Chapter 149: Cancer: The Disease and Treatment

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UPDATE SUMMARY

Update Summary

March 25, 2023

The following updates to this chapter were made:

- Introduction and Figure 149-1: updated estimated 2023 statistics
- Table 149-1: updated references
- Figure 149-2: corrected reference citation
- The following drugs were either added or removed from Table 149-7 and Systemic Therapy sections due to changes in FDA approvals
  - Chemotherapy: Alkylating agents: Melphalan flufenamide – removed
  - Targeted agents: Small Molecules
    - Specifically Targeting the ABL Myristoyl Pocket (STAMP) Inhibitor, asciminib – added
    - Bruton's Tyrosine Kinase (BTK) Inhibitors: pirobrutinib – added
    - Epidermal Growth Factor Receptor (EGFR) Inhibitors: mobocertinib – added
    - Fibroblast Growth Factor Receptor (FGFR) Inhibitors: futibatinib – added
    - Histone Deacetylase (HDAC) Inhibitors: panobinostat – removed
    - Hypoxia-inducible Factor 2 Alpha (HIF-2α): belzutifan – added
    - Isocitrate Dehydrogenase (IDH) Inhibitors: olutasidenib – added
    - Phosphatidylinositide 3-Kinase (PI3K) Inhibitors: umbralisib – removed
    - Ras Inhibitors: adagrasib - added
  - Targeted agents: mAbs & ADCs
    - Antibodies that target BCMA (B-Cell Maturation Antigen): belantamab mafodotin – removed
    - Antibodies that target folate receptor alpha: mirvetuximab soravtansine – added
    - Antibodies that target tissue factor: tisotumab vedotin – added

        - Bispecific T-cell engagers: mosunetuzumab and teclistamab – added
        - Fusion proteins – tebentafusp – added
        - Immunotherapy – tremelimumab and nivolumab/relatlimab – added
- Table 149-7: corrected reference citation
- Information was added to therapeutic radiopharmaceuticals: Lutetium Lu 177 on lutetium Lu 177 vipivotide tetraxetan
- Information was updated on the following drugs in Table 149-7 and Systemic Therapy sections
    - Targeted agents: small molecules
        - Colony-stimulating factor-i receptor (CSF-IR) inhibitors: pexidartinib, administer with low-fat meal
    - Targeted agents: mAbs & ADCs
        - Antibodies that target CD20: of atumumab and antibodies that target CD52: alemtuzumab, restricted distribution for access
- Information was updated in Systemic Therapy, targeted agents: small molecules
    - BRAF inhibitors section – dabrafenib holds agnostic approval for solid tumors harboring V600E mutation
    - CDK inhibitors section – revised section to generalize indications of palbociclib, ribociclib, and abemaciclib in combination with endocrine therapy
    - EGFR inhibitors section – revised section to focus more on osimertinib and mobocertinib
    - HER2 Inhibitors – revised antidiarrheal prophylaxis for neratinib to include dose escalation strategy
    - PI3K Inhibitors – revised indications for idelalisib and duvelisib

KEY CONCEPTS

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1. Carcinogenesis is a multistep process that includes initiation, promotion, conversion, and progression.

2. Cancer cells demonstrate unique traits that distinguish them from normal cells. Cancer cells can stimulate their own growth, resist inhibitory signals, avoid programmed cell death, grow new blood vessels (angiogenesis), invade local tissues, and spread to distant sites (ie, metastases).

3. Screening programs are designed to detect cancers in asymptomatic people who are at risk of a specific cancer.

4. Diagnosis and staging inform the treatment goals and help select the most appropriate anticancer therapy. The treatment goal may be cure, control, or palliation. The therapy may include a combination of surgery, radiation therapy, or systemic anticancer agents. Systemic anticancer agents include chemotherapy, targeted agents, and immunotherapy.

5. Chemotherapy inhibits cancer growth by killing rapidly proliferating cells. These agents can be categorized as either cell-cycle phase-specific, targeting one specific phase of the cell cycle, or cell-cycle phase-nonspecific, targeting all proliferating cells regardless of their place in the cell cycle. Cell-cycle phase-specific chemotherapy is generally administered more frequently or as a continuous infusion, and cell-cycle phase-nonspecific chemotherapy is usually administered less frequently.

6. Small-molecule targeted agents inhibit kinases or enzymes responsible for activating various proteins involved in intracellular signaling cascades. These agents treat cancer by correcting a dysregulated signaling pathway.

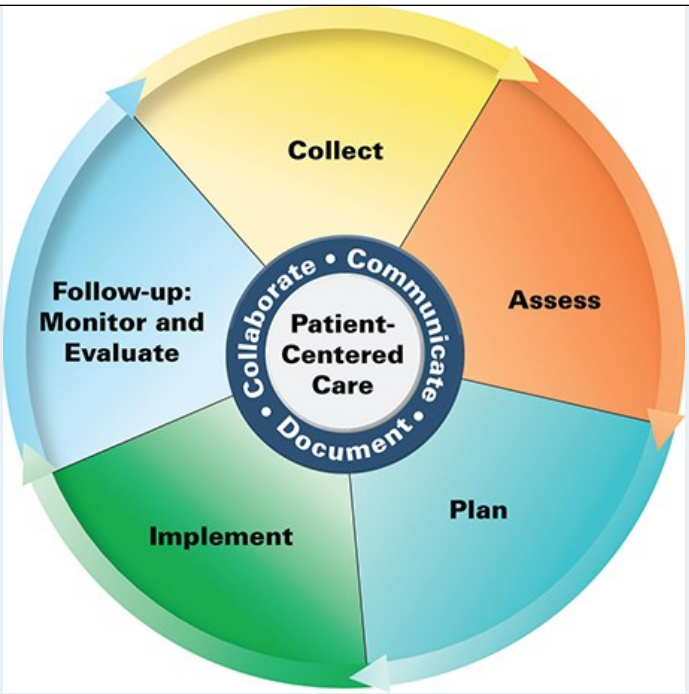
7. A monoclonal antibody (mAb) is a type of targeted therapy that recognizes an antigen preferentially expressed on cancer cells or immune cells or that targets growth factors responsible for cancer growth. These antibodies can also be used to deliver drugs, radioisotopes, or toxins to the antigen-expressing cells.

