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Washington Drug Utilization Review (DUR) Board Meeting

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Agenda Topics

- Overview of Disease State
- Indications
- Dosage & Formulations
- Guideline Updates

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COPD Agents:

- ASTHMA AND COPD AGENTS : ANTICHOLINERGICS
- ASTHMA AND COPD AGENTS : PHOSPHODIESTERASE 4 INHIBITORS
- ASTHMA AND COPD AGENTS : LONG ACTING MUSCARINIC AGENT / LONG ACTING BETA AGONIST COMBINATIONS
- ASTHMA AND COPD AGENTS : LONG ACTING MUSCARINIC AGENTS

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Immunomodulators, Asthma

- Asthma and COPD Agents: Monoclonal Antibodies

Disease State Description

- Prevalence of asthma in the United States (US) continues to rise
  - More than 25 million Americans have asthma, and over 4 million of these are children
- The National Asthma Education and Prevention Program (NAEPP) has defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role
  - In susceptible individuals, inflammation may cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing
  - These episodes are usually associated with airflow obstruction that is often reversible, either spontaneously or with treatment
  - The inflammation also causes an increase in bronchial hyper-responsiveness to a variety of stimuli
- Studies have demonstrated the efficacy of inhaled corticosteroids (ICS) in improving lung function, reducing symptoms, reducing frequency and severity of exacerbations, and improving the quality of life (QoL) of patients with asthma
  - The 2007 National Heart, Lung, and Blood Institute (NHLBI) states that inhaled glucocorticoids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma
  - The 2019 GINA full report advises that all patients with asthma should receive ICS-containing controller treatment to reduce risk of serious exacerbations and to control symptoms

Centers for Disease Control and Prevention (CDC), 2022

Guidelines

- Global Initiative for Asthma (GINA), 2022
  - The guidelines offer a control-based management plan to adjust treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects
  - Equally important in this process is identifying the patient's own goals regarding their asthma management to ensure improved outcomes
  - In patients whose asthma is not adequately controlled on the preferred controller despite good adherence and correct technique, a step up in treatment may be added until control is achieved. This can be a short-term or sustained step up in therapy. If control is maintained for at least 3 months on the current regimen, treatment can be stepped down to the lowest step and dosage that maintains control
  - Patients should be started on treatment based on symptoms, with infrequent symptoms beginning at Step 1 and patients with the most frequent, severe, or debilitating symptoms beginning at Step 4
  - Notably, reliever therapy can be considered for symptom management prior to exercise, if needed
  - The GINA 2021 guidelines describe 2 treatment tracks: Track 1 and Track 2 (next slide)
    - In Track 1, the reliever is as-needed low dose ICS-formoterol
    - In Track 2, the reliever is an as-needed SABA, which is the alternative approach when Track 1 is not an option or is not preferred for patient-specific reasons

Guidelines

- Global Initiative for Asthma (GINA), 2022

Step	Track 1	Track 2	Other Controller Options
1	▪ As-needed low dose ICS/formoterol	▪ Low dose ICS (whenever SABA is taken) ▪ With as-needed SABA	--
2	▪ **As-needed low dose ICS/formoterol**	▪ **Low dose maintenance ICS** ▪ With as-needed SABA	▪ Low dose ICS (whenever SABA is taken) or daily LTRA or add HDM SLIT
3	▪ Low dose maintenance ICS/formoterol ▪ With as-needed low dose ICS/formoterol	▪ Low dose maintenance ICS/LABA ▪ With as-needed SABA	▪ Medium dose ICS or add LTRA or add HDM SLIT
4	▪ Medium dose maintenance ICS/formoterol ▪ With as-needed low dose ICS/formoterol	▪ **Medium/high dose maintenance ICS/LABA** ▪ With as-needed SABA	▪ Add LAMA or add LTRA or switch to high dose ICS
5	▪ **Add on LAMA**; refer for phenotypic assessment ± anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL4R (dupilumab) ▪ **Consider high dose ICS/formoterol** ▪ With as-needed low dose ICS/formoterol	▪ **Add on LAMA;** refer for phenotypic assessment ± anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL4R (dupilumab) ▪ **Consider high dose ICS/LABA** ▪ With as-needed SABA	▪ Add azithromycin (adults) or add LTRA or add low dose oral corticosteroid (considering adverse effects)

Guidelines

- American College of Chest Physicians (CHEST), 2020
  - A 2020 Expert Panel Report on the management of chronic cough due to asthma and non-asthmatic eosinophilic bronchitis (NAEB) in adults and adolescents addresses the role of ICS in these patients
  - For patients with chronic cough due to asthma as a unique system (cough variant asthma), they recommend ICS as first-line treatment
  - If this is inadequate, the dose may be increased, treatment can be switched to a leukotriene inhibitor, or an ICS/LABA can be considered
  - ICS are also recommended first-line for chronic cough due NAEB (Grade 2B), although they are not FDA- approved for this use

- National Asthma Education and Prevention Program, 2020
  - Recommend a similar classification of asthma severity and control, to guide in the initiation and adjustment of therapy, respectively
  - Asthma severity and control are defined in terms of 2 domains, impairment and risk
    - The distinction between these domains emphasizes the need to consider separately, asthma's effects on quality of life and functional capacity on an ongoing basis (e.g., in the present), along with risks for adverse events, such as exacerbations and progressive loss of pulmonary function
  - The group recommends a step-wise approach to asthma management, which is detailed in the table below. In addition, all asthma patients should have a SABA inhaler for use on an as-needed basis
  - As needed ICS with formoterol is recommended instead for patients 5 to 11 years of age at steps 3 and 4 (as low-dose or medium-dose, respectively), but a SABA is recommended as an alternative
  - For combinations of an ICS and a LABA for patients ≥ 5 years of age, the group states a single inhaler is preferable

Immunomodulators, Asthma

- **Dupixent (dupilumab)**
  - June 2021: FDA approved 200 mg/1.14 mL single-dose auto-injector (pre-filled pen) for use in patients ≥ 12 years old; was already approved as 200 mg/1.14 mL pre-filled syringe and auto-injector and 300 mg/2 mL auto-injector & pre-filled syringe
  - **October 2022: FDA has expanded the indication of add-on maintenance treatment with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma to patients ≥ 6 years old (previously indicated for those ≥ 12 years of age)**
  - **Indications**
    - **Asthma: as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma**
    - Atopic Dermatitis: for the treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Can be used with or without topical corticosteroids
    - Chronic Rhinosinusitis with Nasal Polyposis: as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP)
    - **Limitations of use: Not indicated for relief of acute bronchospasm or status asthmaticus**
  - **Dosage**
    - **Stratified by indication, age, and weight (See TCR/PI)**
  - **Availability**
    - Injection: 300 mg/2 mL solution in a single-dose pre-filled pen; Injection: 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield
    - **Injection: 200 mg/1.14 mL solution in a single-dose pre-filled pen**; Injection: 200 mg/1.14 mL solution in a single-dose pre-filled syringe with needle shield
    - Injection: 100 mg/0.67 mL solution in a single-dose pre-filled syringe with needle shield

