition of retinal detachment/tear to the postmarketing surveillance section.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/022465Orig1s020ltr.pdf

Temodar® (Temozolomide)

On April 2, the FDA approved the addition of the risk for diabetes insipidus and the reactivation of certain infections, such as cytomegalovirus and hepatitis B.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/021029Orig1s028ltr.pdf

Erbitux® (Cetuximab)

On April 10, the FDA approved changes in labeling, specifically, warnings regarding increased tumor progression, increased mortality, and lack of benefit in treating patients with Ras-mutant metastatic colorectal cancer.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125084Orig1s262ltr.pdf

Herceptin® (Trastuzumab)

On April 23, the FDA approved changes in labeling to include changes to the drug interactions section, based on a new nonlinear pharmacokinetic model.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/103792Orig1s5327ltr.pdf

Pomalyst® (Pomalidomide)

On April 23, the FDA approved several changes to the product labeling. Tumor lysis syndrome and pancytopenia were added as well as the risk for angioedema. Results from a study looking at QTc prolongation were included in the updated labeling.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/204026Orig1s005,s006,s008ltr.pdf

Sutent® (Sunitimib)

On April 24, new safety information was added to the approved labeling. The new information pertains to the risk of thrombotic microangiopathy, hemolytic uremic syndrome, and thrombocytopenic purpura. The warnings and precautions section reworded some of the cardiac toxicities. In addition, the risk for a heart attack was added in the risk evaluation and mitigation strategies guide.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/021938Orig1s028,s029ltr.pdf

Cyramza® (Ramucirumab)

On April 24, the FDA approved a new indication for ramucirumab. It is now indicated to be used in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125477Orig1s011ltr.pdf

Tarceva® (Erlotinib)

On April 27, the FDA approved a change in labeling. New data regarding its use in pediatric patients are now included in the FDA-approved labeling.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/021743Orig2s021ltr.pdf

Avastin® (Bevacizumab)

On May 7, the FDA approved a change in labeling for bevacizumab. The addition of a new warning in the warnings and precautions section of embryo-fetal toxicity, along with updates in the subsections on pregnancy and lactation, are now included in the FDA-approved label. This information was also included in the patient counseling information section.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125085Orig1s308ltr.pdf

Zytiga® (Abiraterone Acetate)

On May 20, the FDA approved changes in labeling. Food effect data from studies 212082PCR2008 and 212082PCR1005 were incorporated into the label. In addition, rhabdomyolysis and myopathy were added to the adverse events section of the label.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/202379Orig1s018ltr.pdf

Erivedge® (Vismodegib)

On May 21, the FDA approved numerous updates to the labeling. The majority of these updates pertain to pharmacokinetic data about the drug and its presence in the breast milk, blood, and semen of patients who take vismodegib.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/203388Orig1s005,s006,s007,s008ltr.pdf

Rapamune® (Sirolimus)

On May 28, the FDA approved the addition of a new indication in the label. Sirolimus is now indicated for the treatment of patients with lymphangioleiomyomatosis.
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/021083Orig1s055,021110Orig1s073ltr.pdf

Deferasirox (Jadenu®)

Class: Iron chelator

Indications: Chronic iron overload due to blood transfusions in patients ≥2 years old, chronic iron overload due to non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron concentration (LIC) of at least 5 mg Fe per gram of dry weight (Fe/g dw) and a serum ferritin greater than 300 mcg/L

Dose

- Transfusional iron overload: initial dose 14 mg/kg once daily
- NTDT syndromes: initial dose 7 mg/kg once daily

Dose modifications

- Transfusional iron overload
  - Adjust dose by 3.5 or 7 mg/kg/day every 3 to 6 months based on serum ferritin trends (max 28 mg/kg/day)
- NTDT syndromes
  - Consider increasing to 14 mg/kg once daily after 4 weeks if baseline hepatic iron concentration is >15 mg Fe/g dw
  - Serum ferritin <300 mcg/L, interrupt therapy and obtain hepatic iron concentration
  - Hepatic iron concentration <3 mg Fe/g dw, interrupt therapy and resume treatment when hepatic iron concentration >5 mg Fe/g dw
  - Hepatic iron concentration 3 to 7 mg Fe/ g dw, reduce dose to ≤7 mg/kg
  - Maximum dose 14 mg/kg/day
- Moderate (Child-Pugh B) hepatic impairment: Reduce dose by 50%
- Severe (Child-Pugh C) hepatic impairment: Avoid
- Baseline renal impairment (CrCl 40–60 mL/min); reduce dose by 50%
- Baseline serum creatinine >2 times the upper limit of normal or CrCl < 40 mL/min: Avoid
- Specific dose adjustments for increases in serum creatinine while on treatment

Common adverse effects: Diarrhea, vomiting, nausea, abdominal pain, skin rashes, and increases in serum creatinine

Serious adverse effects: Acute renal failure and death, proteinuria, hepatic failure, gastrointestinal hemorrhage, bone marrow suppression, increased risk of toxicity in elderly, hypersensitivity, skin toxicity, auditory and ocular abnormalities, overchelation

Drug interactions: Deferasirox induces CYP3A4, inhibits CYP2C8 and CYP1A2, and is a substrate of UGT1A1 and UGT1A3. Avoid use with aluminum-containing antacid preparations and bile acid sequestrants.

Deferasirox for Chronic Iron Overload

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Chronic iron overload, or hemochromatosis, occurs when excess iron deposits in the myocardium, liver, pancreas, and other organs, leading to organ failure and death.[1,2] It can occur in patients who require chronic blood transfusions. One unit of red blood cells contains 200–250 mg of iron, and iron overload is common after transfusions of 100 units of red blood cells.[1] Chronic iron overload may also occur in patients with nontransfusion-dependent thalassemia (NTDT). NTDT is characterized by ineffective erythropoiesis and iron often is not effectively excreted.[2]

Chronic iron overload can sometimes be managed by phlebotomy, during which blood is intermittently removed until iron levels return to normal. Patients who cannot be managed with phlebotomy may require iron chelation therapy using parenteral deferoxamine or oral deferasirox.[1] Deferasirox has historically only been available as a soluble tablet, marketed under the brand name Exjade®, which requires dispersion in water, orange juice, or apple juice to make a fine suspension.[3] In March 2015, the U.S. Food and Drug Administration (FDA) approved a new oral tablet formulation of deferasirox, marketed as Jadenu®, to serve as a more convenient option for patients who require therapy for chronic iron overload. Deferasirox is an orally active chelating agent that is selective for iron. It binds iron with high affinity in a 2:1 ratio. While it has very low affinity for zinc and copper, the serum concentration of these trace metals decreases after the administration of deferasirox. The bioavailability of deferasirox oral tablet (Jadenu®) is 36% greater than with deferasirox tablets for oral suspension (Exjade®). In patients switching from deferasirox tablets for oral suspension (Exjade®) to deferasirox oral tablet (Jadenu®), the dose of deferasirox oral tablet (Jadenu®) should be approximately 30% lower, rounded to the nearest whole tablet. The deferasirox oral tablet (Jadenu®) should be swallowed once daily with water or other liquids, preferably at the same time each day, and may be taken on an empty stomach or with a light meal (contains less than 7% fat content and approximately 250 calories). Examples of light meals are a whole wheat English muffin, one small packet of jelly, and 8 fluid ounces of skim milk or a turkey sandwich on whole wheat bread with lettuce, tomato, and a packet of mustard.[4]