8. Immunotherapies are anticancer treatments that simulate or restore the immune system to recognize and eliminate cancer cells. Immune checkpoint inhibitors, cytokines, therapeutic vaccines, and chimeric antigen receptor (CAR) T-cell therapies are types of immunotherapies.

9. Various factors can affect the response and adverse drug reactions a patient may experience with anticancer therapy. When determining the optimal therapy, the health professional should carefully consider patient-specific factors, tumor-specific factors, and treatment goals.

PATIENT CARE PROCESS

Patient Care Process for Cancer



Collect

- Patient characteristics (eg, age, biological sex)
- Patient medical history (eg, comorbidities, prior anticancer therapies)
- Family history, social history, lifestyle factors, and dietary habits
- Current medications and allergies
- Objective data
  - Imaging (eg, PET scan, CT scan, MRI)
  - Tumor characteristics (eg, histology, mutations, stage)
  - Vital signs and laboratory values, including chemistries, organ function, CBC with differential, pregnancy status, hepatitis B serologies, and medication-specific assessments (eg, left ventricular ejection fraction for anthracyclines)
  - Physical exam
  - Pharmacogenomics, if applicable

Assess

- Performance status (see Table 149-8)
- Goals of care (eg, palliation)
- Treatment history (eg, type of treatment, response, tolerability)
- Desire for fertility preservation
- Immunization status

- Barriers to treatment (eg, transportation, insurance, compliance, health literacy)
- Role for nonmedication treatment measures (eg, radiation, surgery)
- Need for genetics counseling, if applicable

Plan

- Anticancer therapy regimen and supportive care
- Monitoring parameters (see Table 149-7)
- Patient education (eg, goals of care, drug-specific information, calendar for cyclic regimens, contraception requirements)
- Restaging timepoints to assess response
- Administration requirements (eg, central venous catheter)

Implement

- Administer immunizations prior to chemotherapy initiation, if possible
- Provide patient education regarding all elements of the treatment plan
- Obtain consent for anticancer therapy
- Schedule follow-up for response and toxicity assessments

Follow-up: Monitor and Evaluate

- Assess adverse drug reactions and supportive care measures
- Assess patient adherence, if applicable
- Assess tumor response to treatment (eg, CT scan)
- Reevaluate goals of care
- Determine adherence to treatment plan

BEYOND THE BOOK

BEYOND THE BOOK

Patient Case

RM is a 64-year-old individual with newly diagnosed stage IV renal cell carcinoma (clear cell histology) who presents to clinic for initiation of anticancer treatment. Given her poor prognostic risk group, the oncologist recommends a vascular endothelial growth factor receptor (VEGFR) inhibitor and/or immunotherapy. Of the first-line therapy options provided in the National Comprehensive Cancer Network, or NCCN, guidelines, her insurance will cover the following: cabozantinib monotherapy; axitinib + pembrolizumab; cabozantinib + nivolumab; ipilimumab + nivolumab; and lenvatinib + pembrolizumab. The oncologist is requesting your assistance with treatment planning and implementation.

- PMH: HTN diagnosed 1.5 years ago, gastrointestinal perforation diagnosed 6 weeks ago, metastatic clear cell, renal cell carcinoma diagnosed 4 weeks ago

- Vitals: O_2 sat: 98% (0.98) RA; HR 82 bpm; BP 179/103 mm Hg; 37.4°C
- Labs:
  - Sodium 137 mEq/L (136-145 mEq/L [mmol/L])
  - Potassium 3.9 mEq/L (3.4-5.1 mEq/L [mmol/L])
  - Chloride 99 mEq/L (98-107 mEq/L [mmol/L])
  - Glucose 96 mg/dL (74-99 mg/dL) (5.3 mmol/L [4.1-5.5 mmol/L])
  - Albumin 4.1 g/dL (3.5-5.2 g/dL) (41 g/L [35-52 g/L])
  - Calcium 10.4 mg/dL (8.6-10.2 mg/dL) (2.60 mmol/L [2.15-2.55 mmol/L])
  - Magnesium 1.7 mg/dL (1.6-2.6 mg/dL) (0.70 mmol/L [0.66-1.07 mmol/L])
  - Creatinine 0.94 mg/dL (CrCl ~80 mL/min) (83 µmol/L [CrCl ~1.33 mL/s])
  - Phosphorous 2.8 mg/dL (2.5-4.5 mg/dL) (0.90 mmol/L [0.81-1.45 mmol/L])
  - ALT 28 U/L (0-33 U/L) (0.47 µkat/L [0-0.55 µkat/L])
  - AST 23 U/L (0-32 U/L) (0.38 µkat/L [0-0.53 µkat/L])
  - T Bili 0.02 mg/dL (0.00-1.2 mg/dL) (0.3 µmol/L [0-20.5 µmol/L])
  - Hgb 10.2 g/dL (11.2-15.7 g/dL) 102 g/L [112-157 g/L]; 6.33 mmol/L [6.95-9.74 mmol/L])
  - Platelets 225 × 10^3/mm^3 (173 × 10^3 – 369 × 10^3/mm^3) (225 × 10^9/L [173 × 10^9 – 369 × 10^9/L])
  - ANC 3.02 × 10^3/mm^3 (1.56 × 10^3 – 6.13 × 10^3/mm^3) (3.02 × 10^9/L [1.56 × 10^9 – 6.13 × 10^9/L])
  - LDH 215 U/L (125 – 220 U/L) (3.58 µkat/L [2.08 – 3.67 µkat/L])

Allergies: NKDA

Medication List: lisinopril 5 mg PO daily

Questions

1. Given all the first-line treatment options for clear cell renal cell carcinoma are covered by the patient's insurance, what treatment option would you recommend for RM at this time?
2. When counseling RM prior to treatment initiation, what adverse drug reactions should be discussed?
3. What monitoring parameters should be considered for the selected treatment regimen?