Immunomodulators, Asthma

- **Tezspire (tezepelumab-ekko)**
  - December 2021: The FDA has approved tezepelumab-ekko (Tezspire), a thymic stromal lymphopoietin (TSLP) blocker, indicated for the add-on maintenance treatment of adult and pediatric patients aged ≥ 12 years with severe asthma; not for relief of acute bronchospasm or status asthmaticus
  - **February 2023: FDA approved a single-use 210 mg/1.91 mL autoinjector for self- or caregiver-administration**
  - **Indications**
    - **The add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma**
    - **Limitations of use: Not indicated for relief of acute bronchospasm or status asthmaticus**
  - **Precautions**
    - Risk Associated with Abrupt Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with TEZSPIRE. Decrease corticosteroids gradually, if appropriate
    - Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy with TEZSPIRE. If patients become infected while receiving TEZSPIRE and do not respond to antihelminth treatment, discontinue TEZSPIRE until the parasitic infection resolves
    - Vaccination: Avoid use of live attenuated vaccines
  - **Dosage**
    - Administer by subcutaneous injection
    - Recommended dosage is 210 mg administered once every 4 weeks
  - **Availability**
    - **Injection:** 210 mg/1.91 mL (110 mg/mL) solution in a single-dose glass vial; 210 mg/1.91 mL (110 mg/mL) solution in a single-dose pre-filled syringe; **210 mg/1.91 mL (110 mg/mL) solution in a single-dose pre-filled pen**

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Glucocorticoids, Inhaled

- Asthma and COPD Agents: Inhaled Corticosteroid Combinations
- Asthma and COPD Agents: Inhaled Corticosteroid

Glucocorticoids, Inhaled

- Armonair Digihaler (fluticasone propionate)
  - **April 2022: FDA approved for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients ≥ 4 years old. Previously, it was only indicated in pediatrics ≥ 12 years old**
  - **Indications**
    - **The maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older**
    - Limitations of use: Not indicated for relief of acute bronchospasm
  - **Precautions**
    - Primary treatment of status asthmaticus or other acute episodes of asthma requiring intensive measures
    - Severe hypersensitivity to milk proteins or any ingredients
  - **Dosage**
    - Starting dosage is based on prior asthma therapy and disease severity
    - Treatment of asthma in patients ≥ 12 years: 1 inhalation of ArmonAir Digihaler 55 mcg, 113 mcg, or 232 mcg twice daily
    - ArmonAir Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events for transmission to the mobile App
  - **Availability**
    - Inhalation powder containing 55 mcg, 113 mcg, or 232 mcg of fluticasone propionate per actuation

Glucocorticoids, Inhaled

- Airsupra (albuterol/budesonide)
  - **January 2023: FDA has approved a new combination of albuterol, a beta2-adrenergic agonist, and budesonide, a corticosteroid, indicated for as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma ≥ 18 years of age**
  - **Indications**
    - **A combination of albuterol, a beta2-adrenergic agonist and budesonide, a corticosteroid, indicated for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older**
  - **Precautions**
    - **Hepatic impairment: Budesonide systemic exposure may increase in patients with severe hepatic impairment. Monitor patients with hepatic disease**
    - **If paradoxical bronchospasm occurs, discontinue treatment immediately and institute alternative therapy**
    - **Cardiovascular effects may occur. Use with caution in patients sensitive to sympathomimetic drugs and patients with cardiovascular disorders**
  - **Dosage**
    - **Recommended Dosage: 180 mcg/160 mcg (administered as 2 actuations of albuterol/budesonide 90 mcg/80 mcg) by oral inhalation as needed for asthma symptoms**
    - **Do not take more than 6 doses (12 inhalations) in a 24-hour period**
  - **Availability**
    - **Inhalation aerosol: Pressurized metered dose inhaler that delivers a combination of albuterol 90 mcg and budesonide 80 mcg per actuation**

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Glucocorticoids, Oral/ Glucocorticoids, Injectable

- Corticosteroids: Glucocorticosteroids

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Erythropoiesis Stimulating Proteins
- Hematopoietic Agents: Erythropoiesis Stimulating Agents (ESAs)

Erythropoiesis Stimulating Proteins - Disease State Description

- **Anemia**
  - A frequent complication, affecting over 3 million Americans
  - Associated with a number of serious diseases, such as chronic kidney disease (CKD), diabetes, heart disease, and cancer, as well as chronic inflammatory conditions like rheumatoid arthritis or inflammatory bowel disease
  - These conditions can cause anemia by interfering with the production of oxygen-carrying red blood cells (RBCs)
  - Sometimes, as in the case of cancer chemotherapy, anemia can be caused by the treatment itself

- **Erythropoietin**
  - A glycoprotein produced in the kidneys that stimulates RBC production from bone marrow
  - Acts on the erythroid progenitor cells in the bone marrow to cause late differentiation and maturity of the RBCs
  - Endogenous production of erythropoietin by the kidney is normally regulated by the level of tissue oxygenation
  - Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis
  - In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 units/mL and may increase 100- to 1,000-fold during hypoxia or anemia
  - In contrast, patients with CKD have impaired production of erythropoietin, which is the primary cause of their anemia
  - Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents

Erythropoiesis Stimulating Proteins - Disease State Description

- **Beta thalassemia**
  - A rare inherited blood disorder marked by the reduction of functional hemoglobin levels, has an incidence of approximately 1 in 100,000 individuals in the general population
  - There are 3 subtypes of beta thalassemia, which are characterized by the severity of symptoms – minor, intermedia, and major
  - Individuals with beta thalassemia major require regular blood transfusions, as often as once every 2 to 4 weeks and are dependent on medical care for survival
  - Treatment for beta thalassemia is highly dependent on type of thalassemia, progression and severity of disease, and the presence or absence of certain symptoms
  - Treatment options may include regular blood transfusions, chelation therapy, folic acid treatment, removal of the spleen and/or gallbladder, and bone marrow transplantation
  - **Luspatercept-aamt (Reblozyl)** is the first FDA-approved erythroid maturation agent, which reduces patient transfusion burden by regulating late-stage RBC maturation
  - It is approved for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell transfusions

Erythropoiesis Stimulating Proteins - Guidelines

- **National Comprehensive Cancer Network (NCCN) Guidelines, 2020**
  - State that erythropoiesis stimulating agents (ESAs) are associated with an increased risk of thrombosis, decreased survival, and shortened time to tumor
  - Physicians are advised to use the lowest ESA dose possible to maintain hemoglobin (Hb) levels sufficient to avoid blood transfusions, to prescribe according to Food and Drug Administration (FDA) guidelines, and to obtain patient consent
  - ESAs should be discontinued once the course of chemotherapy has been completed and anemia resolves
  - There is not enough evidence to support the use of ESAs for the treatment of anemia related to myelosuppressive chemotherapy with curative intent, patients receiving non-myelosuppressive therapy, or patients with cancer not receiving therapy

National Comprehensive Cancer Network, 2020

- **American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH)**
  - Updated their 2010 recommendations for use of erythropoiesis-stimulating agents (ESAs) in patients with cancer
  - Guidelines emphasize the intent of treatment be considered when weighing the benefits and risks of these agents (including thromboembolism)
  - ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin level is < 10 g/dL
    - Another option for these patients is a red blood cell transfusion, depending on the severity of the anemia or other clinical circumstances
    - Hemoglobin may be increased to the lowest concentration needed to avoid or reduce the need for red blood cell transfusions, which may vary by patient and condition
    - They can also be used for low-risk myelodysplastic syndrome
  - Regarding biosimilars, they state clinicians should expect similar results among the various formulations (and biosimilars)
  - The goal hemoglobin should be the lowest value that prevents need for transfusion; ESAs should be discontinued if there is a lack of hemoglobin increase by 1 to 2 g/dL by 6 to 8 weeks