The safety and efficacy of deferasirox for transfusional iron overload was evaluated in trials using the original tablets for oral suspension, Exjade®. There are no clinical data for deferasirox oral tablet (Jadenu®). The accelerated approval of deferasirox tablets for oral suspension (Exjade®) in 2005 for the treatment of transfusional iron overload was based on results from a multicenter, open-label, randomized, control trial comparing deferasirox tablets for oral suspension (Exjade®) and subcutaneous deferoxamine in patients with beta-

thalassemia and transfusional hemosiderosis.[5] A total of 586 patients ≥2 years of age were randomized in a 1:1 ratio to receive either deferasirox tablet for oral suspension or subcutaneous deferoxamine. A majority of the patients (51%) were younger than 16 years old. A majority of the patients (97.4%) had received prior chelation therapy. Doses were determined by baseline liver iron concentrations (LIC). Patients had liver biopsy at baseline and after 12 months to measure LIC.

The primary outcome was a reduction in LIC of ≥3 mg Fe/g dw for baseline values ≥10 mg Fe/g dw, reduction of baseline values between 7 and 10 to <7 mg Fe/g dw, or maintenance or reduction for baseline values <7 mg Fe/g dw. Results demonstrated that 52.9% of patients in the deferasirox group, compared to 66.4% in the deferoxamine group, achieved the primary outcome. Noninferiority to deferoxamine was not achieved; however, this was attributed to the use of lower doses of deferasirox relative to deferoxamine administered to patients with LIC values less than 7 mg Fe/g dw. The mean change in LIC was -2.4 mg Fe/g dw in patients treated with deferasirox and -2.9 mg Fe/g dw in patients treated with deferoxamine. In 2013, deferasirox tablets for oral suspension (Exjade®) were approved for the treatment of chronic iron overload in patients ≥10 years of age with NTDT. Deferasirox tablets for oral suspension (Exjade®) also have been evaluated in other patients with chronic anemias and transfusional hemosiderosis, sickle cell disease, thalassemia major, and NTDT. Controlled clinical trials in patients with myelodysplastic syndromes (MDS) have not been performed.[6-9]

Common adverse reactions associated with deferasirox include abdominal pain, diarrhea, increased creatinine, nausea, vomiting, and rash. Deferasirox is also associated with serious adverse effects that may be fatal, therefore carrying black box warnings for renal failure, hepatic failure, and gastrointestinal hemorrhage. Risk of acute renal failure and death is increased in patients with comorbidities and patients in advanced stages of their hematologic disorders. It is recommended to measure serum creatinine and creatinine clearance (CrCl) twice prior to initiation of therapy and monitor renal function at least monthly thereafter. Creatinine should be monitored weekly for the first month and then at least monthly in patients who have baseline renal impairment or increased risk of acute renal failure. Monitoring for proteinuria monthly is also recommended for all patients. Dose reduction, interruption, or discontinuation based on increases in serum creatinine is recommended. Use is contraindicated in patients with CrCl less than 40 mL/minute or serum creatinine greater than two times the upper limit of normal.[4]

Patients may be at an increased risk of hepatic toxicity if they are older than 55 years or have significant comorbidities, including liver cirrhosis and multiorgan failure. Liver transaminases and bilirubin should be measured in all patients before the initiation of therapy, every 2 weeks during the first month, and at least monthly thereafter. Dose modifications or interruption of treatment for severe or persistent elevations are recommended. For patients with baseline moderate hepatic dysfunction (Child-Pugh class B) the dose should be reduced by 50%. Avoid use in patients with Child-Pugh class C hepatic impairment.[4]

Patients should be monitored for signs and symptoms of gastrointestinal (GI) ulceration and hemorrhage. Risk may be increased in elderly patients with advanced hematologic malignancies or low platelet counts. The risk of GI hemorrhage may be increased when patients are also taking nonsteroidal anti-inflammatory drugs, corticosteroids, oral bisphosphonates, or anticoagulants. Deferasirox use is contraindicated in patients with platelet counts of less than 50 x10^9/L.[4]

Other serious adverse events that require monitoring and potential dose modification or discontinuation include bone marrow suppression, hypersensitivity, skin toxicity, auditory and ocular abnormalities, and overchelation. Elderly patients appear to be at an increased risk of experiencing toxicity with deferasirox. Skin reactions can range from mild to moderate rashes to severe reactions such as Stevens-Johnson syndrome and erythema multiforme. Auditory and ocular abnormalities have been described as high-frequency hearing loss, decreased hearing, lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders. Therefore, auditory and ophthalmic testing should be performed at baseline and repeated at least every 12 months.[4]

Dosing is dependent on indication. For patients with transfusional iron overload, the starting dose is 14 mg/kg/day. Serum ferritin should be monitored monthly and the dose should be adjusted if needed every 3 to 6 months. Dose adjustments should be made in 3.5 or 7 mg/kg increments. The maximum dose is 28 mg/kg/day. Discontinuation of therapy should be considered if the serum ferritin falls below 500 mcg/L. For patients with NTDT, treatment should be considered only for an LIC of at least 5 mg Fe/g dw and a serum ferritin greater than 300 mcg/L. The starting dose is 7 mg/kg/day. After 6 months, if the LIC remains greater than 7 mg Fe/g dw, increase the dose to a maximum of 14 mg/kg/day. However, if the baseline LIC is greater than 15 mg Fe/g dw, the dose may be increased to 14 mg/kg/day after 4 weeks. Dose adjustments should be made in 3.5 or 7 mg/kg increments. The maximum dose is 14 mg /kg/day. Monitor serum ferritin monthly and LIC every 6 months. Interrupt treatment when serum ferritin is less than 300 mcg/L and obtain an LIC to determine whether the LIC has fallen to less than 3 mg Fe/g dw. Resume treatment when the LIC is greater than 5 mg Fe/g dw. Available tablet strengths are 90 mg, 180 mg, and 360 mg, and doses should be rounded to the nearest tablet size.[4]

