Continuing Education

Cancer Overview and 2018 FDA Treatment Updates

Authors:
Amber N. Keeton, Pharm.D.
Harrison School of Pharmacy, Auburn University

Elizabeth Leane Reynolds, Pharm.D.
Harrison School of Pharmacy, Auburn University

J. Trent Wood, Pharm.D.
Harrison School of Pharmacy, Auburn University

Corresponding Author:
Wesley T. Lindsey, Pharm.D.
Associate Clinical Professor
Drug Information Center
Harrison School of Pharmacy, Auburn University

Universal Activity #: 0178-0000-18-104-H01-P | 1.25 contact hours (.125 CEUs)

Initial Release Date: November 30, 2018 | Expires: March 15, 2021

Objectives

After completing this continuing education, the reader should be able to:

1. Describe the FDA approval process, the different types of novel drug approval pathways, and the difference between them.
2. Discuss the guideline screening recommendations for prostate and breast cancer.
3. Recognize new prostate, breast, leukemia, and lymphoma treatment option(s) and who would benefit.
4. Describe the role of androgens in the proliferation of prostate tumors.
5. Distinguish between HR+/HR- and HER2+/HER2- and how is it used to guide breast cancer treatment.
6. Discuss the differences between leukemia and lymphoma.

Introduction

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. While the reason for cancer development is unknown, there are many known risk factors such as tobacco use and excess body weight as well as non-modifiable factors such as genetic mutations, hormones, and immune conditions. The most common new cancer diagnoses in the United States are prostate (male), and breast (women), followed by lung and bronchus, then colon and rectum.[1]

From 2017 through March of 2018, 52 new drugs were approved by the FDA, 14 of which are for the treatment of various types of cancers.[2,3] The FDA has two approval options for which a new drug can reach the market: standard and novel.[2] The purpose of the standard FDA drug approval process is to evaluate medications that demonstrate at best minor improvements over current therapies.[4] It requires that a clinical benefit be shown before approval can be granted. This process can take many years to develop. Beyond the standard pathway, the FDA implemented new pathways to expedite the approval of "novel drugs," which are medications that treat a serious or life-threatening condition and serve a previously unmet need. The novel drug approval process is broken down into four different pathways: fast track, breakthrough, accelerated approval, and priority review. The pathways are defined by the FDA and shown in table 1 below.[5] As opposed to the standard pathway, the novel drug approval pathways allow the use of surrogate endpoints that are possible predictors of efficacy rather than long-term clinical trials; for example, a surrogate endpoint for cancer could be a reduction in tumor size.[5] The FDA allows new drug applications to progress through multiple different pathways. For instance, Calquence® (acalabrutinib) is a new FDA approved agent for the treatment of lymphoma and was placed into the accelerated, breakthrough, and priority review pathways. By allowing a promising new treatment for a serious illness to be placed into several designated pathways it ensures the medication can be made available to the public as soon as possible.[5]

Table 1: FDA Novel Drug Approval Pathways[5]

Fast-track	Fast track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
Breakthrough	A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.
Accelerated	These regulations allow drugs for serious conditions that fill an unmet medical need to be approved based on a surrogate endpoint.
Priority	A Priority Review designation means FDA's goal is to take action on an application within 6 months.

While most pharmacists may not directly deal with chemotherapy, many will interact with cancer patients; therefore, familiarity with their cancer regimens will be helpful. This continuing education focuses on three common types of cancer (blood, breast, and prostate) in addition to newly approved drugs for their treatment from 2017 through March of 2018.

Prostate Cancer

The American Cancer Society estimates that in 2018, there will be 164,690 new cases of prostate cancer in the United States with an estimated 29,430 deaths.[6] In Alabama alone, they estimate 2,460 cases in 2018. The most common risk factors for the development of prostate cancer include age, race, and family history.[7] Prostate cancer is rare in men under the age of 40, but risk increases sharply each decade thereafter with men over 65 accounting for more than 70% of diagnosed cases. African-Americans have the highest worldwide prevalence which is double the Caucasian population. Family history and genetics play a role in the development of prostate cancer in that men with a brother or father that have been diagnosed with prostate cancer have a 2-fold increased risk. In addition, diet has been linked to the development of prostate cancer with the Mediterranean diet having the lowest incidence. The consumption of diets high in red meat and milk have been associated with an increased risk.

In the early stages of prostate cancer when the disease is localized, patients are usually asymptomatic.[7] As the cancer spreads locally, the patient typically develops ureteral dysfunction including frequency, hesitancy, and dribbling as well as impotence. As the disease progresses further, the patient may experience symptoms such as back pain, lower extremity edema, fractures, anemia, and unexplained weight loss. Before routine screening was recommended, prostate cancer was usually not discovered until the cancer had spread locally and the patient experienced the previously mentioned symptoms. However, now most prostate cancers are discovered while the patient is still asymptomatic. The 2018 NCCN guidelines recommend a blood test of prostate specific antigen (PSA), a protein produced by prostate gland cells.[8] This guideline recommends patients begin screening at the age of 45 and should be repeated every 1-2 years in men with PSA levels $\geq$1.0 ng/mL, and 2-4 year intervals for PSA <1 ng/mL. The guidelines recommend against the use of a digital rectal exam (DRE) as stand-alone screening. Instead, it should be used as a complementary test to PSA. Another guideline produced by the American Cancer Society in 2010 has similar recommendations in that they

recommend screening via PSA levels with or without DRE.[9] This guideline recommends men at average risk begin testing at age 50, men with a higher risk (African American or one first degree relative diagnosed at age <65) begin testing at 45 years old, and men with an appreciably higher risk (multiple family members diagnosed at age <65) begin testing at 40 years old. They recommend yearly testing in men with a PSA ≥2.5 ng/mL and screening every 2 years in patients with a PSA ≤2.5 ng/mL.