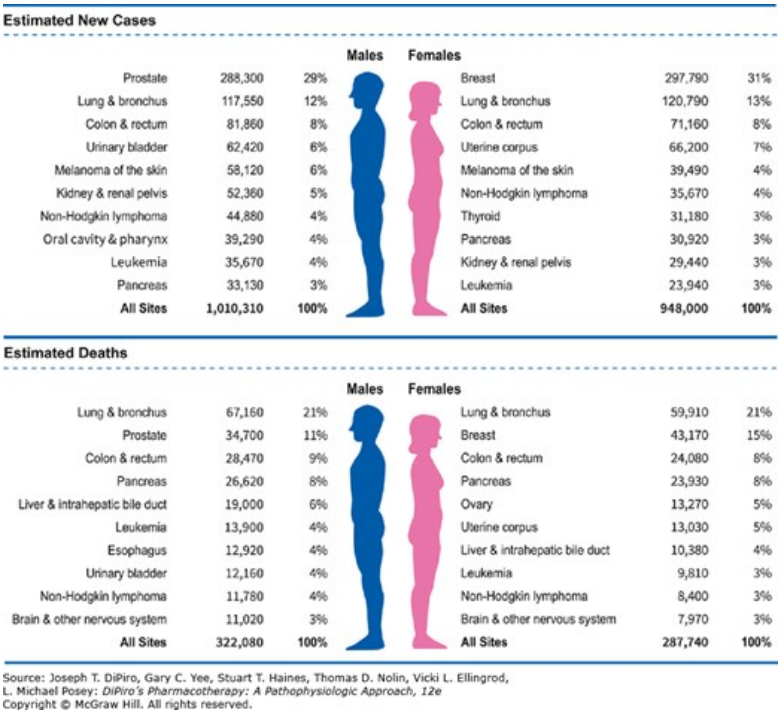
INTRODUCTION

Cancer is a group of many different diseases characterized by uncontrolled cellular growth, local tissue invasion, and distant metastases. It is the second leading cause of death in Americans. In the United States, nearly 2 million cases of cancer are projected to occur in 2023, with an estimated 600,000 deaths.[1] Figure 149-1 shows the estimated incidence of common cancers and cancer-related deaths. The most common cancers are prostate, breast, and lung cancer. The most common cause of cancer-related death in the United States is lung cancer, accounting for approximately 130,000

deaths each year. These cancers are discussed in further detail in subsequent chapters.

FIGURE 149-1

Estimated 2023 cancer incidences (top) and deaths (bottom) in the United States for males and females. Estimates are rounded to the nearest 10 and exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. *(Reprinted, with permission, from Siegel RL, Miller KD, Wagle NS, et al. Cancer Statistics. CA Cancer J Clin. 2023;73(1):17-48.)*



Health professionals treating patients with cancer should have a thorough understanding of the pharmacokinetic, pharmacodynamic, and pharmacogenomic properties of all available anticancer agents, in addition to the reported safety and efficacy of each agent in each cancer population. Health professionals should critically evaluate, summarize, and communicate the essential information to other health professionals, patients, and caregivers. This chapter defines the etiology, pathology, diagnosis, staging, and screening; introduces anticancer therapies and their related adverse drug reactions; and provides general information on how to administer systemic anticancer agents safely.

ETIOLOGY OF CANCER

Normal healthy cells are strictly regulated, with stimulatory and inhibitory signals in a delicate balance. For normal cells to become cancer cells, it is believed that a physical, chemical, or biological agent must damage the cell and cause a genetic and/or epigenetic alteration that is subsequently propagated during cell division. Cancer cells eventually acquire multiple alterations, and these alterations lead to uncontrolled proliferation, invasion, and metastases.

Carcinogenesis

The mechanisms by which cancers occur are incompletely understood. A cancer is thought to develop from a cell in which the normal mechanisms that control cell growth and proliferation are altered. Current evidence supports the concept of carcinogenesis as a multistage process that is genetically regulated.[2,3] The first step in this process is *initiation*, which requires exposure of normal cells to carcinogens. These carcinogens produce genetic alterations that, if not repaired, result in irreversible cellular changes. The changed cell may subsequently have an altered response to their environment that provides a selective growth advantage and permits the development of a clonal population of cancer cells. During the second step, known as *promotion*, carcinogens or other factors alter the environment to favor growth of the altered cell population compared to normal cells. Promotion could be affected by chemoprevention strategies (strategies to lower cancer risk), including changes in lifestyle and diet. At some point, the

altered cell becomes cancerous (*conversion* or *transformation*). Depending on the cancer, 5 to 20 years may elapse between the initiation and the development of a clinically detectable cancer. The final stage, called *progression*, involves further genetic alterations that lead to increased cell proliferation. The critical elements of this phase include invasion into local tissues and the development of metastases.

Substances that may act as carcinogens include a myriad of chemical, physical, and biologic agents. Chemical exposures may occur by occupational and environmental means or by lifestyle habits. Some chemicals associated with cancer include aniline dye, asbestos, and benzene. Aniline dye is a known cause of bladder cancer; benzene is a known cause of leukemia, and asbestos is a known cause of mesothelioma. As shown in Table 149-1, some medications and hormones used for therapeutic purposes are also classified as carcinogens. Physical agents that act as carcinogens include ionizing radiation and ultraviolet light; radiation induces mutations by forming free radicals that damage deoxyribonucleic acid (DNA) and other cellular components. Biologic agents that are associated with certain cancers include natural compounds (ie, viruses) or pollutants. The Epstein-Barr virus may be an important factor in the initiation of Burkitt lymphoma. Similarly, infection with the human papilloma virus (HPV) is a cause of cervical and head-and-neck cancers. Hereditary factors, age, and gender may also contribute to the development of cancer.