Deferasirox undergoes hepatic metabolism primarily through glucuronidation by UGT1A1, and to a lesser extent UGT1A3. The concomitant use of deferasirox with potent UGT inducers such as rifampicin, phenytoin, phenobarbital, and ritonavir may decrease the efficacy of deferasirox. It is a moderate inhibitor of CYP1A2 and CYP2C8, and a weak inducer of CYP3A4. Patients should be monitored for decreased effectiveness of any concomitant medications that are metabolized by CYP3A4 such as oral hormonal contraceptives, simvastatin, and cyclosporine. Deferasirox has a lower affinity for aluminum than for iron, however the use of aluminum-containing antacids with deferasirox should be avoided. The use of bile acid

sequestrants should also be avoided because they may decrease the efficacy of deferasirox. If bile acid sequestrant use cannot be avoided, consider increasing the initial dose of deferasirox by 50% and monitoring serum ferritin levels.[4]

Deferasirox is pregnancy category C. Adverse events were observed in animal reproduction studies. There are no adequate or well-controlled studies using deferasirox in pregnant women. The manufacturer recommends that deferasirox should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus. It is not known whether deferasirox is excreted in human milk. Deferasirox and its metabolites were excreted in rat milk. Because there is potential for serious adverse reactions to a nursing infant, the manufacturer recommends that a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.[4]

Chronic iron overload can be a serious, life-threatening condition, and treatment options are limited or often inconvenient. Deferasirox oral tablet (Jadenu®) is a new formulation of a currently existing iron chelating agent. The convenience and relative ease of administration of this new formulation may be desirable for patients. Deferasirox is associated with several severe adverse events and requires close monitoring.

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Dinutuximab (Unituxin®)

Class: Anti-GD2 monoclonal antibody
Indication: High-risk neuroblastoma
Dose: 17.5 mg/m^2/day intravenous infusion over 10 to 20 hours for 4 consecutive days; maximum five cycles
Dose modifications: For neurological eye disorders, interrupt infusion until resolution of event then decrease the dose by 50% (8.75 mg/m^2/day). Decrease the infusion rate by 50% for mild to moderate infusion-related reactions. Interrupt the infusion for prolonged or severe infusion-related reactions, moderate to severe capillary leak syndrome, hypotension, severe infection, or sepsis.
Common adverse effects: Pain, capillary leak syndrome, hypersensitivity reactions, fever, hypotension, hypokalemia, thrombocytopenia, and infection
Serious adverse effects: Capillary leak syndrome and infection
Drug interactions: None known; no drug interaction studies have been conducted.

Dinutuximab for High-Risk Neuroblastoma

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Neuroblastoma is a relatively common pediatric malignancy, accounting for 7% of cancers in patients younger than 15 years, or approximately 700 cases annually in the United States.[1,2] Peak incidence is to 2 years of age. The majority of cases occur in patients younger than 5 and the median age at diagnosis is 19 months.[2] Arising from the sympathetic nervous system, neuroblastoma can present during fetal development and has the unique capability of spontaneous resolution. Staging and risk stratification of neuroblastoma have historically varied; regardless, the majority of patients have demonstrated a good prognosis with a 5-year overall survival (OS) exceeding 90% in those with low- to intermediate-risk disease. Conversely, patients with high-risk neuroblastoma continue to have a 5-year OS rate of 40%–50% despite aggressive therapy, including chemotherapy, radiation, surgery, autologous stem cell transplantation, and immunotherapy.[1,2]

Although no risk factors have been identified that would predispose a patient to the development of neuroblastoma, a mutation in the ALK gene or amplification of the MYCN gene have been correlated to subtypes of the disease.[2] Biologic features such as these are utilized in combination with other characteristics to risk stratify each patient and ultimately determine his or her therapy. Various risk stratification tools have been referenced in the literature, the most common of which are the International Neuroblastoma Staging System (INSS), the International Neuroblastoma Risk Group (INRG) classification system, and the Children's Oncology Group Neuroblastoma Risk Grouping. These systems account for various prognostic markers, tumor histology and biology, presence of lymph node involvement, treatment response, tumor site, and patient age at diagnosis. Based on these data, patients are stratified as low, intermediate, or high risk, which further determines the treatment course.[1,2]

Standard treatment for high-risk patients is multimodal, traditionally consisting of chemotherapy, differentiating agents, surgery, radiation, and autologous hematopoietic stem cell transplantation (HSCT).[2-4] Induction therapy often is comprised of five cycles of cisplatin, doxorubicin, etoposide, and cyclophosphamide given every 28 days, followed by surgery and radiation for local control.[3] Between 1991 and 1996 the Children's Cancer (Oncology) Group randomized 379 patients to myeloablative chemotherapy (carboplatin, etoposide, melphalan, and total-body irradiation) with stem cell rescue or chemotherapy alone (cisplatin, etoposide, doxorubicin, and ifosfamide). A second randomization phase evaluated 258 patients who received either 13-cis-retinoic acid (RA) or placebo.[3,4] Mean event-free survival (EFS) at 3 years was 34% in the HSCT arm versus 22% in those receiving chemotherapy alone (p = .034), although OS did not significantly differ between the two groups.[3] Five-year EFS remained significant (30% versus 19%, p = .0434) while no significant difference in OS was reported (39% versus 30%, p = .3917). Three years after the second randomization, EFS was 46% in those patients who received 13-cis-RA compared with 29% in those who received placebo (p =.027), regardless of whether the patient had previously undergone HSCT; however, a difference in OS was not demonstrated. At 5 years, EFS did not maintain significance (42% versus 31%, p = .1219) and no OS survival difference was demonstrated (50% versus 39%, p = .1946). Collectively, patients who received HSCT and 13-cis RA had a 5-year EFS of 50% versus 20% (p = .0038) in those who received chemotherapy alone and a 5-year OS of 59% versus 36% (p = .054).[4] Based on these results, HSCT and differentiation therapy were established as the standard of care.

Despite these advancements, additional consolidation therapy has been investigated to further improve long-term outcomes. Dinutuximab, previously known as ch14.18, is a chimeric monoclonal antibody against GD2, a disialoganglioside that is commonly overexpressed on the surface of neuroblastoma and melanoma cells.[1,5,6] When used in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-RA in high-risk neuroblastoma patients who have had at least a partial response following first-line therapy, EFS and OS were improved as compared with RA alone.[7] Dinutuximab leads to lysis of neuroblastoma cells via antibody-dependent cell-mediated cytotoxicity, the effects of which have been enhanced with GM-CSF and cytokines, such as IL-2.6,[8] It is worth noting that GD2 also is normally expressed in melanocytes, neurons, and peripheral pain fibers.[5,6]