Currently, treatment for prostate cancer is dependent on the stage of the disease, risk of recurrence, and life expectancy.[10] Initial therapy for the treatment of cancer can range from observation alone in patients with a limited life-expectancy to more aggressive therapy in other patients. Treatment options can include radiation therapy, prostatectomy, lymph node dissection, androgen-deprivation therapy, and luteinizing hormone-releasing hormone (LHRH) agonists.

In the early stages of prostate cancer, androgens promote the proliferation of the tumor.[7] By blocking these androgens, especially testosterone which accounts for 95% of androgens, it is possible for tumor regression. In some cases, the tumor continues to grow despite hormone therapy.[11] Such cases are known as castration-resistant and account for approximately 10-20% of prostate cancer. In February of 2018 the FDA approved Erleada® (apalutamide), the first FDA approved treatment of non-metastatic, castration-resistant prostate cancer. Erleada® works by inhibiting androgen receptors which leads to a decrease in tumor volume by increasing apoptosis and decreasing tumor cell proliferation. It is dosed 240 mg once daily in combination with gonadotropin-releasing hormone (GnRH) therapy.[12] Treatment can be continued until disease progression or unacceptable toxicity. In a clinical trial of 1207 non-metastatic, castration-resistant prostate cancer patients comparing Erleada® to placebo, the mean metastasis-free survival was 40.5 months in patients taking Erleada® compared to 16.2 months in patients on placebo.[11] The most common side effects noted with Erleada® are fatigue (39%), hypertension (14-25%), skin rash (19-24%), hypercholesterolemia (76%), hyperglycemia (70%), hypertriglyceridemia (67%), hyperkalemia (32%), diarrhea (20%), anemia (70%), leukopenia (47%), and lymphocytopenia (41%).[12,13] Erleada® is a strong inducer of CYP3A4, therefore patients taking medications that are substrates of this enzyme may see decreased efficacy in those medications.[11,12]

Breast Cancer

Breast cancer is the most common cancer among women.[14] One in eight women in the United States will be diagnosed with breast cancer in their lifetime with varying rates across racial and ethnic groups. Caucasian and African- Americans have the highest incidence with 128.1 and 124.3 cases per 100,000 people, respectively. For all racial and ethnic groups, most breast cancers are diagnosed at an early stage when tumors are small and localized. There is a higher proportion of advanced stage diagnosis and mortality in African-American women and other minority groups more so than Caucasian women. Despite these differences, overall mortality rates from breast cancer in the United States have declined since 1990. This decline is attributed to improvements in both early detection and treatment.

Gender and age are the two variables most strongly associated with the occurrence of breast cancer.[14] While breast cancer is generally thought of as a disease confined to women, in 2016 there were approx. 2,600

cases of male breast cancer in the United States. Although male gender breast cancer is rare, it is associated with a poor prognosis and a higher mortality rate. The incidence of breast cancer increases with advancing age.

The risk of a woman developing breast cancer before the age of 50 years is about 1 in 53.[14] The risk increases to 1 in 44 between the ages of 50-59, 1 in 29 between the ages to 60-69, and 1 in 15 for women 70 years and older. Other variables play a part in determining a woman's risk for developing breast cancer. These risk factors are discussed in more detail below; however, mathematical models that calculate a woman's risk for developing breast cancer with relationship to various factors are available online through The National Cancer Institute (NCI).[15] These calculators are designed for healthcare professionals to project a woman's individualized risk for invasive breast cancer over a 5-year period over her lifetime.

Many endocrine factors that relate to the total duration of a woman's menstrual life have been linked to the incidence of early breast cancer.[14] Early menarche, defined as menstruation beginning before 12 years of age, a late age of natural menopause (55 years or later), nulliparity (no children) and a late age at first birth (age $\geq$ 30 years) increases the cumulative lifetime risk of breast cancer development. Conversely, bilateral oophorectomy before 40 years of age reduces the risk of developing breast cancer.

Both personal and family history play a role in determining a woman's risk of developing breast cancer.[14] Women who have a personal history of breast cancer have an increased risk of developing contralateral breast cancer. Women who have dense breast tissue have reduced sensitivity to mammography detection and an increased risk of cancer, estimated to be between 4 to 5 times that of women the same age with little density. Ten percent of all breast cancers in the United States can be attributed to a familial link. Although women with a family history of breast cancer are at an increased risk, the diagnosis of breast cancer in young women is still uncommon.

Germ-line mutations in either BRCA1 or BRCA2 are associated with an increased risk for breast and ovarian cancers.[14] These are tumor suppressor genes that are important in maintaining genomic integrity and DNA repair. The probability of having one of these gene mutations is related to ethnicity and family history with the highest rate of occurrence in Jewish individuals of Eastern European descent. Genetic testing for these mutations is now widely available, but testing is generally only recommended when there is a personal or family history suggestive of hereditary cancer.

Possible relationships between fat intake and steroid hormone metabolism have led to an emphasis on dietary fat as a possible etiologic agent for breast cancer.[14] Studies have demonstrated a positive correlation between higher dietary fat intake and breast cancer risk, which is stronger in postmenopausal women. There is still much to be learned; however, a low-fat diet seems to be a reasonable approach to potentially reducing the risk of breast cancer.

The NCCN 2017 guideline recommendations for breast cancer screening are summarized in Table 2 below.