TABLE 149-1

Selected Drugs and Hormones Known to Cause Cancer in Humans

Drug or Hormone	Type of Cancer
Alkylating agents (eg, chlorambucil, mechlorethamine, melphalan, procarbazine, and nitrosoureas)	Leukemia
Anabolic steroids	Liver
Anthracyclines (eg, doxorubicin)	Leukemia
Antiestrogens (tamoxifen)	Endometrium
Antithymocyte globulin	Lymphoma
BRAF inhibitors (dabrafenib, encorafenib, vemurafenib)	Primary malignancies
BTK inhibitors (acalabrutinib, ibrutinib, zanubrutinib)	Second primary malignancies
Cisplatin	Leukemia
Coal tars (topical)	Skin
Cobimetinib	Primary cutaneous malignancies
Elotuzumab	Second primary malignancies
Filgrastim	Leukemia
Isatuximab	Second primary malignancies
Lenalidomide	Second primary malignancies
PARP inhibitors (olaparib, niraparib, talazoparib)	MDS/AML
Pioglitazone	Bladder
Steroidal estrogens (estrogen replacement therapy, oral contraceptives)	Endometrium, breast, liver
Epipodophyllotoxins (etoposide)	Leukemia
Immunosuppressive drugs (cyclosporine, azathioprine)	Lymphoma, skin
Oxazaphosphorines (cyclophosphamide, ifosfamide)	Urinary bladder, leukemia
Tacrolimus	Lymphoma
Tazemetostat	Second malignancy
TNF-α inhibitors	Leukemia, skin
Voriconazole	Skin

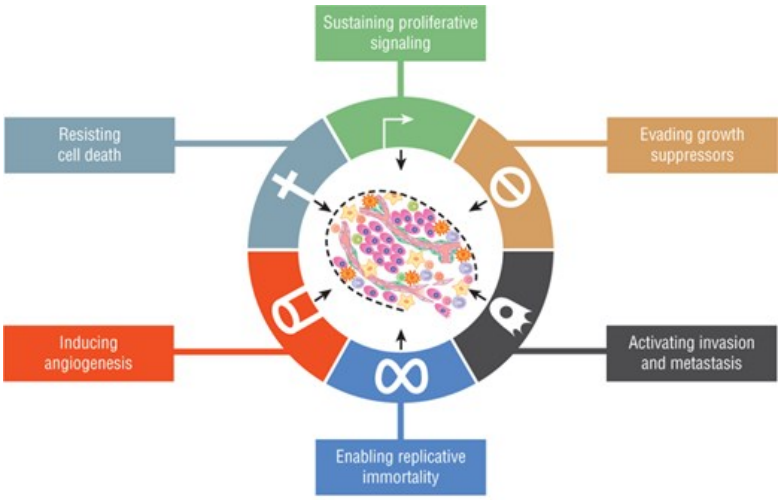
FDA-approved package inserts. *Data from References 4.*

Genetic Alterations

In recent years, there has been marked progress in our understanding of the genetic changes that lead to the development of cancer.[2,3] Two types of genes play an important role in the development of cancer: oncogenes and tumor suppressor genes. Figure 149-2 illustrates the acquired capabilities of cancer cells that differ from normal cellular function.[5]

FIGURE 149-2

Functional capabilities acquired by cancer cells, including angiogenesis, self-proliferation, insensitivity to antigrowth signals and limitless growth potential, metastasis, and antiapoptotic effects. It is thought that most, if not all, cancer cells acquire these functions through a variety of mechanisms, including activation of oncogenes and mutations in tumor suppressor genes. *(Reprinted from Cell, Vol 144(5), Hanahan D, Weinberg RA, The Hallmarks of Cancer: The Next Generation, Copyright © 2011, with permission from Elsevier.)*



Oncogenes

Oncogenes develop from normal genes, called proto-oncogenes. Proto-oncogenes are present in all cells and are essential regulators of normal cellular functions. Genetic alterations of the proto-oncogene through point mutation, chromosomal rearrangement, or gene amplification can activate the oncogene. Carcinogens may cause these genetic alterations (somatic mutations), or these alterations may be inherited (germline mutations). After activation, the oncogene produces either excessive amounts of the normal gene product or an abnormal gene product. The result is dysregulation of normal cell growth and proliferation, which imparts a distinct growth advantage to the cell and increases the probability of transformation. For example, the erythroblastic leukemia viral oncogene (*ErbB*) family members are oncogenes that mediate cell proliferation and differentiation through activation of intracellular signaling pathways. As an oncogene, the *ErbB* gene product is typically mutated, overexpressed, or amplified, resulting in excessive cellular proliferation, invasion, and metastasis in several cancers. Table 149-2 lists examples of oncogenes by their cellular function.

TABLE 149-2

Examples of Oncogenes and Tumor Suppressor Genes

Gene	Associated Human Cancer
Oncogenes	
ALK	Lung cancer, lymphomas, neuroblastoma, and ovarian cancer
BCR-ABL	ALL, CML
BCL-2	B-cell lymphomas, myeloid leukemia
BRAF	Colon cancer, lung cancer, melanoma, ovarian cancer, thyroid cancer
ERBB1	Colon cancer, glioblastoma multiforme, lung cancer
ERBB2	Breast cancer, gastric cancer, lung cancer
FLT3	AML, colorectal cancer
KIT (CD117)	Acute leukemia, GIST
MET	Lung cancer, colon cancer, melanoma, endometrial cancer
MYC	AML, breast cancer, lung cancer, pancreatic cancer, retinoblastoma, B- and T-cell lymphomas
PI3KCA	Lung cancer, ovarian cancer, breast cancer, lymphoma
RAS (NRAS, HRAS, KRAS)	Colon cancer, melanoma, ovarian cancer, thyroid cancer
ROS1	Lung cancer, cholangiocarcinoma
RET	Lung cancer, thyroid cancer
Tumor Suppressor Genes	
APC	Colon cancer, thymus cancer
BRCA1, BRCA2	Breast cancer, ovarian cancer, prostate cancer
MSH2, MLH1, PMS1, PMS2, MSH6	Colon cancer
NF1, NF2	Leukemias, melanoma
TP53	Multiple cancers
PTEN	Lung cancer, ovarian cancer
RB1	Bladder cancer, retinoblastoma, sarcoma
VHL	Renal cell cancer

Data from My Cancer Genome. Available at http://www.mycancergenome.org/

Tumor Suppressor Genes

Tumor suppressor genes regulate and inhibit inappropriate cellular growth and proliferation.[2] Genetic alterations result in loss of control over normal cell growth. *Retinoblastoma* 1 and *TP53* are examples of tumor suppressor genes. Mutation of *TP53* is one of the most common genetic alterations associated with cancer. The normal gene product of *TP53* is responsible for negative regulation of the cell cycle (ie, a series of cellular events that lead to the division and duplication of a cell), allowing the cell cycle to halt for repairs, corrections, and responses to other external signals. Inactivation of *TP53* following a genetic alteration removes this checkpoint, allowing genetic alterations to accumulate within a cell. Mutation of *TP53* is linked to a variety of cancers. For example, a germline mutation in which an individual has only one functional copy of *TP53* is associated with Li-Fraumeni syndrome, a syndrome characterized by multiple cancers by early adulthood. Another important function of *TP53* may be modulation of cytotoxic drug effects; loss of *TP53* is associated with anticancer drug resistance.