Dinutiximab was approved by the U.S. Food and Drug Administration (FDA) via priority review as an orphan drug on March 10, 2015. Concurrently, the FDA also provided United Therapeutics with a pediatric disease priority review voucher which will allow priority review to an anticipated drug application.[9] Approval was granted based on data from three trials (*n* = 1021), one of which was the Children's Oncology Group phase 3 randomized study (ANBL0032) of 226 patients with high-risk neuroblastoma who lacked progressive disease after the completion of induction chemotherapy, autologous HSCT, and radiation. Enrolled between October 2001 and January 2009, patients had to be ≤30 years of age at diagnosis, be on day 50–100 posttransplant with at least a partial response prior to transplant, and have adequate organ function. Patients with residual disease after HSCT were enrolled but not randomized and were not included in analysis of the primary endpoint. Study participants had a median age of 3.8 years, 80% had INSS stage 4 disease, and most had unfavorable histology. Slightly less than half of patients enrolled had amplification of V-Myc Avian Myelocytomatosis Viral Oncogene Neuroblastoma Derived Homolog (MYCN) while just more than half were hyperdiploid. Following transplant, 78% of patients had either a complete or very good partial response. Patients in the standard therapy arm received six cycles of isotretinoin 160 mg/m2/day divided into two doses for 14 days of a 28-day cycle. Those randomized to immunotherapy were given five cycles of dinutuximab 25 mg/m^2/day for 4 consecutive days of a 28-day cycle. Additionally, they received isotretinoin 160 mg/m^2/day during the last 2 weeks of each of the five dinutuximab cycles, as well as during cycle 6 during which it was administered as monotherapy. Cycles 1, 3, and 5 also included GM-CSF 250 g/m^2/day for 14 days starting 3 days prior to dinutuximab, while cycles 2 and 4 included a 4-day continuous intravenous (IV) infusion of IL-2 dosed at 3 x 10^6 IU/m^2/day during week 1 and 4.5 x 10^6 IU/m2/day during week 2, given concurrently with dinutuximab. The primary endpoint was EFS with OS as a secondary endpoint.[10]

The median follow-up was 2.1 years (4 days–6.9 years) and baseline characteristics were similar between the two groups. After 83 events had been reported, the study met early stopping criteria based on superior EFS in the immunotherapy group compared with standard therapy. Of the 226 patients evaluated, 63% were alive 3 years following treatment with dinutuximab, GM-CSF, IL-2, and isotretinoin versus 42% who received isotretinoin alone. OS was not significantly different between the two groups (84% versus 76%, *p* = .1). Reported prognostic factors demonstrated that patients with INSS stage 4 disease had a decreased EFS compared with those with stage 2, 3, or 4S (*p* = .003). In addition, OS was shown to be worse in patients with diploidy versus hyperdiploidy (*p* = .003). Both EFS and OS were improved in those patients who had a complete or very good partial response prior to HSCT (*p* = .04 and .02, respectively).[10]

More than one-third of patients experienced grade 3 or 4 pain (51%), lymphopenia (51%), pyrexia (40%), thrombocytopenia (39%), hypokalemia (37%), anemia (34%), and neutropenia (34%). Other common grade 3 or 4 adverse events included infusion reactions (25%), capillary leak syndrome (23%), hyponatremia (23%), and increased alanine aminotransferase (23%). Despite premedication with morphine, 85% of patients reported pain, which was described as abdominal/back/extremity pain, generalized pain, chest pain, and arthralgias. Peripheral neuropathy also has been reported, though this appears to be more severe in adults as compared with pediatric patients. Infusion reactions can be severe, including anaphylaxis, most of which occurred within 24 hours of completing the infusion.[11] The development of human antichimeric antibodies (HACA) has been reported in approximately 15%–20% of patients receiving dinutuximab.[5,6,8,11,12] The majority of cases appear to be dose related and occur upon reexposure in cycles 2 and beyond. Antibody development may also vary based on the transplant prep regimen and degree or method of immunosuppression that is utilized.[5,6,8]

The safety of dinutuximab has not been established in geriatric patients or in patients with renal or hepatic impairment. Reproductive studies also have not been performed with dinutuximab; however, a risk for fetal harm does exist because monoclonal antibodies are known to cross the placenta, particularly during the third trimester. Women of childbearing age should employ effective contraception while undergoing treatment with dinutuximab and for 2 months following therapy. Because human IgG is present in breast milk, breast feeding is discouraged while receiving dinutuximab.[11]

Although the pharmacokinetic parameters of dinutuximab vary between children and adults, a volume of distribution (Vd) of 5.4 L and a terminal half-life of 10 days are reported in the prescribing information.[11] Within the pediatric population specifically, a high degree of variability has been suggested for both Vd and clearance. It is known that the clearance of dinutuximab in children is approximately six times higher than that of adults, thus the half-life is shorter. Clearance of the drug has been shown to increase upon repeated administration with shorter half-lives reported during the second cycle when compared with the first. Ultimately, a pharmacokinetic study by Desai and colleagues demonstrated that dinutuximab follows a two-compartment model.[12] After 4 days of therapy, the mean concentration was 10 g/mL, compared with 0.21 g/mL 28 days after therapy was initiated; thus approximately 57% of the dose remained at day 4 while 2% was present at day 28. Clearance was found to be higher in females than males (2.3 L/m^2/day versus 1.6 L/m^2/day, *p* = .06). The mean steady state Vd was 0.55 L/kg.[12] Although GD2 normally is expressed in neurons, dinutuximab does not appear to cross the blood-brain barrier.[6]

Dinutuximab is supplied as a 17.5 mg/5 mL (3.5 mg/mL) single-use vial. Vials must be refrigerated and should remain in the supplied carton until use so they are protected from light. Dinutuximab should not be given as an IV push or undiluted as an IV bolus. To prepare the recommended dose, one vial should be injected into 100 mL of 0.9% sodium chloride. Patients should be hydrated with normal saline at 10 mL/kg over 1 hour immediately prior to each dinutuximab dose. Additional premedications include an antihistamine such as diphenhydramine 0.5–1 mg/kg (max = 50 mg) IV over 10–15 minutes and acetaminophen 10–15 mg/kg (max = 650 mg), each starting 20

minutes prior to dinutuximab. If tolerated, the patient should continue to receive diphenhydramine every 4 to 6 hours during the infusion. Ibuprofen may be used every 6 hours as needed for fever or pain. Each patient should also receive IV morphine 50 mcg/kg immediately prior to the first dose, followed by a continuous infusion of morphine at a rate of 20–50 mcg/kg/hour. The morphine drip should continue for 2 hours following the last dose of dinutuximab. Patients should have doses of IV morphine available as needed, which can be given as often as every 2 hours during the infusion. Medications such as gabapentin and lidocaine may be used to augment the patient's pain regimen. Following the appropriate premedications and adequate hydration, dinutuximab should be administered as an IV infusion of 17.5 mg/m^2/day over 10 to 20 hours for 4 consecutive days. The recommended initial infusion rate is 0.875 mg/m^2/hour for 30 minutes, which can be gradually escalated to a maximum rate of 1.75 mg/m^2/hour based on tolerability. The infusion rate of dinutuximab may be decreased for reactions that are responsive to treatment, such as rash, fever, rigors, or itching. Therapy should be suspended for symptoms such as bronchospasm, angioedema, capillary leak syndrome, hypotension, infection, sepsis, or neurologic disorders of the eye. Patients should be educated on the potential of serious adverse reactions such as anaphylaxis and capillary leak syndrome. They should also be counseled on the risk of severe pain and neuropathy. Patients should notify their healthcare provider if they experience pain, neuropathy, visual changes, or any signs or symptoms of capillary leak syndrome, anaphylaxis, infection, hypotension, anemia, thrombocytopenia, hypokalemia, hyponatremia, or hypocalcemia.[11]