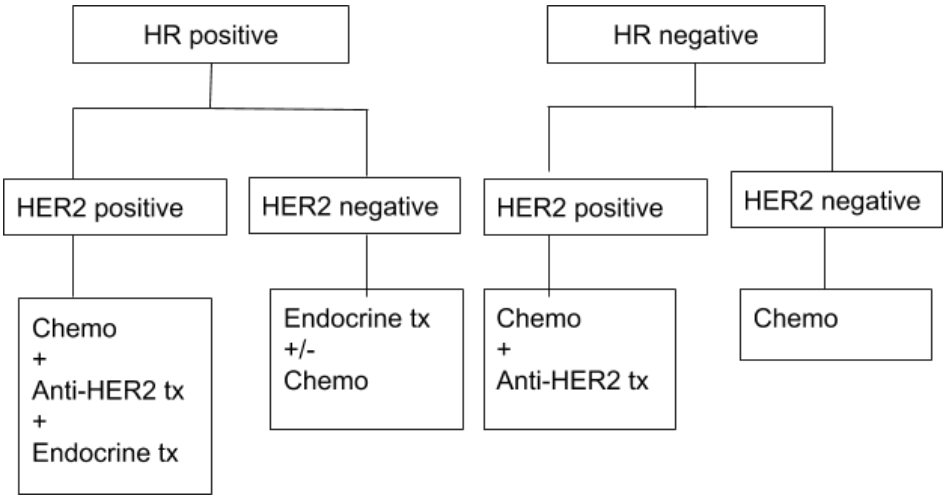
Table 2: Breast cancer screening recommendation per NCCN 2017 guideline recommendations[16]

NCCN 2017 guidelines	Average risk	High risk*
Breast self-examination	Age ≥ 25	All ages
Clinical breast examination by a healthcare professional	Age ≥ 25-39 • Every 1-3 years Age ≥ 40 • Annually	All ages: every 6-12 months
Mammography	Age ≥ 40: annually	Age ≥ 25: annually
Breast MRI	n/a	Annually for patients with: • prior thoracic radiation therapy and ≥ 25 years old • lifetime risk > 20% • strong family history or genetic predisposition and ≥ 25 years old • History of lobular carcinoma in situ

* High risk is defined by any of the following: prior thoracic radiation therapy before age 30 years, 5-year lifetime risk of ≥1.7% of invasive breast cancer in women ≥35 years old, lifetime risk of >20% as defined by models that are largely based on family history, strong family history or genetic predisposition, lobular carcinoma in situ, or prior history of breast cancer.

Breast cancer treatment depends on the involvement of lymph nodes and tumor size.[14] Most patients presenting with breast cancer today have a small invasive tumor with no lymph node involvement (stage I), or a small invasive tumor with axillary lymph node involvement (stage II). Surgery alone can cure most patients with stage I breast cancer and about half of patients with stage II breast cancer. Treatment of patients with breast cancer larger than 1 cm or with positive lymph nodes are based on whether the breast cancer is hormone receptor (HR) positive or negative as well as the presence or absence of human epidermal growth factor receptor-2 (HER2). Figure 1 below defines treatment options based on the previously mentioned variables.

Figure 1. Treatment options for breast cancer [14]



Adapted from Barnett CM, Boster BL, Michaud LB. Chapter 128: Breast Cancer. Pharmacotherapy: A Pathophysiologic Approach, 10th edition. [AUHSOP Intranet, cited 2018 Apr 2]. Available from: http://accesspharmacy.mhmedical.com/content.aspx?sectionid=146074631&bookid=1861&Resultclick=2

There were 3 new breast cancer treatments approved for use by the FDA in 2017: Verzenio® (abemaciclib), Kisqali® (ribociclib), and Nerlynx® (neratinib).[17] Verzenio® (abemaciclib) was approved by the FDA in September of 2017 for the treatment of HER2 negative, HR positive, advanced or metastatic breast cancer with one of the following indications:[18-21]

1. Use in combination with an aromatase inhibitor for initial endocrine therapy
2. Use with fulvestrant for progression following endocrine therapy
3. Monotherapy for progression following endocrine therapy and prior chemotherapy.

Verzenio® works by inhibiting cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), by inhibiting these kinases (CKD4 &CDK6) the complex required for progression of the cell cycle is unable to form, which prevents cancer cell growth. MONARCH-3, a study in 493 postmenopausal women with HR-positive, HER2 negative advanced metastatic breast cancer with no prior systemic therapy received either Verzenio® 150 mg or placebo twice daily with an aromatase inhibitor (either letrozole or anastrozole).[18,22] This trial measured the percent of patients whose tumors completely or partially shrank after treatment (objective response rate). Approximately 20% of patients taking Verzenio® experienced complete or partial shrinkage of their tumors in 9 months. MONARCH-2, a study in 669 women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy received either Verzenio® or placebo plus fulvestrant. This trial measured the length of time tumors did not grow after treatment (progression-free survival). The progression-free survival for patients taking Verzenio® with fulvestrant was about 16 months compared to 9 months for patients taking placebo with fulvestrant. The most common adverse reactions (incidence $\geq$ 20%) are diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia. Major drug interactions include CYP3A inhibitors and inducers for which concomitant use should be avoided. The recommended starting dose is 150 mg twice daily if used in combination with fulvestrant or an aromatase inhibitor or 200 mg twice daily if used as monotherapy.

Kisqali® (ribociclib) was approved for use by the FDA in March of 2017 for the treatment of HER2 negative, HR positive, postmenopausal women with metastatic or advanced breast cancer in combination with an aromatase inhibitor for initial endocrine-based treatment.[23-26] Kisqali® is a cyclin-dependent kinase inhibitor that is selective for CDK4 and CDK6. It works similarly to Verzenio® by blocking CDK4 & CDK6 to prevent the formation of the complex required for progression of the cell cycle, thereby preventing cancer cell growth. MONALEESA-2, a study of 668 women with HR-positive, HER-2 negative, advanced breast cancer who received no prior therapy for advanced disease received either Kisqali® 600mg orally once daily for 21 days or placebo once daily for 21 days plus letrozole 2.5mg orally once daily for 28 days with a 7 day off period.[23,27] Women taking Kisqali® plus letrozole experienced a longer time period before their tumors worsened in comparison to women who took placebo plus letrozole. Overall survival data is not available at this time; however, women taking Kisqali® plus letrozole had an average time of approximately 20 months before they experienced tumor worsening as

compared to 15 months in the women receiving placebo plus letrozole. The most common adverse reactions (incidence ≥ 20%) are neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, and back pain. Major drug interactions include CYP3A4 inhibitors, inducers, and substrates, as well as medications that prolong the QT interval for which concomitant use should be avoided. Recommended starting dose is 600 mg orally once daily for 21 consecutive days followed by a 7 day off period.