DNA Repair Genes

Another important type of gene that plays a role in cancer development is the DNA repair gene. Their normal function is to repair DNA damaged by environmental factors or errors in DNA that occur during replication.[2] If not corrected, these errors can result in alterations that activate oncogenes or inactivate tumor suppressor genes. Subsequently, more genetic alterations accumulate within a cell, and the risk for transformation increases for the altered cell population. Specifically, DNA repair genes can affect mismatch repair, single-strand break repair, and double-strand break repair. For example, poly ADP ribose polymerase (PARP) is a family of proteins responsible for DNA repair and programmed cell death by affecting multiple repair mechanisms.[6] PARP1 is a member of the PARP family that plays a role in repairing single-strand DNA breaks. Deficiencies in DNA repair genes have been discovered in breast, colon, and ovarian cancers.

Accumulation of Genetic Alterations

It has become evident that a single genetic alteration is probably insufficient to initiate cancer. Most cancers acquire multiple somatic genetic alterations; some alterations may make no contribution to the development of cancer (eg, passenger mutations), while other alterations likely support the ongoing survival of cancer (eg, driver mutations). Scientists postulate that combinations of alterations are required for carcinogenesis and that the next generation of cells inherits each alteration. Thus, several detectable genetic alterations may be present in cancer. Although early alterations are found in premalignant lesions and established cancers, later alterations are found only in established cancer. This theory of sequential genetic alteration has been demonstrated in colon cancer. In colon cancer, the initial genetic alteration is believed to be loss of the *APC, or adenomatous polyposis coli* gene, which results in the formation of a small benign polyp (ie, abnormal tissue growth in a mucus membrane). An oncogenic mutation of ras genes is often the next step, leading to enlargement of the polyp. Loss of function of DNA mismatch repair enzymes may occur at many points during the transformation. Loss of *TP53* and another gene, believed to be the *deleted in colorectal cancer, or DCC,* gene, completes the transformation. Loss of *TP53* may be a late event in the development and progression of colon cancer and other cancers.

Four genes have been associated with DNA mismatch repair: *mutL homologue 1, mutS homologue 2, mutS homologue 6*, and *postmeiotic segregation increased 2*. When one or more of these proteins is mutated or missing, mistakes made during DNA replication may not be recognized or repaired. As a result, the tumor cell has a higher frequency of mutations known as mismatch repair deficient (dMMR). Tumors with a defective mismatch repair system may contain thousands of somatic mutations.[7] When a high number of these mutations accumulate within microsatellites (short repeating sequences of DNA), the tumor is characterized as microsatellite instability-high (MSI-H). As discussed later in the chapter, dMMR and MSI-H tumors are more susceptible to immune checkpoint inhibitors.

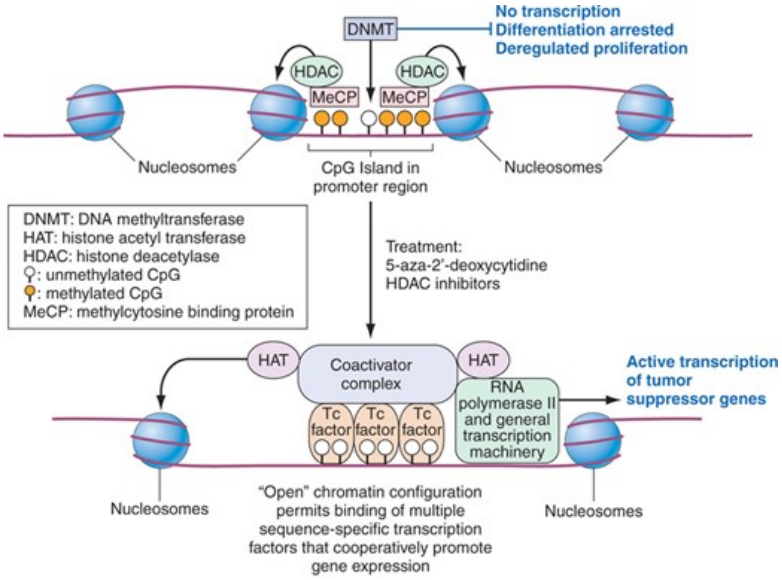
Epigenetic Alterations

Epigenetics refers to changes in gene expression that occur without altering the DNA sequence. The two most common mechanisms of epigenetic regulation include methylation and histone modification. DNA methylation commonly occurs at CpG dinucleotides (or islands) and is catalyzed by DNA methyltransferases (DNMTs). Histones are basic proteins associated with DNA in the nucleosome. These proteins may be modified by acetylation, methylation, or phosphorylation on their N-terminal tail. These modifications play a role in transcriptional regulation. For example, histone deacetylases (HDAC) repress transcription, and histone acetylases activate transcription. Epigenetic changes may be involved in the development of

cancer by either priming the cell or making it susceptible to genetic alterations associated with the development of cancer. For example, hypermethylation at CpG dinucleotides found near tumor suppressor genes can switch these genes off and promote cancer development. Anticancer agents, identified as inhibitors of DNMT or HDAC, target these modifications. Figure 149-3 shows the effects of these inhibitors on methylation, chromatin formation, and transcription.