With an overall poor prognosis, high-risk neuroblastoma requires intensive, multimodal treatment. Dinutuximab, in combination with GM-CSF, IL-2, and isotretinoin has been demonstrated to improve EFS in those patients who have at least a partial response following autologous stem cell transplant. Adverse effects, including infusion reactions, capillary leak syndrome, and significant pain, can be severe, despite premedications. Further studies plan to investigate the safety and efficacy of dinutuximab in its currently proposed combination, as well as in combination with other agents such as lenalidomide, irinotecan, temozolomide, and temsirolimus. Vaccine therapy, allogeneic HSCT, and various chemotherapy regimens and doses also are being evaluated to improve survival in high-risk neuroblastoma. Although the toxicity profile can be daunting, dinutuximab has provided a significant improvement in outcomes, particularly in those who respond well after first-line therapy.

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Nivolumab (Opdivo®)

Class: Human programmed death receptor-1 (PD-1)–blocking monoclonal antibody
Indications: Unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor
Metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy
Dose: 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity
Dose modifications: Hold dose for grade 2 pneumonitis, grade 2 or 3 colitis, aspartate aminotransferase/alanine transaminase (AST/ALT) 3–5 x upper limit of normal (ULN) or total bilirubin > 1.5–3 x ULN, creatinine > 1.5–6 x ULN or > 1.5 x baseline, or any other severe or grade 3 treatment-related adverse reactions. Nivolumab can be resumed in patients whose adverse reactions recover to grade 0 to 1. Permanently discontinue for any life-threatening grade 4 adverse reaction, grade 3 or 4 pneumonitis, grade 4 colitis, AST/ALT > 5 x ULN or total bilirubin > 3 x ULN, creatinine > 6 x ULN, any severe or grade 3 treatment-related adverse reaction that recurs, inability to reduce corticosteroid dose to ≤10 mg of prednisone or equivalent per day within 12 weeks, or persistent grade 2 or 3 treatment-related adverse reactions that do not recover to grade 1 or resolve within 12 weeks after last dose.
Common adverse effects: Rash, fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, constipation
Serious adverse effects: Immune-mediated reactions such as pneumonitis, colitis, hepatitis, nephritis, and hypothyroidism/hyperthyroidism
Drug interactions: No formal pharmacokinetic drug-drug interaction studies have been conducted.

Nivolumab for Non-Small Cell Lung Cancer

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Lung cancer is the leading cause of cancer death in the United States, claiming more than 158,000 lives each year. The prognosis remains poor, with only 16.8% of patients alive 5 years or more after diagnosis. More than 85% of all lung cancers are categorized as non-small cell lung cancer (NSCLC), which is further specified into the histologic types of nonsquamous (adenocarcinoma, large cell, and NSCLC not otherwise specified) and squamous cell carcinoma. The nonsquamous histologies can present with an activating mutation in EGFR or rearrangement in the EML4-ALK genes, which are both targetable with oral medications.[1] Unfortunately, pure squamous cell NSCLC patients rarely present with these targetable mutations, therefore conventional chemotherapy, specifically a platinum doublet, remains the standard of care.

For patients with squamous NSCLC, a platinum doublet regimen containing gemcitabine, paclitaxel, or vinorelbine is recommended as first-line treatment. Previous data have shown the benefit of cisplatin plus gemcitabine over cisplatin plus pemetrexed in squamous NSCLC. Cisplatin plus gemcitabine demonstrated an increase in overall survival (OS), although not statistically significant, compared with cisplatin plus pemetrexed for squamous histology (10.8 versus 9.4 months, respectively; [hazard ratio {HR} = 1.23; 95% confidence interval {CI}: 1.00–1.51; p = .05]).[2] Despite thorough research, treatment options for squamous NSCLC are limited when compared with options for nonsquamous histology. After a patient progresses on or after a platinum-based therapy, options include single-agent systemic therapy, best supportive care, or clinical trials. Docetaxel was approved as second-line therapy in 1999 based on superior overall response rates to vinorelbine or ifosfamide (6.7%–10.8% with docetaxel versus 0.8% for both vinorelbine and ifosfamide; p = .001 and p = .036 respectively). OS did not differ between the groups, ranging from 5.5 to 5.7 months.[3] Due to the paucity of highly effective agents in the subsequent-line setting for squamous cell NSCLC, the search for novel agents has expanded past conventional chemotherapy.

Nivolumab is a fully human IgG4 antibody second in the class of immune agents targeting the programmed death receptor-1 (PD-1). The PD-1 receptor is expressed on activated T cells and engaged by the ligands PD-L1 and PD-L2, which are expressed by tumor cells and infiltrating immune cells. Activation of PD-1 via the ligands results in inhibition of T-cell activation, allowing tumor cells to escape recognition and elimination by the immune system. Nivolumab disrupts PD-1—mediated signaling to restore antitumor immunity.[4] Nivolumab was first approved by the U.S. Food and Drug Administration (FDA) in December 2014 for unresectable or metastatic melanoma. In March 2015 nivolumab gained approval for metastatic squamous NSCLC with progression on or after platinum-based chemotherapy based on the CheckMate-017 trial.

The CheckMate-017 trial was a randomized, open-label, international, phase 3 study that compared nivolumab with docetaxel as subsequent therapy following failure on a platinum-containing regimen in patients with advanced squamous NSCLC. Nivolumab was given at a dose of 3 mg/kg intravenously every 2 weeks and docetaxel was given at a dose of 75 mg/m^2 intravenously every 3 weeks. A total of 260 patients (131 in nivolumab group, 129 in docetaxel group) were assessed for efficacy and safety. The primary endpoint of OS was superior for nivolumab at 9.2 months compared with docetaxel at 6.0 months (HR = 0.59; 95% CI: 0.44– 0.79; p < .001). Nivolumab was also superior for progression-free survival at 3.5 months versus 2.8 months

for docetaxel (HR = 0.62; 95% CI: 0.47– 0.81; $p < .001$). The median time to response did not differ between the two groups (2.2 versus 2.1 months for nivolumab and docetaxel, respectively).[4]

Nivolumab proved to be better tolerated than docetaxel. Events of any grade occurred in 58% of patients in the nivolumab group and the most frequently reported events were fatigue (16%), decreased appetite (11%), and asthenia (10%). Events of any grade occurred in 86% of patients in the docetaxel group and the most frequently reported events were neutropenia (33%), fatigue (33%), alopecia (22%), and nausea (23%). In addition, grade 3 or 4 events were reported in fewer patients in the nivolumab group (7% vs 55% in docetaxel group). Discontinuation of treatment due to treatment-related adverse events occurred less frequently with nivolumab versus docetaxel (3% versus 10%, respectively) and no deaths were attributed to nivolumab compared with three deaths attributed to docetaxel.[4]