Nerlynx® (neratinib) was approved by the FDA in July of 2017 for use as an extended adjuvant treatment of early stage breast cancer with HER2 overexpression, following adjuvant trastuzumab based therapy.[28-31] Nerlynx® works by irreversibly inhibiting epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and HER4. The safety and efficacy of Nerlynx® was investigated in 2840 patients with early stage HER2 positive breast cancer within 2 years of completing treatment with adjuvant trastuzumab.[28,32] This trial measured the time period before cancer returned (invasive disease-free survival). Women in the Nerlynx® group had a 94.2% invasive disease-free survival at 24 months compared with the placebo group who had a 91.9% invasive disease-free survival at 24 months. The most common adverse effects (≥ 20%) are diarrhea, nausea, vomiting, abdominal pain, and fatigue. Major drug interactions include gastric acid reducing agents, strong or moderate CYP3A4 inducers and inhibitors, and P-glycoprotein substrates for which concomitant use should be avoided if possible. For H2-receptor antagonists, separate doses by 3 hours. Antidiarrheal prophylaxis with loperamide is recommended with the first dose of Nerlynx® and should continue during the first 2 months of treatment. Patient should be instructed to maintain 1-2 bowel movements per day. The recommended dose of Nerlynx® is 240 mg once daily with food for 1 year.

Hematologic Cancers

While hematologic cancers are not as prevalent as other cancers such as prostate and breast; the FDA has approved several new medications for the treatment of leukemia and lymphoma in the past year and a half. The three main types of hematologic cancers are leukemia, lymphoma, and myeloma.[33] These types of cancers originate in the bone marrow causing abnormal stem cells to uncontrollably proliferate leading to complications in the immune and circulatory system. Abnormal white blood cells (WBCs), red blood cells (RBCs), and platelets proliferate becoming cancerous cells, therefore the body is unable to fight off infections or maintain normal processes. The stem cell will develop into a myeloid or lymphoid stem cell.[34] The myeloid stem cell differentiates into red blood cells, platelets, and myeloblasts which become granulocytes. The lymphoid stem cells become lymphoblasts which differentiate into B-cells and T-cells**.** Complete treatment plans for these cancers include chemotherapy, radiation therapy, and stem cell transplant. [35]

Leukemia

Leukemia is a type of blood cancer that causes rapid proliferation of abnormal stem cells which are not able to fight off infections or perform physiologic activities. Leukemia can be acute or chronic. There are four major types of leukemia:

- Acute lymphocytic leukemia (ALL) is rapid growing immature WBCs and is the most common type of cancer in children.[36]
- Acute myeloid leukemia (AML) is when the bone marrow makes too many

immature RBCs and platelets and does not differentiate into WBCs. There are 8 different subtypes of AML.[37] In 2017, it is estimated about 21,000 people in the U.S. have AML with around 10,000 deaths.[38]

- Chronic lymphocytic leukemia (CLL) is a slow growing cancer in which lymphocyte cells build up in the bone marrow over time. Many patients are typically asymptomatic and can have this cancer for years before signs and symptoms develop.[39]
- Chronic myeloid leukemia (CML) is a genetic change in immature myeloid cells. Myeloid cells go on to become mature WBC, RBC, and platelets. Patients with CML have an abnormal gene called BCR-ABL causing immature myeloid cells to slowly grow and over time these cells build in the bone marrow.

Recently the FDA approved three new agents for acute leukemias. Current treatments for AML include chemotherapy given in cycles with multiple (typically 4-5) antineoplastic agents.[40] There is a three-phase treatment process for AML: induction, consolidation, and maintenance. The purpose of the induction phase is to kill as many leukemia cells as possible and inducing remission. This phase is usually the first month of treatment. The consolidation phase, or post remission phase, goal is to kill any lingering leukemia cells that may be present and lasts a few months. The maintenance phase is to prevent the cancer from returning and typically lasts 2-3 years. Table 3 is a chart of chemotherapy agents most commonly used for leukemias:

Table 3: Common chemotherapy agents for the treatment of blood cancers[34]

Generic	Trade	Mechanism of action
Asparaginase erwinia chrysanthemi	Erwinaze®	Asparaginase catalyzes the deamidation of asparagine to aspartic acid and ammonia, reducing circulating levels of asparagine. Leukemia cells lack asparagine synthetase and are unable to synthesize asparagine. Asparaginase reduces the exogenous asparagine source for the leukemic cells, resulting in cytotoxicity specific to leukemic cells.
Clofarabine	Clolar®	Purine nucleoside analog to prevent cell replication and repair
Cyclophosphamide		Alkylating agent (Nitrogen Mustard) that prevents cells division
Cytarabine	Cytosar-U®	Antimetabolite pyrimidine analogue that inhibits DNA synthesis
Daunorubicin	Cerubidine®	Anthracycline and topoisomerase II inhibitor which prevents DNA intercalation and stops cell replication
Doxorubicin		Anthracycline and topoisomerase II inhibitor which prevents DNA intercalation and stops cell replication