ASCO/ASH, 2010

Erythropoiesis Stimulating Proteins

- **daprodustat (Jesduvroq)**
  - **February 2023: FDA approved daprodustat, a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor, as the first oral treatment for anemia due to CKD in adults who have been receiving dialysis for ≥ 4 months**
  - **Indications:**
    - **A hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor indicated for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least four months**
    - **Limitations of Use: Not shown to improve quality of life, fatigue, or patient well-being. Not indicated for use; As a substitute for transfusion in patients requiring immediate correction of anemia; In patients not on dialysis**
  - **Warning & Precautions**
    - **BBW: Jesduvroq increases the risk of thrombotic vascular events, including major adverse cardiovascular events (MACE)**
    - **BBW: Targeting a hemoglobin level greater than 11 g/dL is expected to further increase the risk of death and arterial venous thrombotic events, as occurs with erythropoietin stimulating agents (ESAs), which also increase erythropoietin levels**
    - **Pregnancy: May cause fetal harm**
    - **Hepatic Impairment: Reduce the starting dose in patients with moderate hepatic impairment (Child-Pugh Class B). Not recommended in severe hepatic impairment (Child-Pugh Class C)**
    - **Malignancy: May have unfavorable effects on cancer growth. Not recommended if active malignancy**
  - **Dosage:**
    - **See PI/TCR for starting dosage based on hemoglobin level, liver function and concomitant medications, and for dose titration and monitoring recommendations**
  - **Formulations:**
    - **Tablets: 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg**

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Gaucher's Disease

- Hematopoietic Agents: Gaucher Disease

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Colony Stimulating Factors

- Hematopoietic Agents: Granulocyte Colony Stimulating Factors (G-CSF)

Disease State Description - Colony Stimulating Factors

- Myelosuppressive chemotherapy can induce neutropenia (< 500 neutrophils/µL or < 1,000 neutrophils/µL and a predicted decline to ≤ 500/µL during the 48 hours after the dose) and febrile neutropenia (≥ 38.3°C orally or ≥ 38°C sustained over 1 hour) which is a dose-limiting toxicity of chemotherapy
- Febrile neutropenia can cause increased diagnostic and treatment costs, prolonged hospitalizations, and broad-spectrum antibiotic use which may necessitate chemotherapy dose reductions, treatment delays, and may ultimately compromise treatment outcomes
- The risk of febrile neutropenia is dependent on treatment and dose intensity, which is often underreported
- Colony stimulating factors (CSF) are hematopoietic growth factors that have been shown to decrease the likelihood of neutropenic complications resulting from chemotherapy and to improve relative chemotherapy dose intensity
  - Colony stimulating factors act on hematopoietic cells and stimulate proliferation, differentiation commitment, and some end-cell functional activation
- Prophylactic CSF use can reduce the severity, risk, and duration of febrile neutropenia and decrease rates of infection and hospitalizations
  - Eflapegrastim-xnst (Rolvedon), filgrastim (Neupogen), filgrastim-aafi (Nivestym), filgrastim-ayow (Releuko), filgrastim-sndz (Zarxio), pegfilgrastim (Neulasta), pegfilgrastim-apgf (Nyvepria), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-jmdb (Fulphila), pegfilgrastim-bmez (Ziextenzo), pegfilgrastim-fpgk (Stimufend), pegfilgrastim-pbbk (Fylnetra), and tbo-filgrastim (Granix) are granulocyte colony-stimulating factors (G-CSF)
  - Sargramostim (Leukine) is a granulocyte-macrophage colony stimulating factor (GM-CSF)

National Comprehensive Cancer Network, 2023

Guidelines - Colony Stimulating Factors

- **The National Comprehensive Cancer Network (NCCN) v1.2023**
  - Practice Guidelines for Hematopoietic Growth Factors in patients with solid tumors and lymphoid blood cancers
  - Due to the recent approval, pegfilgrastim-apgf (Nyvepria) and filgrastim-ayow (releuko) are not currently addressed by NCCN
  - Safety data appear similar between filgrastim (Neupogen), pegfilgrastim (Neulasta), and their biosimilars, and the subcutaneous (SC) route is preferred for all agents
  - To date, there are insufficient head-to-head comparative studies on the clinical benefits of G-CSFs and GM-CSFs
  - Subcutaneous filgrastim, tbo-filgrastim, and pegfilgrastim have a category 1 recommendation stating there is high-level evidence from randomized, controlled clinical trials, and there is uniform NCCN consensus that they prophylactically reduce the risk of febrile neutropenia. However, the guidelines advise caution should be used with prophylactic use of G-CSFs administered with chemotherapy and radiation concurrently

Colony Stimulating Factors

- **pegfilgrastim-fpgk (Stimufend)**
  - **September 2022: FDA approved Stimufend, a biosimilar of the reference drug pegfilgrastim (Neulasta), indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. It carries the limitation of use that it is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation**
  - **Indications**
    - **A leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia**
    - **Limitations of Use: Not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation**
  - **Precautions**
    - **Fatal sickle cell crises: Discontinue treatment if sickle cell crisis occurs**
    - **Glomerulonephritis: Evaluate and consider dose-reduction or interruption of treatment if causality is likely**
  - **Dosage**
    - **Patients with cancer receiving myelosuppressive chemotherapy o 6 mg administered subcutaneously once per chemotherapy cycle**
    - **Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy**
  - **Availability**
    - **Injection: 6 mg/0.6 mL solution in a single-dose pre-filled syringe for manual use only**

Colony Stimulating Factors

- **eflapegrastim-xnst (Rolvedon)**
  - **September 2022: FDA approved eflapegrastim-xnst, a leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult pts with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia; not indicated for the mobilization of peripheral progenitor cells for hematopoietic stem cell transplantation**
  - **Indications**
    - **A leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in adult patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with clinically significant incidence of febrile neutropenia**
    - **Limitations of Use: Rolvedon is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation**
  - **Precautions**
    - **Fatal sickle cell crises: Discontinue treatment if sickle cell crisis occurs**
    - **Glomerulonephritis: Evaluate and consider dose-reduction or interruption of treatment if causality is likely**
  - **Dosage**
    - **Recommended Dose: 13.2 mg administered subcutaneously once per chemotherapy cycle**
    - **Administer approximately 24 hours after cytotoxic chemotherapy. Do not administer within the period from 14 days before to 24 hours after administration of cytotoxic chemotherapy**
  - **Availability**
    - **Injection: 13.2 mg/0.6 mL solution in a single-dose prefilled syringe**