FIGURE 149-3

Epigenetic regulation of gene expression in cancer cells. CpG islands within the promoter and enhancer regions of the gene are methylated, resulting in the complexes with HDAC activity. Chromatin is in a condensed conformation that inhibits transcription (upper figure). Inhibitors of DNMT with inhibitors of HDAC confer a chromatin structure that allows transcription (lower figure). *(Reproduced, with permission, from Longo DL. Cancer cell biology and angiogenesis. In: Longo DL, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine. 18th ed. New York, NY: McGraw Hill; 2012.)*



An oncometabolite is a metabolite whose abnormal accumulation may result in epigenetic dysregulation and carcinogenesis. Isocitrate dehydrogenase (IDH) 1 and 2 are enzymes involved in cellular metabolism through the conversion of isocitrate to alpha-ketoglutarate (αKG).[8] Mutations in *IDH1* and *IDH2* have been identified in gliomas and acute myeloid leukemia (AML) and result in the conversion of αKG to D-2-hydroxyglutarate. Elevated levels of D-2-hydroxyglutarate, an oncometabolite, inhibit αKG-dependent histone and DNA demethylases, which have been associated with impaired cellular differentiation. Anticancer agents have been developed to inhibit the mutant variants of IDH1 and 2 enzymes, thereby restoring myeloid differentiation.

PATHOLOGY OF CANCER

Cancer cells demonstrate several characteristics that differentiate them from normal cells. These traits include uncontrolled proliferation in which the cell cycle is no longer strictly regulated. Genetic alterations permit activation of multiple oncogenes and suppression of various tumor suppressor genes, releasing the cancer cells from the strict regulation observed with healthy cells. The cancer cells subsequently undergo multiple cell divisions, allowing the tumor size to increase exponentially. Cancer cells also resist programmed cell death by inhibiting apoptosis and senescence (aging). Lastly, cancer cells grow new blood vessels, invade new local tissue, and spread to distant sites.

Cell Cycle

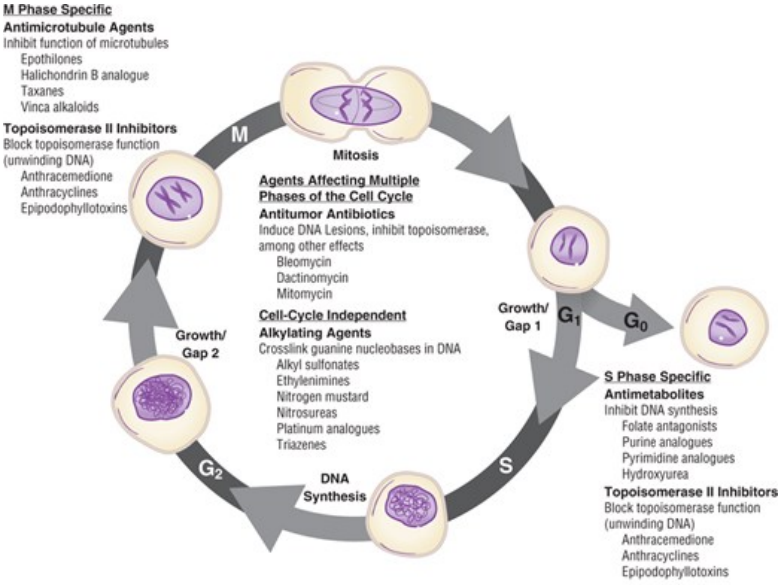
The cell cycle incorporates a series of events by which normal and cancer cells divide and make new cells. This process is strictly regulated in healthy cells. Oncogenes and tumor suppressor genes provide the stimulatory and inhibitory signals that regulate the cell cycle. These signals converge on a

molecular system in the nucleus known as the cell-cycle clock. The function of the clock in healthy cells is to integrate the signal input and determine if the cell cycle should proceed. The clock is composed of a series of interacting proteins, the most important of which are cyclins and cyclin-dependent kinases (CDKs). Cyclins and CDKs promote entry into the cell cycle and are overexpressed in several cancers. CDK inhibitors have been identified as important negative regulators of the cell cycle.

The cell cycle proceeds from one cell division to the next. The cycle involves five phases: DNA replication (S phase), cell division (M phase), two resting phases (G_1 and G_2), and a nondividing state (G_0 phase). In the first resting phase, G_1, the cell grows in size and decides to commit to the cell cycle or remain in a resting state. If the cell is normal, the cell will move into the S phase to synthesize its DNA. Next, the cell enters the second resting phase, G_2, in which the cell prepares to divide. In the M phase, the cell enters mitosis and yields two daughter cells. If the cell is not healthy, the cell can stop dividing and initiate apoptosis. Figure 149-4 depicts the cell cycle and the phases of activity for some chemotherapy agents.

FIGURE 149-4

Cell-cycle activity for chemotherapy. Cell-cycle phase-specific chemotherapy is most active during a particular phase. Cell-cycle phase-nonspecific chemotherapy may have activity in more than one phase. In many cases, it is likely that chemotherapy cytotoxicity involves multiple intracellular sites of action and may not be linked to specific cell-cycle events.



Four checkpoints exist within the cell cycle, one in each phase of the cell cycle, and serve as quality control checkpoints. The cell will not proceed to the next phase unless all requirements for the current phase are met. Complexes of cyclin and CDK regulate these checkpoints. These complexes lead to the activation of other proteins that are responsible for the specific events of each phase of the cell cycle. The first checkpoint is called the restriction site. *Retinoblastoma* complexed to a transcription factor called E2F controls the restriction site. The presence of this complex prevents cell-cycle progression. A cell can proceed beyond the G_1 restriction site and continue into the S phase when cyclin–CDK complexes phosphorylate *Retinoblastoma* and target it for degradation. A cell may alternatively withdraw into the G_0 phase in the presence of antimitogenic or the absence of mitogenic factors.

Defense Systems

When the normal regulatory mechanisms for cell growth fail, backup defense systems may be activated. The secondary defenses include apoptosis (programmed cell death or suicide) and cellular senescence. Apoptosis is a normal mechanism of cell death required for tissue homeostasis. This process is regulated by oncogenes and tumor suppressor genes and is also a mechanism of cell death after exposure to cytotoxins. Overexpression of oncogenes responsible for apoptosis may produce an "immortal" cell, which has increased potential for malignancy. For example, *B-cell lymphoma 2* (*BCL-2*) is normally located on chromosome 18, but it may be translocated to chromosome 14 in proximity to the immunoglobulin heavy chain gene.