Generic	Trade	Mechanism of action
Idarubicin	Idamycin PFS®	Anthracycline and topoisomerase II inhibitor which prevents DNA intercalation and stops cell replication
Ifosfamide		Alkylating agent (Nitrogen Mustard) that prevents cell division
Mercaptopurine	Purixan®	Antimetabolite purine analogue, acts as a false metabolite to incorporate into DNA therefore inhibiting synthesis
Methotrexate		Antimetabolite/Antifolate, irreversibly binds to inhibit DNA synthesis
Nelarabine	Arranon®	Antimetabolite purine analogue, acts as a false metabolite to incorporate into DNA therefore inhibiting synthesis
Pegaspargase	Oncaspar®	Pegaspargase is a modified version of L-asparaginase, conjugated with polyethylene glycol. Leukemia cells require exogenous asparagine; normal cells can synthesize asparagine. Asparagine depletion in leukemic cells leads to inhibition of protein synthesis and apoptosis. Asparaginase is cycle-specific for the G1 phase of the cell cycle.
VSLI (vincristine sulfate liposome injection)	Marqibo®	Vinca Alkaloid are cytotoxic by disrupting the microtubules function during cell division (metaphase)

Adapted from Shead D, Hanisch LJ, and Clarke R. NCCN Clinical Practice Guidelines Oncology, Acute Lymphoblastic Leukemia. 2017 (2) 1-94. Available from: https://www.nccn.org/patients/guidelines/all/index.html#1

Biologic medications are also commonly used such as tyrosine kinase inhibitors (TKIs).[40] For patients positive with the BCR-ABL protein, TKIs (rituximab and blinatumomab) are a targeted therapy approach that inhibit the signal leukemia cells receive in order to grow.

In August 2017, the FDA approved IDHIFA® (enasidenib) for adults with relapsed or refractory AML with a isocitrate dehydrogenase-2 (IDH2) mutation which occurs in about 9-19% of patients with this type of cancer.[41,42] Patients with the IDH2 mutation have a poor prognosis and until IDHIFA® there were no treatment options for this population.[43] The normal IDH2 enzyme is essential for myeloid stem cell differentiation. A mutated IDH2 causes abnormal myeloid stem cell proliferation. IDHIFA® inhibits the proliferation of these abnormal myeloblast and induces normal differentiation. It is dosed 100 mg orally once daily until disease progression or intolerable toxicity and for a minimum of 6 months. The efficacy was studied in 199 patients with relapsed or refractory AML positive for IDH2 mutation. Twenty-three percent of patients in the study had a complete response which was defined as no evidence of disease and blood counts (platelets >100,000 uL and ANC >1,000 uL) within 6 months. In clinical trials about 14% of patients treated with IDHIFA® experienced life-threatening differentiation syndrome which the FDA has labeled this as a black box warning. Differentiation syndrome, or sometimes referred to as retinoic acid syndrome, occurs when agents

block stem cell differentiation. This creates miscommunication between the myeloblast cells causing them to infiltrate into the lungs and vasculature causing pulmonary and pericardial effusion.[44] The most common adverse reactions include hyperbilirubinemia (81%), hypocalcemia (74%), nausea (50%), diarrhea (43%), and hypokalemia (41%).

In August 2017 the FDA approved Rydapt® (midostaurin) for the treatment of newly diagnosed AML in patients who have a FLT3 gene mutation.[45] FLT3 is a tyrosine kinase receptor that has an important role in stem cell proliferation and survival. There are two types of this mutation: FLT3-ITD and FLT3-TKD which accounts for approximately 37% of all patients with AML. Patients with FLT3-ITD have a poor prognosis due to high rates of relapse .[46] Rydapt® is to be used in combination with induction phase of cytarabine and daunorubicin and consolidation phase cytarabine. For AML, Rydapt® is dosed 50 mg orally twice daily with food. The most common adverse reactions are febrile neutropenia, nausea, mucositis, epistaxis, musculoskeletal pain, hyperglycemia, and respiratory tract infections. Rydapt® is a strong CYP3A4 inhibitor and inducer therefore it should not be taken concomitantly with other medication with CYP3A4 interactions. The efficacy was studied in 717 patients with newly diagnosed patients with FLT3 gene mutation. Patients received Rydapt®50 mg once daily with food or placebo, plus daunorubicin 60 mg/m2 for 3 days and cytarabine 200 mg/m2 for 7 days. The efficacy analysis was performed 3.5 years after randomization and the Rydapt® plus standard therapy was superior to placebo plus standard therapy, HR 0.77 (95% CI 063-0.95) and p-value is 0.016. There was a 23% increase in overall survival for patients in the Rydapt group versus placebo.

Besponsa® (intotuzumab ozogamicin) was also FDA approved in August 2017 for relapsed or refractory B-cell ALL. [47,48] Besponsa® is a CD-22 directed antibody-drug conjugate which is involved in the development of B-cells and is expressed on the surface of many B-cell lineage tumors. It is a 0.9mg powder for reconstitution that is administered as a 1-hour infusion given in a series for up to six cycles. The first cycle starts on day one 0.8mg/m2, followed by day eight 0.5mg/m2, and lastly day fifteen is 0.5mg/m2. Cycles two through six are dosed depending on treatment response. Patients who have a complete response are dosed 0.5mg/m2 and patients who have not achieved complete response are dosed at 0.8mg/m2 on days 1, 8, and 15. Major reactions include myelosuppression (51%), injection site reaction (2%), QT interval prolongation (3%) and hepatic veno-occlusive disease (14%). Efficacy was evaluated in 218 patients and 73% had complete remission within 2 cycles.