Although rare, immune-related adverse events have been reported in trials of patients receiving nivolumab for solid tumor malignancies. Rates of immune-mediated events have been reported as follows: pneumonitis 2.2%–6%, colitis 0.9%–2.2%, hepatitis 1.1%, nephritis 0.7%–0.9%, hypothyroidism 4.3%–8%, and hyperthyroidism 1.7%–3%. There are specific recommendations on when to withhold treatment and initiate corticosteroids or permanently withhold treatment based on the severity of the suspected immune-related adverse event. If corticosteroids need to be administered, initiate at a dose of 0.5 to 2 mg/kg/day prednisone equivalents based on adverse event and severity with adjustments in dose based on patient response. For immune-mediated hypothyroidism, initiate hormone replacement. For immune-related hyperthyroidism, initiate appropriate medical management.[5]

Although nivolumab is only FDA-approved for squamous NSCLC, data presented at the American Society of Clinical Oncology Annual Meeting in June 2015 showed benefit in nonsquamous NSCLC. The CheckMate-057 randomized, phase 3 trial compared nivolumab with docetaxel in patients with nonsquamous NSCLC who had progressed on or after platinum-based chemotherapy. Median OS for nivolumab and docetaxel was 12.2 months and 9.4 months, respectively (HR = 0.73; 95% CI: 0.59–0.89; $p = .0015$). As well as improved efficacy, grade 3 to 5 adverse events occurred less often in the nivolumab group (10%) compared with the docetaxel group (54%).[6] Based on these data, the National Comprehensive Cancer Network (NCCN) panel recommends nivolumab as subsequent therapy for patients with nonsquamous NSCLC who have progressed on or after platinum-based therapy.[1]

Both CheckMate-017 and CheckMate-057 trials evaluated PD-L1 expression in patients to determine a relationship to prognosis or predict a response to nivolumab.[4,6] CheckMate-017 reported that PD-L1 expression was neither prognostic nor predictive of any of the efficacy endpoints.[4] CheckMate-057 reported PD-L1 expression to be associated with treatment benefit with nivolumab.[6] More expansive data on the subject of PD-L1 expression effects on nivolumab efficacy are expected to be reported in the future.

The mean elimination half-life of nivolumab is 26.7 days. No clinically important differences in clearance have been noted in patients with mild to severe renal impairment or those with mild hepatic impairment; therefore, there are no dose adjustments recommended for patients with renal or hepatic impairment. However, nivolumab has not been studied in patients with moderate to severe hepatic impairment. There have been no formal drug interaction studies conducted at this time. Animal reproduction studies have shown increased abortion and premature infant death, therefore nivolumab should be avoided in pregnant women. Females of reproductive potential should continue to use effective contraception for at least 5 months after the last dose of nivolumab.[5]

Nivolumab is supplied as a solution in 40 mg/4 mL and 100 mg/10 mL single-use vials. The required volume should be withdrawn from the vial and transferred into an intravenous container containing either 0.9% sodium chloride injection, USP or dextrose injection, USP to a final concentration of 1 to 10 mg/mL. The prepared product for infusion should be stored at room temperature for no more than 4 hours, or under refrigeration at 2°C–8°C (36°F–46°F) for no more than 24 hours. Nivolumab should be administered as an infusion over 60 minutes through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding in-line filter (pore size of 0.2–1.2 m). No other medication should be administered through the same line.[5]

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Panobinostat (Farydak®)

Class: Histone deacetylase inhibitor
Indication: Treatment of multiple myeloma (in combination with bortezomib and dexamethasone) in patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent
Dose: 20 mg once every other day for three doses each week during weeks 1 and 2 of a 21-day treatment cycle
Dose modifications: Reduce the starting panobinostat dose to 10 mg with strong CYP3A inhibitors. Management of adverse drug reactions may require treatment interruption or dose reductions. If dose reduction is required, the dose of panobinostat should be reduced in increments of 5 mg. If the dosing of panobinostat is reduced below 10 mg given three times per week, discontinue panobinostat. Keep the same treatment schedule (3-week treatment cycle) when reducing dose
Common adverse effects: Thrombocytopenia, neutropenia, anemia, diarrhea, and fatigue
Serious adverse effects: Hemorrhage and hepatoxicity
Black box warning: Severe and fatal cardiac ischemic events, severe arrhythmias, ECG changes, and severe diarrhea have been reported.
Drug interactions: Panobinostat is primarily metabolized via CYP 3A4 with minor metabolism via CYP2C19 and 2D6. Avoid coadministration with sensitive CYP2D6 substrates and strong CYP3A inducers.

Panobinostat for Multiple Myeloma

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Multiple myeloma is a neoplasm of the plasma cells. It is characterized by the proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, renal dysfunction, and lytic lesions in the bone.[1,2] Myeloma represents approximately 1.6% of new cancer diagnoses in the United States with an estimated 27,000 new cases to be diagnosed in 2015.[3] Thanks to advances in therapy and the advent of novel agents, such as proteasome inhibitors and immunomodulatory agents, the survival of myeloma patients has increased dramatically in recent years. Five-year overall survival for myeloma patients from 1975 to 1977 was 24.7% compared with 48.5% from 2005 to 2011.[4] The median age of myeloma diagnosis is 69 years.[3]

Newly diagnosed multiple myeloma patents are generally stratified by eligibility for autologous stem cell transplant.[1,2,5] Those deemed to be transplant eligible receive combination therapy including a steroid and novel agents (proteasome inhibitors and/or immunomodulatory agents).[1,2,5] Nontransplant eligible patients receive combination therapy but also may receive melphalan as upfront treatment.[1,2,5] In the relapsed setting, patients may repeat regimens if sufficient time has elapsed or may receive a different combination of novel therapy and traditional chemotherapy agents.[1,2,5]

Panobinostat is a histone deacetylase inhibitor (HDACi) that was granted approval by the U.S. Food and Drug Administration (FDA) on February 23, 2015.[6] Histones are proteins that are incorporated into the DNA strand and allow the strand to be condensed to form chromatin.[7] Alterations in the rates of histone acetylation and deacetylation can result in abnormal cellular growth and ultimately tumor formation.[7] Several cancer types have been shown to express alterations in both histone deacetylase and histone acetyltransferase.[7]

Three other HDACi have been approved—pralatrexate injection (Folotyn®), romidepsin (Istodax®), and belinostat (Beleodaq®). Panobinostat is the first HDACi approved for multiple myeloma. It is currently indicated for the treatment of multiple myeloma (in combination with bortezomib and dexamethasone) in patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.[6]

The National Comprehensive Cancer Network (NCCN) guidelines now list panobinostat in combination with bortezomib and dexamethasone as a category 1 recommendation for patients with previously treated multiple myeloma.[5] The FDA approval of panobinostat was based on data from the multicenter, phase 3 PANORAMA-1 trial, which was conducted at 215 centers in 34 countries.[8] The trial included 768 relapsed/refractory multiple myeloma patients who had received 1–3 therapies. Patients were randomized in a 1:1 ratio to receive bortezomib and dexamethasone plus either panobinostat or placebo.[8] Panobinostat was given at a dose of 20 mg by month on days 1, 3, 5, 8, 10, and 12 of a 3-week cycle.