Colony Stimulating Factors

- **pegfilgrastim-cbqv (Udenyca)**
  - **December 2022: FDA approved an expanded indication to increase survival in patients who are acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)**
  - **Indications**
    - **A leukocyte growth factor indicated to**
      - Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia
      - **Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)**
    - Limitations of Use: Not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation
  - **Precautions**
    - Fatal sickle cell crises: Discontinue treatment if sickle cell crisis occurs
    - Glomerulonephritis: Evaluate and consider dose-reduction or interruption of treatment if causality is likely
  - **Dosage**
    - **Acute Radiation Syndrome:**
      - **Two doses, 6 mg each, administered subcutaneously one week apart**
      - **Administer the first dose as soon as possible after suspected or confirmed exposure to myelosuppressive doses of radiation, and a second dose one week after**
      - **Use weight-based dosing for pediatric patients weighing less than 45 kg; refer to PI/TCR**
  - **Availability**
    - Injection: 6 mg/0.6 mL in a single-dose prefilled syringe for manual use only; 6 mg/0.6 mL in a single-dose prefilled autoinjector

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Sickle Cell Agents

- Hematopoietic Agents: Sickle Cell Anemia

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Oncology, Oral – Hematologic

Oncology, Oral- Hematological - Overview of Disease State

- IMMUNE MODULATORS : THALIDOMIDE ANALOGUES
  - **Lenalidomide**
  - Pomalidomide
  - Thalidomide
  - Pomalyst
  - Revlimid
- ONCOLOGY AGENTS : ALKYLATING AGENTS - ORAL
  - Myleran
- ONCOLOGY AGENTS : ANTIMETABOLITES – ORAL
  - Onureg
  - Mercaptopurine
  - Purixan
  - Tabloid
- ONCOLOGY AGENTS : ANTINEOPLASTICS MISC – ORAL
  - Hydrea
  - Hydroxyurea
  - Matulane
- ONCOLOGY AGENTS : BCL-2 INHIBITORS – ORAL
  - Venclexta
- ONCOLOGY AGENTS : HISTONE DEACETYLASE INHIBITORS – ORAL
  - Farydak
  - Zolinza
- ONCOLOGY AGENTS : ISOCITRATE DEHYDROGENASE-1 (IDH1) INHIBITORS – ORAL
  - **Rezlidhia**
  - **Tibsovo**
- ONCOLOGY AGENTS : ISOCITRATE DEHYDROGENASE-2 (IDH2) INHIBITORS – ORAL
  - Idhifa
- ONCOLOGY AGENTS : JANUS ASSOCIATED KINASE (JAK) INHIBITORS – ORAL
  - Inrebic
  - Jakafi
  - Vonjo
- ONCOLOGY AGENTS : PHOSPHATIDYLINOSITOL 3-KINASE (PI3K) INHIBITORS – ORAL
  - **Copiktra**
  - Zydelig
- ONCOLOGY AGENTS : PROTEASOME INHIBITORS – ORAL
  - **Ninlaro**
- ONCOLOGY AGENTS : XPO1 INHIBITORS – ORAL
  - Xpovio

Oncology, Oral- Hematological – Overview of Disease State

- **Graft versus Host Disease (GVHD)**
  - GVHD is an immune-mediated disease that can result following hematopoietic stem cell transplant (HSCT) when the transplanted cells (graft) recognize the recipient's body as foreign
    - Organ systems most commonly impacted by acute GVHD (aGVHD) include the skin, GI tract, and liver
  - Chronic GVHD (cGVHD) is generally an extension of acute GVHD that often develops more than 100 days after transplant, but it can also occur in those without acute GVHD
  - Symptoms include ocular manifestations (e.g., burning, irritation, photophobia, pain), oral or gastrointestinal (GI) manifestations (e.g., food sensitivity, oral dryness, pain, weight loss), respiratory manifestations (e.g., wheezing, dyspnea, cough), and neuromuscular manifestations (weakness, neuropathic pain, muscle cramps)
- **Treatment**
  - The American Society for Blood and Marrow Transplantation (re-named The American Society for Transplantation and Cellular Therapy [ASTCT] in 2019) published a clinical practice guideline in 2012 around the first- and second-line treatment of aGVHD
    - These guidelines state that corticosteroids are the standard of care for the initial treatment of aGVHD and note that the literature does not support the choice of any specific agent for secondary therapy of aGVHD
    - These guidelines were published prior to the May 2019 FDA approval of ruxolitinib (Jakafi) for the treatment of corticosteroid-refractory aGVHD in adult and pediatric patients ≥ 12 years of age
  - In 2019, the NCCN published their first set of clinical practice guidelines around hematopoietic cell transplantation (HCT)
    - The 3.2021 version of these guidelines recommend ruxolitinib as a category 1 option for patients with steroid-refractory aGVHD
  - The National Institutes of Health (NIH) recommend that corticosteroids are most commonly the initial systemic therapy choice for most patients with moderate to severe cGVHD
    - Adjunctive supportive care may also be used (e.g., artificial tears, artificial saliva). Ibrutinib was the first drug approved for cGVHD in patients who have failed ≥ 1 systemic treatment, but many other therapies have been used off-label and for primary or secondary therapy (e.g., low-dose methotrexate, mycophenolate mofetil [CellCept], sirolimus [Rapamune])
    - The NCCN 3.2021 guidelines list ibrutinib as a category 2A recommendation for steroid-refractory cGVHD along with multiple other agents also listed as category 2A recommendations

Oncology, Oral- Hematological – Overview of Disease State

- **Waldenström's macroglobulinemia**
  - Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL) is a B-cell disorder presenting as bone marrow infiltration with lymphoplasmacytic cells that are CD19+, CD20+, and CD22+
  - The 1.2022 NCCN guideline recommends treating only those patients who are symptomatic
    - These symptoms may include hyperviscosity, neuropathy, symptomatic adenopathy or organomegaly, amyloidosis, cryoglobulinemia, and cytopenias
    - Both zanubrutinib and ibrutinib with or without rituximab are listed as options for primary treatment (both category 1, preferred), while ixazomib combined with rituximab and dexamethasone is a category 2A, other recommended regimen for primary therapy
    - For patients who have received previous therapies for Waldenström's macroglobulinemia, zanubrutinib and ibrutinib with or without rituximab are category 1, preferred regimens. Acalabrutinib is a category 2A, other recommended treatment option
    - Up to 40% of WM patients may have recurrent mutations in the CXCR4 gene and certain CXCR4 mutations may confer resistance to ibrutinib; therefore, the NCCN guidelines recommend consideration of CXCR4 gene mutation testing for patients being initiated on ibrutinib therapy as a category 2A, useful in certain circumstances recommendation
  - No current US guidelines exist for the treatment of erythema nodosum leprosum, hypereosinophilic syndrome, or chronic eosinophilic leukemia

Oncology, Oral- Hematological – Overview of Disease State

- **Philadelphia chromosome positive (Ph+) ALL**
  - Ph+ ALL is rare in pediatric cases of ALL, occurring in approximately 2% of cases. In contrast, approximately 25% of adult cases of ALL are Ph+