Lymphoma

The lymphatic system is a network of vessels that run throughout the body to transport cellular debris. The lymph fluid is transported to the lymph node where it is filtered and lymphocytes within the nodes fight infection.[49] Lymphoma is a cancer that starts in the lymphatic system and affects the body's immune system. There are two types of lymphoma: Hodgkin's and non-Hodgkin's. There are 5 subtypes of Hodgkin's lymphoma which are uncommon due to the Reed-Sternberg cells which are large multinucleated lymphocytes that are found only in Hodgkin's lymphoma.[50,51] Non-Hodgkin's lymphoma (NHL) has over 25 subtypes and is much more common in the United States.[52] The American Cancer Society estimates for 2018 in the U.S. about 76,680 people will have NHL and about 19,910 people will die.[53] NHL can also be

classified as slow growing like follicular lymphoma or aggressive like B-cell lymphoma.[54] Current first line therapy for follicular lymphoma includes R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) and Bendamustine and rituximab.[55]

In September 2017, the FDA approved Aliqopa (copanlisib) as a third line agent for follicular lymphoma.[56,57] More specifically this new medication is for patients with relapsed follicular lymphoma who have had two prior systemic therapies. Follicular lymphoma is a slow growing cancer that usually goes undetected until later stages (III and IV) and can be difficult to treat with chemotherapy.[58] Aliqopa® is the first PI3K inhibitor which plays an important role in B-cell receptor signaling. It works by blocking the signal responsible for malignant B-cell proliferation and function therefore decreasing the cancer growth. It is administered as a 60 mg one-hour infusion to be given on days 1, 8, 15 of a 28-day treatment cycle. Adverse events include increased risk for infection (19%), hyperglycemia (41%), hypertension (26%), and neutropenia (24%). Drug interactions include CYP3A4 inducers and inhibitors. In the presence of strong CYP3A4 inhibitor the Aliqopa® dose should be decreased to 45 mg. Efficacy of Aliqopa® was studied in the CHRONOS-1 single arm trial in which included 104 patients with relapsed follicular B-cell NHL with two prior treatments (rituximab plus an alkylating agent regimen). The patients received Aliqopa® 60 mg one-hour infusion on days 1, 8, and 15 of treatment. The overall response rate for the treatment group was 59% (14% complete response and 44% partial response) with median time to response of 1.7 months.

Calquence® (acalabrutnib) was approved in October 2017 for the treatment of mantle cell lymphoma.[59,60] Mantle cell lymphoma is a rare and aggressive form of non-Hodgkin lymphoma in which B lymphocytes from the mantle zone (outer portion of lymph node follicle) grow uncontrollably. The uncontrollable growth of these MCL cells lead to the enlargement of lymph nodes and after entering the bloodstream can travel to other lymph nodes and organ systems.[60] This new agent inhibits the Bruton tyrosine kinase (BTK) signaling pathway which is responsible for B lymphocyte proliferation, trafficking, chemotaxis, and adhesion.[61] By blocking this BTK signaling pathway, there is less malignant B lymphocyte proliferation and survival. In a phase II single arm trial evaluating the efficacy of Calquence® on 124 MCL patients, 81% of patients responded to treatment (40% complete and 41% partial response) at a median 15.2-month follow-up. The median time to best response was 1.9 months.[62] The most common side effects seen with this new agent include headache, fatigue, diarrhea, and myalgia among others.[61] Additionally, Calquence® is a substrate of CYP3A4, therefore other drugs blocking this enzyme may increase the serum concentration of Calquence®.

Conclusion

In conclusion, the FDA's expedited process has resulted in many new drug approvals for serious and life threatening medical conditions, such as cancer. The focus for this continuing education topic is prostate cancer, breast cancer, and blood cancers including leukemia and lymphoma. New prostate cancer treatment Erleada® (apalutamide) for the treatment of non-metastatic, castration-resistant prostate cancer showed improved survival (mean 40.5 months) versus placebo (16.5 months) in this cancer that was previously difficult to treat. New breast cancer treatments include: Verzenio® (abemaciclib) for advanced or metastatic breast cancer which increased

progression-free survival by 7 months compared to placebo, Nerlynx® (neratinib maleate) to reduced risk of breast cancer returning by 2.3% compared to placebo in 24 months, and Kisqali® (ribociclib) for postmenopausal advanced breast cancer which showed improvement in time till tumor worsening by 5 months compared to placebo. New leukemia drugs include: IDHIFA® (enasidenib) for adults with relapsed or refractory AML with a isocitrate dehydrogenase-2 (IDH2) mutation, Rydapt® (midostaurin) for the treatment of newly diagnosed AML who have FLT3 gene mutation, and Besponsa® (intotuzumab ozogamicin) for relapsed or refractory B-cell AML. New lymphoma drugs include: Aliqopa® (copanlisib) as a third line agent for follicular lymphoma and Calquence® (acalabrutnib) for the treatment of mantle cell lymphoma. The new cancer treatment options made available by the FDA's novel drug approval programs offer promising developments to these life-threatening disease states.

References

1. Cancer Facts and Figures 2018. The American Cancer Society. [updated 2018, cited 2018 Mar 30]. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf
2. 2017 New drug therapy approvals. FDA US Food & Drug Administration. 2018 Jan. Available from: https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ReportsBudgets/UCM591976.pdf
3. Novel Drug Approvals for 2018. FDA US Food & Drug Administration. [updated 2018 Mar 21, cited 2018 Mar 30]. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm592464.htm
4. Frequently asked questions about the FDA drug approval process. U.S. Dept of Health and Human Services. [updated 2017 Feb 7, cited 2018 Mar 30]. Available from: https://www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm279676.htm#4).
5. Development & Approval Process (Drugs). FDA US Food & Drug Administration. [updated 2018 Jan 16, cited 2018 Mar 30]. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018 Jan;86(1):7-30.
7. Norris LB, Kolesar JM. Chapter 131: Prostate cancer. In DiPiro J.T. Talbert R.L., Yee G.C., Matzke G.R., Posey L (Eds), Pharmacotherapy: A Pathophysiologic Approach, 10e [AUHSOP Intranet]. New York: McGraw-Hill Education; 2014. [cited 2018 April 2]. Available from: https://accesspharmacy.mhmedical.com/book.aspx?bookID=1861#130942264
8. Carroll PR, Parsons JK, Andriole G, Bahnson RR, Castle EP, Catalona WJ, et al. Prostate cancer early detection. NCCN Clinical Practice Guidelines in Oncology. NCCN. 2018;1:1-50.
9. Wolf A, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin. 2010 Mar;60(2):70-98.
10. Mohler JL, Lee RJ, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, et al. Prostate cancer. NCCN Clinical Practice Guidelines in Oncology. NCCN. 2018;2:1-86.
11. FDA approves new treatment for certain type of prostate cancer using novel clinical trial endpoint. FDA US Food & Drug Administration. [updated 2018 Feb 14, cited 2018 April 2]. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm596768.htm