Primary endpoint for the PANORAMA-1 trial was progression-free survival (PFS).[8] Median PFS in the panobinostat group was 11.99 months compared with 8.08 months in the placebo group ($p < .0001$).[8] Two-year PFS was higher in the panobinostat group versus placebo (20.6% versus 8.4%; p value not reported). Overall survival data was not fully mature at study publication; however, the difference were not statistically significant (33.64 months for panobinostat versus 30.39 months for placebo).[8]

Median duration of treatment was shorter in the panobinostat group than in the placebo group (5 months versus 6.1 months).[8] The most common reasons for discontinuation were adverse reactions (34% with panobinostat versus 17% with placebo) and disease progression (21%

with panobinostat versus 40% with placebo).[8] The most common adverse reactions in the panobinostat group included diarrhea (68%), peripheral neuropathy (61%), asthenia or fatigue (57%), and nausea (36%). Grade 3 or 4 reactions were reported in 96% of patients receiving panobinostat and 82% of those receiving placebo.[8] The most common grade 3 or 4 reactions included diarrhea, asthenia or fatigue, and peripheral neuropathy. All were more common in the panobinostat group than in the placebo group.[8] In addition, hematologic toxicities—including lymphopenia and thrombocytopenia—were more common in the panobinostat group. A total of 48 deaths occurred in the trial; 30 (8%) in the panobinostat group and 18 (5%) in the placebo group.[8] Of these deaths, 11 (3%) in the panobinostat group and 7 (2%) in the placebo group were possibly related to the study drug.[8] Manufacturer labeling includes black box warnings for both cardiovascular and gastrointestinal events.[6] Due to possible severe and fatal cardiac ischemic events, severe arrhythmias, and electrocardiogram (ECG) changes obtain ECG and electrolytes at baseline and periodically during treatment as clinically indicated.[6] In addition, patients should be monitored for severe diarrhea during treatment.[6] Antidiarrheal treatment should be initiated if diarrhea occurs.[6] Treatment with panobinostat should be interrupted for severe diarrhea. Clinicians should consider reducing the dose or discontinuing panobinostat.[6]

Panobinostat may cause embryo-fetal harm.[6] Panobinosat was teratogenic in animal reproduction studies with rats and rabbits. Pregnancy should be ruled out prior to treatment.[6] Women of reproductive potential should avoid pregnancy and use an effective form of contraception during therapy and for 1 month after treatment. Males should use condoms during therapy and for 3 months after treatment.[6]

Panobinostat is extensively hepatically metabolized via reduction, hydrolysis, oxidation, and glucuronidation.[6] CYP3A4 accounts for approximately 40% of hepatic elimination.[6] Patients with mild hepatic dysfunction (bilirubin ≤1 times upper limits of normal [ULN] and aspartate aminotransferase [AST] > 1 times ULN or bilirubin >1 to 1.5 times ULN and any AST) should receive an initial dose of 15 mg.[6] For those with moderate hepatic impairment (bilirubin >1.5 to 3 times ULN and any AST), panobinostat doses should be reduced to 10 mg.[6] Panobinostat should be avoided in patients with severe hepatic impairment.[6] In addition, panobinostat should be held for any hepatic impairment that occurs during treatment and resumed when liver function returns to baseline.[6] Panobinostat is excreted in both feces (44%–77%; <4% as unchanged drug) and urine (29%–51%; <3% as unchanged drug).[6] Manufacturer labeling does not include dosage adjustments for renal impairment.[6]

Due to its metabolism by the CYP system, coadministration with strong CYP3A4 inducers or sensitive CYP2D6 substrates should be avoided.[6] If a patient also is receiving a strong CYP3AA4 inhibitor, the starting dose of panobinostat should be reduced to 10 mg.[6] The approved package insert also provides dosage adjustments for toxicity. If a dose reduction is required, the dose of panobinostat should be reduced in increments of 5 mg. If the dosing is reduced below 10 mg given three times per week, discontinue panobinostat. Keep the same treatment schedule (3-week treatment cycle) when reducing dose.[6]

Panobinostat is available as a 10-, 15-, or 20-mg oral capsule.[6] Patients should take panobinostat at approximately the same time on scheduled days with or without food.[6] Capsules should be swallowed whole with a full glass of water and should not be opened, crushed, or chewed.[6] Instruct patients to store panobinostat at room temperature.[6] Patients should also inform their physician if any severe adverse events, including diarrhea, occur.[6]

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Ramucirumab (Cyramza®)

Class: Vascular endothelial growth factor (VEGF) receptor 2 inhibitor

Indication: Metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine

Dose: Administer ramucirumab 8 mg/kg intravenously every 2 weeks prior to fluorouracil, leucovorin, and irinotecan (FOLFIRI) continue until disease progression or unacceptable toxicity. Premedicate prior to each dose of ramucirumab with an intravenous histamine H_1 antagonist.

Dose modifications: There is no recommended dose adjustment for patients receiving ramucirumab who have renal impairment. In addition, there is no dose adjustment recommended for patients with mild hepatic impairment (total bilirubin within upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or total bilirubin > 1.0–1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin > 1.5–3.0 times ULN and AST) based on population pharmacokinetic analysis. However, clinical deterioration has been reported in patients with Child-Pugh B or C cirrhosis following treatment with single-agent ramucirumab. Infusion rate should be reduced by 50% for grade 1 or 2 infusion-related reaction and permanently discontinued for grade 3 or 4 infusion-related reaction. Infusion should be interrupted if severe hypertension occurs until it is controlled with medical management and permanently discontinued for severe, uncontrolled hypertension. Ramucirumab treatment should be withheld for urine protein ≥ 2 g/24 hours and then reinitiated at a reduced dose of 6 mg/kg when urine protein is < 2 g/24 hours. For recurrent urine protein ≥ 2 g/24 hours, treatment should be withheld and reinitiated at a reduced dose of 5 mg/kg when urine protein is < 2 g/24 hours. Therapy should be permanently discontinued for urine protein > 3 g/24 hours or in the setting of nephrotic syndrome. Therapy also should be permanently discontinued for arterial thrombotic events, grade 3 or 4 bleeding, gastrointestinal perforation, or reversible posterior leukoencephalopathy syndrome (RPLS).