- **Treatment**
  - The 2.2021 National Comprehensive Cancer Network (NCCN) guidelines recommend incorporation of a tyrosine kinase inhibitor (TKI) in the frontline regimen for Ph+ ALL as an established standard of care for adolescents/young adults and adult patients
    - The TKI may be combined with either chemotherapy or corticosteroids depending on the patient's age and comorbidities
    - TKI options for induction therapy of Ph+ ALL in adolescents, young adults, and adult patents include imatinib (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), and ponatinib (Iclusig)
    - The NCCN states that dasatinib and imatinib are the preferred TKIs for induction therapy while ponatinib is preferred as part of the hyper-CVAD chemotherapy regimen
    - In addition, the NCCN ALL guidelines also note bosutinib (Bosulif) is an option but state there is limited data for that particular TKI in Ph+ ALL
    - Mutation testing for the ABL gene should be considered as this mutation can confer greater resistance or susceptibility to a particular TKI, and the choice of a specific TKI should also be based on disease-related features
    - Pediatric patients with Ph+ ALL are also candidates for TKI therapy
  - The 3.2021 NCCN guidelines for pediatric ALL specifically list combined treatment regimens containing imatinib or dasatinib
    - A study by the Children's Oncology Group (COG) utilizing imatinib for children with Ph+ ALL demonstrated a 5-year event-free survival of 70% (standard error, ± 12%) which is superior to historical controls prior to the introduction of imatinib

Oncology, Oral- Hematological – Overview of Disease State

- **Folicular Lymphoma**
  - FL is the most common subtype of indolent NHL
  - Indolent lymphomas make up about 40% of all NHL with FL being the most common indolent NHL
  - Due to the indolent nature of FL, the median survival is approximately 10 years

- **Treatment**
  - The 5.2022 B-cell lymphoma NCCN guidelines list lenalidomide plus rituximab as a category 2A, preferred regimen in both the first-line setting and the second-line therapy
  - Chlorambucil (Leukeran), with or without rituximab (category 2A), is listed as a first- or second-line therapy option for the elderly or infirm patients with FL

Oncology, Oral- Hematological

- **ivosidenib (Tibsovo)**
  - **May 2022: FDA approved new indication for Tibsovo for use in combination with azacitidine for newly diagnosed AML with a susceptible IDH1 mutation, as detected by an FDA-approved test, in adults ≥ 75 years old, or who have comorbidities that preclude use of intensive induction chemotherapy. It was already approved for the treatment of relapsed or refractory AML and locally advanced or metastatic cholangiocarcinoma**
  - **Indication**
    - **Newly Diagnosed Acute Myeloid Leukemia (AML): In combination with azacitidine or as monotherapy for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy**
    - Relapsed or refractory AML: For the treatment of adult patients with relapsed or refractory AML
    - Locally Advanced or Metastatic Cholangiocarcinoma: For the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma who have been previously treated
  - **Warnings and Precautions**
    - QTc Interval Prolongation: Monitor electrocardiograms and electrolytes. If QTc interval prolongation occurs, dose reduce or withhold, then resume dose or permanently discontinue treatment
    - Guillain-Barré Syndrome: Monitor patients for signs and symptoms of new motor and/or sensory findings. Permanently discontinue treatment in patients who are diagnosed with Guillain-Barré syndrome
    - BBW: Patients treated with Tibsovo have experienced symptoms of differentiation syndrome, which can be fatal. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution
  - **Dosage**
    - 500 mg orally once daily with or without food until disease progression or unacceptable toxicity
    - Avoid a high-fat meal
  - **Availability**
    - Tablets: 250 mg

Oncology, Oral- Hematological

- **FDA Communications**
  - **duvelisib (Copiktra)**
    - **February 2022:**
      - **REMS modified to remove the follicular lymphoma indication from the Healthcare Provider REMS letter, Professional Society REMS letter, Fact Sheet, and the Copiktra REMS Program website**
    - **July 2022:**
      - **The FDA has issued a safety communication regarding the increased risk of death with duvelisib demonstrated in a clinical trial comparing the drug to ofatumumab**
      - **The trial also found that duvelisib was associated with a higher risk of serious side effects**
      - **The FDA plans to hold a public meeting to discuss the findings and whether Copiktra should continue to be prescribed for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)**
  - **idelalisib (Zydelig)**
    - **February 2022:**
      - **Gilead announced the voluntary withdrawal of indications for the treatment of relapsed follicular B-cell non-Hodgkin lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL) which were approved under an Accelerated Approval based on objective response rates of 54% and 58%, respectively**
      - **The decision to withdraw these indications is based on an ongoing challenge of enrolling patients in the confirmatory trial. Zydelig's indication for relapsed chronic lymphocytic leukemia (CLL) will remain**
    - **April 2022:**
      - **REMS modification to update the materials to align with the withdrawal of the FL and SLL indications and associated proposed modifications to the approved Zydelig REMS**
    - **July 2022:**
      - **The REMS program has been removed because a communication plan is no longer necessary to ensure the benefits of the drug outweigh the risks**

Oncology, Oral- Hematological

- **FDA Communications (Continued)**
  - **ixazomib (Ninlaro)**
    - **May 2022:**
      - **Indication revised with limitation of use stating it is not recommended in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials**
      - **Warnings and ADR sections revised throughout with updated trial data, and addition of Stevens-Johnson syndrome, a subsection for increased mortality in the maintenance setting, new clinical studies for increased mortality in the maintenance setting, and a subsection for lack of efficacy in patients with newly diagnosed multiple myeloma**

- **New Generic**
  - **lenalidomide- September 2022:**
    - **FDA approved first generic for Revlimid 2.5 mg and 20 mg capsules from Dr. Reddy's**

Oncology, Oral- Hematological

- **olutasidenib (Rezlidhia)**
  - December 2022: FDA has approved olutasidenib, an isocitrate dehydrogenase-1 (IDH1) inhibitor, for treatment of adult patients with relapsed or refractory AML with susceptible IDH1 mutation as detected by an FDA-approved test
  - Indication
    - An isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test
  - Warnings and Precautions
    - Hepatotoxicity: Monitor liver function tests during treatment. If hepatotoxicity occurs, interrupt and reduce or discontinue treatment
    - BBW: Patients treated with Rezlidhia have experienced symptoms of differentiation syndrome, which can be fatal. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution
    - Lactation: Advise not to breastfeed
  - Dosage
    - Recommended dosage: 150 mg orally twice daily, until disease progression or unacceptable toxicity
    - Take on an empty stomach at least 1 hour before or 2 hours after a meal
  - Availability
    - Capsules: 150 mg

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Oncology, Oral – Breast

Oncology, Oral- Breast - Overview of Disease State

- ONCOLOGY AGENTS : ANTIESTROGENS – ORAL
  - **Orserdu**
  - Soltamox
  - Toremifene

- ONCOLOGY AGENTS : ANTIMETABOLITES – ORAL
  - Capecitabine
  - Mercaptopurine
  - Onureg
  - Purixan
  - Tabloid
  - **Xeloda**

- ONCOLOGY AGENTS : PHOSPHATIDYLINOSITOL 3-KINASE (PI3K) INHIBITORS – ORAL
  - Copiktra
  - Piqray
  - Vijoice

Overview of Disease State - Oncology, Oral- Breast

- **Breast Cancer**
  - Breast cancer is the most common site of cancer for women in the United States (US), accounting for 30% of all cancer diagnoses, and is second only to lung cancer as a cause of cancer death in American women
  - It is estimated that there will be 287,850 new cases of breast cancer diagnosed in the US in 2022 and there will be an estimated 43,250 deaths. The incidence of breast cancer in US women continues to increase by about 0.5% per year
  - Known risk factors that may be contributing to this increased incidence of breast cancer include a decline in fertility rates and an increase in body weight. Despite this increasing incidence, death rates from breast cancer have declined by 42% since 1989, largely due to improvements in both early detection and treatment
  - The overall 5-year survival for women diagnosed with breast cancer is 90%., Patients who present with localized disease have a 99% 5-year survival rate; however, prognosis for patients presenting with distant metastatic disease is much poorer, with a 5-year survival rate of only 29%
  - Breast cancer is most frequently diagnosed in women between the ages of 55 to 74 with the median age at diagnosis being 63 years. Rarely, breast cancer may be diagnosed in men. Other risk factors include various endocrine, genetic, environmental, and lifestyle factors. Some of these risk factors are modifiable, some are not, and the impact of these factors are variable