12. Apalutamide. In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc. [updated 2018 Mar 26, cited 2018 April 2]. Available from: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6615150#f_adverse-reactions
13. Apalutamide. In: Clinical Pharmacology online [AUHSOP Intranet]. Tampa, FL: Elsevier [Updated 2018 Mar 2, cited 2018 April 2]. Available from: http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=5013&sec=monadve&t=0
14. Barnett CM, Boster BL, Michaud LB. Chapter 128: Breast Cancer. Pharmacotherapy: A Pathophysiologic Approach, 10th edition. [AUHSOP Intranet, cited 2018 Apr 2]. Available from: http://accesspharmacy.mhmedical.com/content.aspx?sectionid=146074631&bookid=1861&Resultclick=2
15. Breast Cancer Risk Assessment Tool. National Cancer Institute (updated 2011 May 16, cited 2018 Apr 2). Available from: https://www.cancer.gov/bcrisktool/Default.aspx
16. Bevers TB, Helvie M, Bonaccio E, et al. Breast Cancer Screening and Diagnosis. National Comprehensive Cancer Network (2017 Jun 2, cited 2018 Apr 2). Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf
17. Novel Drug Approvals for 2017. US Food & Drug Administration. (updated 2018 Feb 2, cited 2018 Apr 3). Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm537040.htm
18. Verzenio® (abemaciclib) Prescribing Information. Eli Lilly and Company, LLC. Indianapolis, IN. (revised 2018 Feb, cited 2018 Apr 2). Available from: http://pi.lilly.com/us/verzenio-uspi.pdf
19. Verzenio ®(abemaciclib). In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc. [Updated 2018 Mar 19, cited 2018 Mar 31]. Available from: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6548917
20. Verzenio ®(abemaciclib). In: Clinical Pharmacology online [AUHSOP Intranet]. Tampa, FL: Elsevier [Updated 2017 Sep 29, cited 2018 Mar 31]. Available from: http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=4978&sec=mondesc&t=0
21. Verzenio® (abemaciclib). In: Micromedex 2.0 [AUHSOP Intranet]. Greenwood Village, CO: Thomson Reuters (Healthcare), Inc. [updated 2018 Feb 28, cited 2018 Mar 31]. Available from http://www.micromedexsolutions.com
22. Drug Trial Snapshot: Verzenio®. U.S. Food & Drug Administration (updated 2017 Oct 20, cited 2018 Apr 2). Available from: https://www.fda.gov/drugs/informationondrugs/ucm580765.htm
23. Kisqali® (ribociclib) Prescribing Information. Novaritis Pharmaceutical Corporation. East Hanover, NJ. (revised 2017 Mar, cited 2018 Feb 2). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf
24. Kisqali® (ribociclib). In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc. [Updated 2018 Mar 19, cited 2018 Mar 31]. Available from: http://online.lexi.com/lco/action/search?q=kisqali&t=name&va=kisqali
25. Kisqali® (ribociclib). In: Clinical Pharmacology online [AUHSOP Intranet]. Tampa, FL: Elsevier [Updated 2017 Mar 17, cited 2018 Mar 31]. Available from: http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=4927&sec=mondesc&t=0
26. Kisqali® (ribociclib). In: Micromedex 2.0 [AUHSOP Intranet]. Greenwood Village, CO: Thomson Reuters (Healthcare), Inc. [updated 2018 Feb 20, cited 2018 Mar 31]. Available from http://www.micromedexsolutions.com
27. Drug Trials Snapshot: Nerlynx®. US Food & Drug Administration (updated 2017 July 24, cited 2018 Apr 2). Available from: https://www.fda.gov/drugs/informationondrugs/ucm568138.htm
28. Nerlynx® (neratinib) Prescribing Information. Puma Biotechnology, Inc., Los Angeles, CA. (revised 2017 July, cited 2018 Apr 2). Available from: https://nerlynx.com/pdf/full-prescribing-information.pdf