Common adverse effects (in combination with FOLFIRI): Diarrhea, decreased appetite, epistaxis, hypertension, neutropenia, stomatitis, and thrombocytopenia

Serious adverse effects (in combination with FOLFIRI): Diarrhea, intestinal obstruction, and febrile neutropenia

Drug interactions: Belimumab and bisphosphonate derivatives

Ramucirumab for Metastatic Colorectal Cancer (mCRC)

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Colorectal cancer is one of the most common cancers worldwide with approximately 1.4 million cases diagnosed each year.[1] Of those patients, approximately 50%–60% will develop metastatic disease.[1,2] First-line treatment for metastatic disease in a patient appropriate for intensive therapy typically utilizes a fluoropyrimidine agent either alone or in combination with other active agents such as oxaliplatin or irinotecan.[2]

Vascular endothelial growth factor (VEGF) binding has been demonstrated to initiate endothelial proliferation and formation of new blood vessels, known as angiogenesis. The inhibition of microvascular growth thus is believed to retard the growth of all tissues, including metastatic tissue. The AVF2107 trial reported both a progression-free survival (PFS) and overall survival (OS) benefit with the addition of an antiangiogenesis monoclonal antibody, bevacizumab, to the irinotecan with bolus 5-FU and leucovorin (IFL) regimen which ultimately led to its approval by the U.S. Food and Drug Administration (FDA) in combination with any 5FU (fluorouracil) regimen, for the treatment of mCRC.[3] In both the TML and VELOUR studies, continuation of VEGF blockade in the second-line setting was found to offer a modest, but statistically significant, OS benefit of 1.4 months.[4,5] Current National Comprehensive Cancer Network (NCCN) guidelines do not indicate a preference for the addition of a biologic agent as part of initial therapy, but the panel does state that bevacizumab may be continued in the second-line setting.[2] In addition, the panel makes a recommendation for bevacizumab over ziv-aflibercept and ramucirumab when an angiogenic agent is utilized in the second line in light of toxicity and cost.[2]

Ramucirumab is a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist that targets the extracellular domain of the receptor to block signaling from ligands including VEGF-A, VEGF-C, and VEGF-D.[1,2] Inhibition of ligand-induced VEGFR2 activity subsequently reduces proliferation and migration of human endothelial cells.[1,6] Ramucirumab has previously shown efficacy for the treatment of gastric cancer and non-small cell lung cancer and gained FDA approval for those indications in late 2014.[6-9]

Based upon results of the phase 3 RAISE trial, the U.S. Federal Drug Administration (FDA) approved ramucirumab in April 2015 for use in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer following progression on a regimen containing bevacizumab, oxaliplatin, and a fluoropyrimidine in the first-line setting.[10] The RAISE trial was a randomized, placebo-controlled, multinational trial conducted between December 2010 and August 2013. The trial enrolled patients at 24 centers and randomized them to receive

either 8 mg/kg intravenous ramucirumab plus FOLRIRI or matching placebo plus FOLFIRI every 2 weeks until disease progression, unacceptable toxicity, or death.[1] Eligible patients were at least 18 years of age with pathologically confirmed colorectal cancer, known KRAS exon 2 mutation status, Eastern Cooperative Oncology Group performance status of 0 or 1, and disease progression during or within 6 months of the last dose of first-line combination chemotherapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.[1] All patients received either 8 mg/kg ramucirumab or placebo as a 60-minute infusion followed by the FOLFIRI regimen, which consisted of 180 mg/m^2 intravenous irinotecan given over 90 minutes, followed by or given concurrently with 400 mg/m^2 intravenous leucovorin given over 120 minutes, followed by 400 mg/m^2 fluorouracil given as an intravenous bolus over 2–4 minutes then 2,400 mg/m^2 fluorouracil given as a continuous infusion over 48 hours.[1] The primary endpoint of the trial was OS, defined as time from randomization until death. Secondary endpoints included PFS, the proportion of patients who achieved an objective response rate (complete or partial response), and disease control (complete response, partial response, or stable disease).[1]

A total of 1,072 patients were enrolled with 536 assigned to each group, of which 889 (83%) had received first-line bevacizumab for at least 3 months.[1] In the primary efficacy analysis, median OS was improved at 13.3 months (95% confidence interval [CI]: 12.4–14.5) for patients in the ramucirumab cohort compared with 11.7 months (10.8–12.7) for the placebo cohort (stratified hazard ratio [HR] = 0.844; 95% CI: 0.730–0.976; log rank p = .0219). PFS was 5.7 months (95% CI: 5.5–6.2) in the ramucirumab arm versus 4.5 months (95% CI: 4.2–5.4) in the placebo arm (HR = 0.793; 95% CI: 0.697–0.903; log rank p = .0005). Objective response rates were not statistically different between groups; 13.4% in the ramucirumab arm versus 12.5% in the placebo arm (p = .63).[1]

In the safety analysis, it was found that 59 patients (11%) discontinued study treatment due to adverse events in the ramucirumab arm versus 23 (4%) in the placebo arm.[1] Four hundred and thirty-eight patients (82%) in the ramucirumab arm required at least one dose modification (reduction, delay, or omission of any study drug) compared with 395 patients (75%) in the placebo arm. A higher number of grade 3 or worse adverse events were reported in the ramucirumab arm compared with the placebo arm (418 [79%] versus 329 [62%]) with the most common (occurring in more than 5% of patients) including neutropenia, hypertension, diarrhea, and fatigue.[1] Diarrhea and fatigue were reported with similar frequency among both groups, and the incidence of febrile neutropenia did not differ between groups (19 [4%] versus 14 [3%]); however, the incidence of grade 1 or 2 bleeding/hemorrhage events, grade 3 or worse hypertension, and proteinuria was higher in the ramucirumab arm.[1] It is recommended to monitor thyroid function during treatment with ramucirumab because thyroid dysfunction occurred in 2.6% of patients in the FOLFIRI plus ramucirumab arm in the RAISE trial as compared with 0.9% of patients in the FOLFIRI plus placebo arm.[1,6] There was no sustained difference in quality of life reported among patients in the RAISE trial as assessed by the European Organization for Research and Treatment of Cancer questionnaires, Quality of Life Questionnaire Core-30, and the EuroQol five-dimension, which assessed health-related quality of life.[1]

Ramucirumab is recognized as causing fetal harm based on animal models that have shown correlation between angiogenesis, VEGFR2, and critical aspects of embryofetal development. However, there are no data in pregnant women to make a full assessment of drug-associated risks. Females should be informed about the potential risk to a fetus while they receive treatment with ramucirumab. In addition, females should be advised not to breastfeed while receiving treatment with ramucirumab.[6]

The results of the RAISE trial demonstrate that ramucirumab improved OS in the second-line setting after progression on or after treatment with bevacizumb, oxaliplatin, and a fluoropyrimidine in patients with metastatic colorectal cancer, albeit only by 1.6 months. These results prove comparable to those seen in the TML and VELOUR studies, which demonstrated an OS benefit of 1.4 months in the second-line setting in similar patient populations.[1,4,5] Given the marginal benefit of this agent and questionable cost-benefit ratio, further analysis is underway to determine whether prognostic biomarkers may help to identify patients who may benefit most from this therapy.[1]

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