Oncology, Oral- Breast

- capecitabine (Xeloda)
  - **December 2022: FDA approved indications to include treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as part of combination chemotherapy regimen; treatment of adults with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease as component of combination regimen; & adjuvant treatment of adults with pancreatic adenocarcinoma as part of combination chemotherapy regimen**
  - **Indication**
    - **Breast Cancer, Colorectal Cancer, Gastric, Esophageal, or Gastroesophageal Junction Cancer, and Pancreatic Cancer**
  - **Warnings and Precautions**
    - **BBW: Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking Xeloda concomitantly with oral vitamin K antagonist**
    - **Based on findings from animal reproduction studies and its mechanism of action, Xeloda can cause fetal harm when administered to a pregnant woman**
  - **Dosage**
    - **Stratified by indication and BSA**
  - **Availability**
    - **Tablets: 150 mg and 500 mg**

Oncology, Oral- Breast

- elacestrant (Orserdu)
  - **January 2023: FDA approved elacestrant, an estrogen receptor antagonist, for tx of postmenopausal women or adult men, with ER+, HER2-, ESR1-mutated advanced or metastatic breast cancer with disease progression following ≥ 1 line of endocrine therapy**
  - **Indication**
    - **An estrogen receptor antagonist indicated for the treatment of postmenopausal women or adult men, with ERpositive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy**
  - **Warnings and Precautions**
    - **Embryo-Fetal Toxicity: Can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception**
    - **Hepatic impairment: Avoid use in patients with severe hepatic impairment (Child-Pugh C). Reduce the dosage for patients with moderate hepatic impairment (Child-Pugh B)**
    - **Dyslipidemia: May cause hypercholesterolemia and hypertriglyceridemia**
  - **Dosage**
    - **Select patients for treatment with Orserdu based on the presence of ESR1 mutations**
    - **The recommended dosage of Orserdu is one 345 mg tablet taken orally, once daily, with food**
  - **Availability**
    - **Tablets: 345 mg and 86 mg**

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Oncology, Injectable

- ONCOLOGY AGENTS : IMIDAZOTETRAZINES – ORAL
- ONCOLOGY AGENTS : NITROGEN MUSTARDS – ORAL
- ONCOLOGY AGENTS : AUTOLOGOUS CELLULAR IMMUNOTHERAPY (CAR-T)
- ONCOLOGY AGENTS : MITOTIC INHIBITORS - ORAL

Oncology, Oral- Injectable - Overview of Disease State

- **ONCOLOGY AGENTS : IMIDAZOTETRAZINES – ORAL**
  - Temodar

- **ONCOLOGY AGENTS : NITROGEN MUSTARDS – ORAL**
  - Mercaptopurine
  - Onureg
  - Purixan
  - Tabloid
  - Xeloda

- **ONCOLOGY AGENTS : AUTOLOGOUS CELLULAR IMMUNOTHERAPY (CAR-T)**
  - Abecma
  - **Breyanzi**
  - Carvykti
  - **Kymriah**
  - Tecartus
  - **Yescarta**

- **ONCOLOGY AGENTS : MITOTIC INHIBITORS – ORAL**
  - Etoposide

Oncology, Oral- Injectable – Overview of Disease State

- **Diffuse Large B Cell Lymphoma (DLBCLs)**
  - The most common type of lymphoma in adults and account for approximately 30% of all NHL
  - There are several subtypes of DLBCL, including DLBCL arising from follicular lymphoma (FL)
  - Some patients with FL may undergo conversion to more aggressive lymphomas, such as DLBCL, and this risk increases over time; transformation of FL to DLBCL occurs in about 15% of patients at an annual of 2% to 3%

- **Treatment**
  - Lenalidomide plus tafasitamab (Monjuvi) is a category 2A, preferred option, while lenalidomide (with or without rituximab) and ibrutinib are both category 2A, useful in certain circumstances options for non-germinal center B-cell like (GCB) DLBCL, and selinexor is an option for DLBCL third line and subsequent therapy, including DLBCL arising from FL after at least 2 prior systemic therapies, including patients with disease progression after transplant or chimeric antigen receptor (CAR) T-cell therapy (category 2A)

Oncology, Oral- Injectable

- axicabtagene ciloleucel (Yescarta)
  - April 2022: FDA approved new indication for Yescarta for the treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL). For this indication, it carries a limitation of use stating it is not indicated for the treatment of patients with primary CNS lymphoma
  - Indication
    - A CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:
      - Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy
      - Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
  - Warnings and Precautions
    - BBW: Cytokine Release Syndrome (CRS), including fatal or lifethreatening reactions, occurred in patients receiving Yescarta
  - Dosage
    - Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of Yescarta
    - Premedicate with acetaminophen and an H1-antihistamine
    - Dosing is based on the number of chimeric antigen receptor (CAR)-positive viable T cells
    - The target dose is 2 × 106 CAR-positive viable T cells per kg body weight, with a maximum of 2 × 108 CAR-positive viable T cells
    - Administer in a certified healthcare facility
  - Availability
    - Available as a cell suspension for infusion
    - Comprises a suspension of 2 × 106 CAR-positive viable T cells per kg of body weight, with a maximum of 2 × 108 CAR-positive viable T cells in approximately 68 mL

Oncology, Oral- Injectable

- tisagenlecleucel (Kymriah)
  - **June 2022: FDA approved new indication for treatment of adults with relapsed or refractory follicular lymphoma after ≥ 2 lines of systemic therapy**
  - **Indication**
    - **A CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of:**
      - Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
      - Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
      - Limitations of Use: Not indicated for treatment of patients with primary central nervous system lymphoma
      - **Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s)**
  - **Warnings and Precautions**
    - BBW: Cytokine Release Syndrome (CRS), including fatal or lifethreatening reactions, occurred in patients receiving Kymriah
  - **Dosage**
    - Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of Kymriah
    - Premedicate with acetaminophen and an H1-antihistamine
    - Dosing is based on the number of chimeric antigen receptor (CAR)-positive viable T cells
    - **Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma and Follicular Lymphoma**
      - **Administer 0.6 to 6.0 x 108 CAR-positive viable T cells intravenously**
  - **Availability**
    - **Adult Relapsed or Refractory Diffuse Large B-cell Lymphoma and Follicular Lymphoma: A single dose contains 0.6 to 6.0 x 108 CAR-positive viable T cells suspended in one to three patient-specific infusion bag(s) for intravenous infusion**