This translocation leads to overexpression of *BCL-2* in lymphoid malignancies, which decreases apoptosis and confers a survival advantage. As another example, loss of *TP53* disrupts normal apoptotic pathways, imparting a survival advantage. Apoptosis may also play an important role as a mechanism of inherent resistance to some chemotherapy agents.

Cellular senescence is another important defense mechanism.[2] Laboratory studies demonstrate that after a cell population has undergone a preset number of doublings, growth stops and the cells die. This is known as senescence, a process that is regulated by telomeres. Telomeres are the DNA segments or caps at the ends of chromosomes. They are responsible for protecting the end of the DNA from damage. With each replication, the length of the telomeres is shortened. After the telomeres are shortened to a critical length, senescence is triggered. In this way, telomeres tally and limit the number of cell doublings. In cancer cells, the function of telomeres is overcome by overexpression of an enzyme known as telomerase. Telomerase replaces the portion of the telomeres lost with each cell division, thereby avoiding senescence and permitting an infinite number of cell doublings.

Immune Evasion

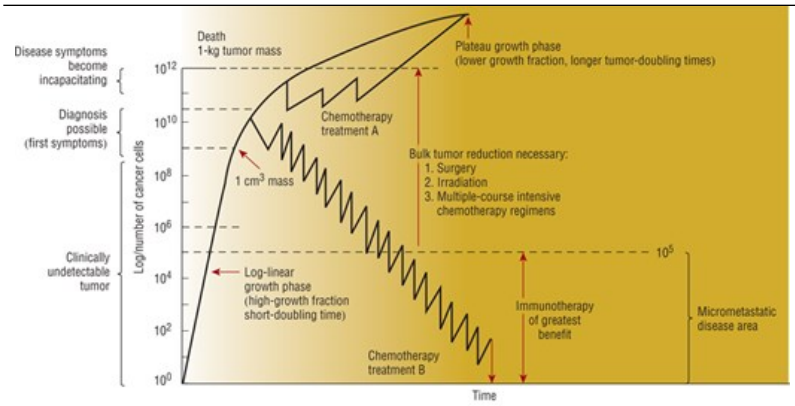
Immunosurveillance, a key feature of the host immune system, is recognizing and eliminating abnormal cells, including malignant cells. Antitumor immunity depends on T-cell identification of tumor antigens: a process regulated in part by various receptor-ligand interactions. Cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) and programmed death-1 (PD-1) are inhibitory receptors expressed on activated T-cells that serve as immune checkpoints. Checkpoints are critical in maintaining self-tolerance and preventing autoimmunity. When these T-cell receptors bind to their respective ligands on tumor cells, B7-1 and PD-ligand-1 (PD-L1), T-cell down-regulation occurs and the tumor is able to evade immunosurveillance. These ligands are overexpressed on multiple types of tumors, and this process represents one of the multiple mechanisms that tumors evade immune elimination. Immune checkpoint inhibitors block the receptor-ligand interactions, reverse the immune down-regulation, and allow for tumor cell elimination.

Cancer Growth

The study of cancer growth forms the foundation for many of the basic principles of modern chemotherapy. The growth of cancerous tumors is based on Gompertzian kinetics (see Fig. 149-5).[2] Gompertz was an insurance actuary who described the relationship between age and expected death. This mathematical model also approximates cancer cell proliferation. In the early stages, cancer growth is exponential, which means that cancer takes a constant amount of time to double its size. During this early phase, most cancer cells are actively dividing. This population of cells is called the growth fraction. The doubling time, or time required for cancer to double in size, is very short. Because cytotoxic chemotherapy agents typically have a greater effect on rapidly dividing cells, cancers are most sensitive to their effects when the cancer is small, and the growth fraction is high. As cancer grows, the doubling time is slowed. The growth fraction decreases, probably owing to cancer outgrowing its blood and nutrient supply or the inability of blood and nutrients to diffuse throughout the mass. Wide variability exists in measured doubling times for different cancers. The doubling time of most solid tumors is about 2 to 3 months, but some cancers have doubling times of only days (eg, aggressive non-Hodgkin lymphoma [NHL]).[9]

FIGURE 149-5

Gompertzian kinetics tumor-growth curve: relationship to symptoms, diagnosis, and various treatment regimens. *(Reproduced, with permission, from Buick RN. Cellular basis of chemotherapy. In: Dorr RT, Von Hoff DD, eds. Cancer Chemotherapy Handbook. 2nd ed. New York, NY: Appleton & Lange/McGraw Hill; 1994:3-14.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Tumor burden impacts diagnosis and treatment (see Fig. 149-5). It takes about 10^9 cancer cells (1 g mass, 1 cm in diameter) for cancer to be clinically detectable by palpation or radiography. A cancer of this size has likely undergone about 30 doublings in cell number. It only takes 10 additional doublings for this 1 g mass to reach 1 kg in size. Cancer possessing 10^{12} cells (1 kg mass) is considered lethal. Thus, a cancer is clinically undetectable for most of its life span. Tumor burden also impacts treatment. The cell kill hypothesis states that a certain percentage of cells will be killed with each course of cytotoxic chemotherapy. For example, if cancer consists of 1,000 cells and the first treatment kills 90% of the cells, then 10% or 100 cells remain. The second treatment kills another 90% of cells, and again only 10% or 10 cells remain. According to this hypothesis, the tumor burden will never reach zero. Cancers consisting of less than 10^4 cells are believed to be small enough for elimination by host factors, including immunosurveillance. The limitations of this theory are that it assumes all cancers are equally responsive to treatment and that resistance to anticancer agents and the development of metastases do not occur.[2]

Invasion and Metastasis

As cancer grows, cancer cells break away or shed from the primary site to invade surrounding tissue and metastasize to distant sites. Metastatic disease is associated with a poorer prognosis and shortened survival compared to earlier disease. The cancer cells invade adjacent tissue or metastasize to distant sites by hematogenous or lymphatic spread, but not all shedded cells result in a metastatic lesion. The shed cells must first find an environment suitable for growth. The onset and time course for metastasis development depends largely on the individual cancer, as illustrated by the diverse patterns of metastasis observed for different cancers. Breast cancer, for example, tends to metastasize very early. Prostate cancer commonly metastasizes to bone, and colon cancer commonly metastasizes to the liver. Other less common modes of disease spread include dissemination via cerebrospinal fluid and transabdominal spread within the peritoneal cavity.