29. Nerlynx® (neratinib). In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc. [Updated 2018 Apr 2, cited 2018 Apr 3]. Available from: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6519378
30. Nerlynx® (neratinib). In: Clinical Pharmacology online [AUHSOP Intranet]. Tampa, FL: Elsevier [Updated 2017 July 20, cited 2018 Mar 31]. Available from: http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=4956&sec=mondesc&t=0
31. Nerlynx® (neratinib). In: Micromedex 2.0 [AUHSOP Intranet]. Greenwood Village, CO: Thomson Reuters (Healthcare), Inc. [updated 2018 Jan 23, cited 2018 Mar 31]. Available from http://www.micromedexsolutions.com
32. Drug Trials Snapshot: Nerlynx. US Food & Drug Administration (updated 2017 July 24, cited 2018 Apr 2). Available from: https://www.fda.gov/drugs/informationondrugs/ucm568138.htm
33. Blood disorders. American Society of Hematology, Washington D.C. [updated 2018, cited 2018 Apr 2]. Available from: http://www.hematology.org/Patients/Blood-Disorders.aspx
34. Shead D, Hanisch LJ, and Clarke R. NCCN Clinical Practice Guidelines Oncology, Acute Lymphoblastic Leukemia. 2017 (2) 1-94. Available from: https://www.nccn.org/patients/guidelines/all/index.html#1
35. Blood cancers. Cancer Treatment Centers of America. [updated 2018, cited 2018 Apr 2]. Available from: https://www.cancercenter.com/terms/blood-cancers/
36. Acute lymphocytic leukemia. Mayo Clinic. [updated 2018, cited 2018 Apr 2]. Available from: https://www.mayoclinic.org/diseases-conditions/acute-lymphocytic-leukemia/symptoms-causes/syc-20369077
37. Acute Myeloid Leukemia. Cancer Center Treatment of America. [updated 2017 Apr 17, cited 2018 Apr 2]. Available from: https://www.cancercenter.com/leukemia/types/tab/acute-myeloid-leukemia/
38. Cancer Stat Facts: Leukemia- Acute Myeloid Leukemia (AML). National Cancer Institute. [updated 2017, cited 2018 Apr 2]. Available from: https://seer.cancer.gov/statfacts/html/amyl.html
39. What is Chronic Lymphocytic Leukemia. American Cancer Society. [updated 2016 Apr 11, cited 2018 Apr 2]. Available from: https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html
40. Shead D, Hanisch LJ, and Clarke R. NCCN Clinical Practice Guidelines Oncology, Acute Lymphoblastic Leukemia. 2017;v2:32-38. Available from: https://www.nccn.org/patients/guidelines/all/index.html#1
41. Cancer Stat Facts: Leukemia-Acute Myeloid Leukemia (AML). National Cancer Institute. [update 2017, cited 2018 Apr 2]. Available from: https://seer.cancer.gov/statfacts/html/amyl.html
42. Green CL, Evans CM, Zhao L, et al. The prognostic significance of IDH2 mutations in AML depends on the location of the mutation Blood 2011 118: 409-12. Available from: (http://www.bloodjournal.org/content/118/2/409?sso-checked=true)
43. IDHIFA®. Prescribing Information. Agios Pharmaceuticals and Celgene Corp, Summit, NJ. [updated 2018 Feb, cited 2018 Apr 2 2018]. Available from: https://idhifapro.com/about-idhifa/#idhifa-for-RR-AML
44. Montesinos P and Sanz MA. The differentiation syndrome in patients with acute promyelocytic leukemia: experience of the pethema group and review of the literature. Mediterr J Hematol Infect Dis 2011; 3(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3248336/
45. Rydapt®. Prescribing Information. Novartis Pharmaceuticals Corporation, East Hanover, NJ. [updated 2017 April, cited 2018 April 2]. Available from: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/rydapt.pdf
46. Small, Donald. FLT3 Mutations: Biology and Treatment. ASH Education, 2006 Jan (1) 178-84. Available from: http://asheducationbook.hematologylibrary.org/content/2006/1/178.long

47. Besponsa. Prescribing Information. Wyeth Pharmaceuticals, Inc, Philadelphia, PA. [updated 2017 Aug, cited 2018 Apr 2]. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=9503)
48. Besponsa®. Dosing and administration. [updated 2018, cited 2018 Apr 2]. Available from: https://www.besponsahcp.com/dosing
49. What is the lymphatic system?. National Lymphoma Network. [updated 2018, cited 2018 Apr 2]. Available from: https://www.lymphnet.org/le-faqs/what-is-lymphedema/what-is-the-lymphatic-system
50. Reed-Sternberg cells. NCI dictionary of cancer terms. National Cancer Institute. [cited 2018 Apr 2]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/reed-sternberg-cell
51. Lymphoma Overview- Patient Version. National Cancer Institute. [cited 2018 Apr 2]. Available from: https://www.cancer.gov/types/lymphoma
52. Freedman, A. What's the difference between Hodgkin's and Non-Hodgkins lymphoma. Dana-Farber Cancer Institute. [updated 2017 Oct, cited 2018 Apr 2]. Available from:http://blog.dana-farber.org/insight/2015/07/what-is-the-difference-between-hodgkin-lymphoma-and-non-hodgkin-lymphoma/
53. Key Statistics for Non-Hodgkin's Lymphoma. American Cancer Society. [updated 2018 Jan 4, cited 2018 Apr 2]. Available from: https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/key-statistics.html
54. Lymphoma Overview.- Patient Version. National Cancer Institute. [cited 2018 Apr 2]. Available from: https://www.cancer.gov/types/lymphoma
55. Zelenetz AD, Gordon LI, Weirda WG, et al. NCCN Clinical Practice Guidelines Oncology, Non-Hodgkin's Lymphomas. 2014 (4). Available from: https://www.nccn.org/about/nhl.pdf
56. Aliqopa®. Prescribing Information. Bayer Healthcare Pharmaceuticals Inc, Whippany, NJ. [updated 2018 Mar, cited 2018 Apr 2]. Available from: https://www.hcp.aliqopa-us.com/mechanism-of-action/
57. Aliqopa®. Interactive Prescribing Information. Bayer Healthcare Pharmaceuticals Inc, Whippany, NJ. [updated 2018 Mar, cited 2018 Apr 2]. Available from: https://www.hcp.aliqopa-us.com/interactive-p
58. Follicular Lymphoma. Leukaemia Foundation. [updated 2018, cited 2018 Apr 2]. Available from: http://www.leukaemia.org.au/blood-cancers/lymphomas/non-hodgkin-lymphoma-nhl/follicular-lymphoma
59. Mantle Cell Lymphoma. Lymphoma Research Foundation. [cited 2018 April 2]. Available from: https://www.lymphoma.org/aboutlymphoma/nhl/mcl/
60. Mantle cell lymphoma facts. Leukemia and Lymphoma Society. 2014 Nov. Available from: https://www.lls.org/sites/default/files/file_assets/mantlecelllymphoma.pdf
61. Acalabrutinib. In: Lexi-Comp Online [AUHSOP Intranet]. Hudson, OH: Lexi-Comp, Inc. [updated Mar 26, 2018, cited April 2, 2018]. Available from: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6564511
62. Markham A, Dhillon S. Acalabrutinib: First global approval. Drugs. 2018;78:139-149. Available from: https://link.springer.com/article/10.1007%2Fs40265-017-0852-8#citeas