Oncology, Oral- Injectable

- lisocabtagene maraleucel (Breyanzi)
  - **July 2022: FDA approved an expansion to indications of large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B to include second line treatment of patients who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age. Previously approved only in patients with relapsed or refractory large B-cell lymphoma after ≥ 2 lines of systemic therapy**
  - **Indication**
    - **A CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:**
      - **Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy (1); or**
      - **Refractory disease to first-line chemoimmunotherapy or relapse after firstline chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age (1)**
      - **Relapsed or refractory disease after two or more lines of systemic therapy**
  - **Dosage**
    - Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of Breyanzi
    - Premedicate with acetaminophen and an H1-antihistamine
    - Dosing is based on the number of chimeric antigen receptor (CAR)-positive viable T cells
    - **See TCR/PI for specific dosing instructions**
  - **Availability**
    - A single dose consists of 1:1 CAR-positive viable T cells of the CD8 and CD4 components, with each component supplied separately in one to four single-dose 5 mL vials (3). Each mL contains ≥1.5 × 106 to 70 × 106 CAR-positive viable T cells

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Oncology, Prostate

- ONCOLOGY AGENTS : ESTROGENS-ANTINEOPLASTIC – ORAL

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Oncology, Oral - Other

- ONCOLOGY AGENTS : IMIDAZOTETRAZINES – ORAL
- ONCOLOGY AGENTS : NITROSOUREAS - ORAL

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Antineoplastic Agents, Topical

- ONCOLOGY AGENTS : SELECTIVE RETINOID X RECEPTOR AGONISTS - ORAL

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Lipotropics, Other

- ANTIHYPERLIPIDEMICS : ADENOSINE TRIPHOSPHATE-CITRATE LYASE INHIBITORS

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Bone Resorption Suppression and Related Agents / Estrogen Agents, Oral/Transdermal

- BONE DENSITY REGULATORS : SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

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CARDIOVASCULAR AGENTS : TRANSTHYRETIN STABILIZERS

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Fabry's Disease

- ENDOCRINE AND METABOLIC AGENTS : FABRY DISEASE AGENTS - ORAL

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Nutritionals, Caloric Agents

- ENDOCRINE AND METABOLIC AGENTS : HOMOCYSTINURIA AGENTS - ORAL

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Urea Cycle Disorders

- ENDOCRINE AND METABOLIC AGENTS : HYPERAMMONEMIA AGENTS – ORAL
- ENDOCRINE AND METABOLIC AGENTS : UREA CYCLE DISORDER AGENTS - ORAL

Urea Cycle Disorders – Overview of Disease State

- **Urea Cycle Disorders (UCD)**
  - Urea cycle disorders (UCDs) are inherited deficiencies of enzymes or transporters that function in the synthesis of urea from ammonia within the body
  - The urea cycle maintains low levels of ammonia that would otherwise accumulate in the blood due to protein breakdown
  - The purpose of the urea cycle, which converts 2 moles of nitrogen (1 from ammonia, 1 from aspartate) to urea, is to transform nitrogen into a water soluble form that may be excreted
  - UCDs are most often related to the first 4 enzymes within the cycle: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), and argininosuccinate lyase (ASL)
  - They may also result from a deficiency in N-acetylglutamate synthetase (NAGS), the enzyme for the cofactor in N-acetylglutamate production
  - Arginase deficiency also affects urea production as arginase is required in the last step of urea production
  - In the United States (US), the combined incidence of the multiple types of UCDs is estimated to be approximately 1 per 20,000 to 25,000 live births; however, some estimate it is much more frequent (1 per 8,000) internationally
  - Most UCDs affect males and females equally. Cases may be inherited or acquired. Those presenting as newborns often develop symptoms within 24 to 48 hours following birth
  - Presentation at birth or childhood is most common; however, UCDs may occur later in life
  - Diagnosis relies on recognition of the elevated ammonia level, further evaluation, amino acid and/or tissue enzyme analysis, and ultimately genetic testing
  - Testing for UCDs is now included in many newborn screening programs
  - The UCD consortium consists of 14 sites in the US, Canada, and Europe, and population data have been published as a result of research from these sites Genetics of hyperammonemia

Urea Cycle Disorders – Overview of Disease State

- **Trans-European Guidelines, 2019**
  - Suggest for the diagnosis and management of urea cycle disorders address all products for acute hyperammonemia. Intravenous sodium benzoate/sodium phenylacetate is indicated for any UCD in this setting
  - Carglumic acid is recommended to treat acute hyperammonemia in patients with for NAGS deficiency and in patients without a UCD diagnosis in combination with other treatments
  - Once stabilized, maintenance therapy with an agent within this class, when appropriate, may be initiated
  - The suggested guidelines recommend nitrogen scavengers (e.g., sodium phenylbutyrate, glycerol phenylbutyrate) at individualized doses to improve metabolic stability in the long term
  - Dividing the dose and administering with ample fluids limits mucositis or gastritis associated with phenylbutyrate products
  - Carglumic acid is recommended first-line for the treatment of NAGS deficiency
  - In addition, protein restriction while maintaining an adequate supply needed for growth is fundamental to treatment of these disorders
  - Select patients with UCDs are also candidates for liver transplant

Urea Cycle Disorders

- sodium phenylbutyrate (Pheburane)
  - July 2022: FDA approved a new formulation of sodium phenylbutyrate oral pellets (Pheburane) as adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with urea cycle disorders (UCDs), involving deficiencies of carbamoylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinic acid synthetase (AS)
  - Indications
    - A nitrogen-binding agent indicated as adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with urea cycle disorders (UCDs), involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC) or argininosuccinic acid synthetase (AS)
    - Limitations of Use: Not indicated for the treatment of acute hyperammonemia
  - Warnings and Precautions
    - Neurotoxicity of Phenylacetate: Increased exposure to phenylacetate, the major metabolite of Pheburane, may be associated with neurotoxicity in patients with UCDs. Consider reducing the dose if neurotoxicity symptoms are present
  - Dosage
    - Treatment should be supervised by a healthcare provider experienced in the treatment of UCDs
    - The recommended dosage measured as sodium phenylbutyrate is:
      - Patients weighing < 20 kg: 450–600 mg/kg/day of sodium phenylbutyrate orally
      - Patients weighing ≥ 20 kg: 9.9–13.0 g/m^2 /day of sodium phenylbutyrate orally
    - Monitor plasma ammonia levels to determine the need for dosage adjustment
    - For patients with hepatic impairment, start at the lower end of the recommended dosing range
  - Availability
    - Oral pellets: 84 g of sodium phenylbutyrate per bottle

Urea Cycle Disorders

- sodium phenylbutyrate (Olpruva)
  - **December 2022: Nitrogen-binding agent FDA approved as an oral suspension for use as adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and peds pts weighing ≥ 20 kg with BSA ≥ 1.2 m^2, with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS)**
  - **Indications**
    - **A nitrogen-binding agent indicated as adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients weighing ≥ 20 kg and with a body surface area (BSA) of 1.2 m^2 or greater, with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS)**
    - **Limitations of Use: Not indicated for the treatment of acute hyperammonemia**
  - **Warnings and Precautions**
    - **Neurotoxicity of Phenylacetate: Increased exposure to phenylacetate, the major metabolite of Olpruva, may be associated with neurotoxicity in patients with UCDs. Consider reducing the dose if neurotoxicity symptoms are present**
  - **Dosage**
    - **Treatment should be supervised by a healthcare provider experienced in the treatment of UCDs**
    - **The recommended dosage is 9.9 -13 g/m^2 /day**
    - **Monitor plasma ammonia levels to determine the need for dosage adjustment**
    - **For patients with hepatic impairment, start at the lower end of the recommended dosing range**
  - **Availability**
    - **For oral suspension: 2 g, 3 g, 4 g, 5 g, 6 g, and 6.67 g of sodium phenylbutyrate as pellets in packets for reconstitution**

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Vasopressin Receptor Antagonists

- ENDOCRINE AND METABOLIC AGENTS : VASOPRESSIN RECEPTOR ANTAGONISTS - ORAL

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Duchenne Muscular Dystrophy
- NEUROMUSCULAR AGENTS : MUSCULAR DYSTROPHY AGENTS

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Immunomodulators, Lupus

- NEUROMUSCULAR AGENTS : SYSTEMIC LUPUS ERYTHEMATOSUS AGENTS

Disease State Description - Immunomodulators, Lupus

- **Systemic lupus erythematosus (SLE)**
  - Lupus is an autoimmune disease that currently affects about 1.5 million Americans, 90% of whom are women
  - Lupus is more prevalent among women of color, and Black patients with lupus are more likely to experience organ-system involvement
  - The most common form of lupus is systemic lupus erythematosus (SLE), which accounts for approximately 70% of all cases; in half of SLE cases, tissue or major organs such as the heart, lungs, kidneys, or brain will be impacted by the disease
    - The other three forms of lupus are cutaneous lupus, drug-induced lupus, and neonatal lupus. One-third of patients with lupus report having a comorbid autoimmune disorder
  - Genetics can play a role in the development of lupus; 20% of patients with lupus have a parent or sibling who has developed or will develop lupus
  - A chronic autoimmune disease of unknown cause that can affect virtually any organ of the body. Immunologic abnormalities, especially the production of a number of antinuclear antibodies (ANA), are a prominent feature of the disease
  - Patients present with variable clinical features ranging from mild joint and skin involvement to life-threatening kidney, hematologic, or central nervous system involvement
  - The clinical heterogeneity of SLE and the lack of pathognomonic features or tests pose a diagnostic challenge for the clinician
  - To complicate matters, patients may present with only a few clinical features of SLE, which can resemble other autoimmune, infectious, or hematologic diseases

- The diagnosis of SLE is generally based on clinical and laboratory findings after excluding alternative diagnoses
  - In the absence of SLE diagnostic criteria, SLE classification criteria are often used by clinicians as guidance to help identify some of the salient clinical features when making the diagnosis
  - Serologic findings are important in suggesting the possibility of SLE, with some antibodies (eg, anti-double-stranded deoxyribonucleic acid [anti-dsDNA] and anti-Smith [anti-Sm]) highly associated with this condition

Disease State Description - Immunomodulators, Lupus

- **Kidney involvement**
  - Kidney involvement is clinically apparent in approximately 50 percent of SLE patients and is a significant cause of morbidity and mortality
  - Thus, periodic screening for the presence of lupus nephritis with urinalyses, quantitation of proteinuria, and estimation of the glomerular filtration rate is an important component of the ongoing management of SLE patients
  - Several forms of glomerulonephritis can occur, and kidney biopsy is useful to define the type and extent of kidney involvement
  - The clinical presentation of lupus nephritis is highly variable, ranging from asymptomatic hematuria and/or proteinuria to nephrotic syndrome and rapidly progressive glomerulonephritis with loss of kidney function

- **Current Treatment Landscape for Lupus Nephritis**
  - Though lupus nephritis is a common progression of SLE, there was no treatment specifically indicated for it until late 2020
  - Providers would typically aim to reduce inflammation in the kidneys and decrease overall immune system activity
  - The treatments used were not effective in preventing new flares or inducing remission

Urea Cycle Disorders

- belimumab (Benlysta)
  - **July 2022: FDA approved for IV administration in patients 5 to 17 years of age with active lupus nephritis who are receiving standard therapy. IV administration was previously approved for adults with active lupus nephritis and patients ≥ 5 years of age with active systemic lupus erythematosus (SLE)**
  - **Indications**
    - **A B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of:**
      - **Patients aged 5 years and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy**
      - **Patients aged 5 years and older with active lupus nephritis who are receiving standard therapy**
    - **Limitations of Use: The efficacy has not been evaluated in patients with severe active central nervous system lupus. Use is not recommended in this situation**
  - **Dosage**
    - **Intravenous Dosage for Adult and Pediatric Patients with SLE or Lupus Nephritis:**
      - **10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Reconstitute, dilute, and administer as an intravenous infusion over a period of 1 hour**
      - **Consider prophylactic premedication for infusion reactions and hypersensitivity reactions**
  - **Availability**
    - **Intravenous Infusion:**
      - **For Injection: 120 mg or 400 mg of belimumab lyophilized powder in single-dose vial for reconstitution and dilution prior to intravenous infusion**
    - Subcutaneous Injection:
      - Injection: 200 mg/mL of belimumab in single-dose prefilled autoinjector or single-dose prefilled syringe

Appendices

Guidelines - Oncology, Oral- Breast

- **Endocrine therapy for HR-positive disease**
  - According to the NCCN V2.2022 guidelines, endocrine therapy should be considered for nearly all patients with HR-positive disease, regardless of menopausal status, age, or HER2 status of the tumor, with the exception of patients with tumors ≤ 0.5 centimeters (cm) where adjuvant endocrine therapy is a category 2B rating
  - For patients recommended to receive both adjuvant endocrine therapy and adjuvant chemotherapy, these therapies should be given sequentially with endocrine therapy following chemotherapy
  - The NCCN guidelines regarding premenopausal women with HR-positive disease recommend tamoxifen for 5 years, with or without ovarian suppression or ablation or the use of an AI for 5 years plus ovarian suppression or ablation (both category 1)
    - After the initial 5 years of therapy, women who are still premenopausal may consider tamoxifen for an additional 5 years to complete 10 years or consider no further adjuvant endocrine therapy (both category 2A)
    - Women who subsequently became postmenopausal after the initial 5 years of adjuvant endocrine therapy may be treated with an AI for an additional 5 years (category 1) or may continue tamoxifen for an additional 5 years to complete 10 years of adjuvant therapy (category 2A)
    - The NCCN guidelines state that the 3 selective AIs, anastrozole, letrozole, and exemestane, have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and neoadjuvant settings and that the optimal duration of treatment with AIs in adjuvant setting is uncertain

Guidelines - Oncology, Oral- Breast

- **Targeted therapy for HER2-positive disease**
  - The 2020 ASCO guideline regarding optimal adjuvant chemotherapy and targeted therapy for early breast cancer gives a moderate rating of approval for the use of extended adjuvant therapy with neratinib following trastuzumab in patients with early-stage HER2-positive breast cancer
  - ASCO states they preferentially favor the use of neratinib in patients with HR-positive and node-positive disease. ASCO further states that neratinib causes substantial diarrhea and diarrheal prophylaxis must be used; patients who begin neratinib within 1 year of trastuzumab completion appear to derive the greatest benefit; and, at a median follow up of 5.2 years, no overall survival (OS) benefit has been observed for the use of extended adjuvant neratinib
  - Likewise, the NCCN guidelines state extended adjuvant neratinib may be considered following adjuvant trastuzumab-containing therapy in HR-positive, HER-2 positive, node positive patients with a perceived high risk of recurrence