For a cancer cell to break away from the primary tumor site, the shed cell and surrounding host tissue must first secrete substances that stimulate angiogenesis. The shed cells must then detach from the primary tumor by expressing proteins that degrade the extracellular matrix, such as matrix metalloproteases, and invade surrounding blood and lymph vessels. The cells must then attach to the vascular endothelium. The cells may proliferate within the lumen of the vessel but most commonly extravasate into the surrounding tissue. The local microenvironment may provide growth factors that can serve as fertilizer to potentiate the development of a metastatic site. At every step, the potential metastatic cell must fight the host immune system. Finally, the metastasis must again initiate angiogenesis to ensure continued growth and proliferation.

Angiogenesis is the development of new blood vessels. This process becomes unregulated in several cancers and supports growth, invasion, and metastasis. Angiogenesis is regulated by pro- and antiangiogenic growth factors, which are released in response to hypoxia and other stresses to the cell. Proangiogenic growth factors include vascular endothelial growth factor (VEGF), fibroblast growth factor, platelet-derived growth factor (PDGF), and tumor necrosis factor-alpha (TNF-α). Antiangiogenic growth factors include interleukin-12, or IL-12, interferon, and tissue inhibitors of metalloproteinases. The best-studied proangiogenic factor is VEGF, whose elevated levels have been associated with a poor prognosis and an increased risk of metastases in many cancers, including breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer, and colon cancer. Similar to other growth factors, VEGF binds to specific receptors located on the extracellular domain: VEGF-receptor (VEGFR)-1, -2, and -3. VEGFR-1 and VEGFR-2 are expressed primarily in endothelial cells and some cancer cells and mediate the biologic effects of VEGF. Each of the receptors induces a different signal transduction pathway. These pathways eventually result in the generation of proteases necessary for the breakdown of the extracellular matrix. Inhibiting the development of new blood vessels can limit or prevent tumor growth.

DIAGNOSIS OF CANCER

Tumors may be either benign or malignant. Benign tumors are noncancerous growths that are often encapsulated, localized, and indolent. Benign tumors are named for the cell or tissue of origin, followed by the suffix-oma. The tumor cells resemble the cells from which they developed. These masses seldom metastasize and rarely recur after being removed. In contrast to benign tumors, malignant tumors invade and destroy the surrounding tissue. The cancer cells are genetically unstable, and loss of normal cell architecture results in cells that are atypical of their tissue or cell of origin. These cells lose the ability to perform their usual functions. This loss of structure and function is called anaplasia. Cancers tend to metastasize, and consequently, recurrences are common after removal or destruction of the primary tumor. Cancers arising from epithelial cells are called carcinomas, and those arising from muscle or connective tissue are called sarcomas. Table 149-3 lists common nomenclature by tissue type.[10]

TABLE 149-3

Tumor Classification by Tissue Type

Tissue of Origin	Benign	Malignant
Epithelial Tissues		
Stratified squamous	Papilloma	Carcinoma (squamous, epidermoid)
Glandular tissue	Adenoma	Adenocarcinoma
Connective tissue		
Fibrous tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
Cartilage	Chondroma	Chondrosarcoma
Muscle		
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Blood and lymphoid cells		
	“Myeloproliferative disorders”	Leukemias
Lymphoid tissue	Plasmacytosis	Plasmacytoma; multiple myeloma; Hodgkin and NHL
Neural tissue		
Glial tissue	“Benign” gliomas	Glioblastoma multiforme; astrocytoma
Nerve sheath	Neurofibroma	Neurofibrosarcoma
Meninges	Meningioma	Malignant meningioma
Other cells		
Pigment-producing cells	Nevus	Melanoma

Adapted from National Cancer Institute: SEER Training Modules Tumor List [cited 2021 July 18]. Available at: https://training.seer.cancer.gov/disease/categories/tumors.html.

Screening

Because cancers are most curable before they metastasize, early detection and treatment have obvious potential benefits. Cancer screening programs are designed to detect cancers in individuals who have not yet developed symptoms. Still screening is only available for a few cancers, such as colon, prostate, breast, lung, and cervical cancers. Available screening tools include a cytology test, the Papanicolaou, or Pap, smear test for cervical cancer, and mammography for breast cancer. Limitations of the available screening tests include false-negative test results (related to the sensitivity of the test), false-positive test results (related to the specificity), and overdiagnosis (true positives not likely to become clinically significant). For example, most abnormal test results identified by screening mammography are false-positive, although the specificity of a mammogram exceeds 90%. For most cancers, a lack of effective screening method and inaccessible anatomic site limits the potential impact of a screening program. Public education on the early warning signs of common cancers is therefore extremely important for facilitating early detection. The American Cancer Society and other organizations publish guidelines for routine screening examinations (see Table 149-4).[11,12]

TABLE 149-4

American Cancer Society Screening Guidelines for Early Detection of Cancer in Average-Risk Asymptomatic Individuals

Cancer	Population	Age (years)	Test or Procedure	Frequency
Breast	Women	40-44	Mammography	Every year, optional
		45-54		Every year
		≥55		Every 1-2 years; depending on life expectancy
Cervical	Individuals with a cervix	25-65	Primary HPV test alone[a]	Every 5 years (preferred)
			Co-testing (cytology [Papanicolaou, or Pap, smear test] and HPV test) every 5 years	Every 5 years; acceptable if access to primary HPV testing is not available
			Cytology (Papanicolaou, or Pap, smear test) alone	Every 3 years; acceptable if access to primary HPV testing is not available
		>65	Options as above	Options as above should be continued until criteria for cessation are met[b]
Colorectal	All	45-75	Fecal immunochemical test	Annual
			High-sensitivity guaiac-based fecal occult blood test	Annual
			Multitarget stool DNA test	Every 3 years
			CT colonography	Every 5 years
			Flexible sigmoidoscopy	Every 5 years
			Colonoscopy	Every 10 years
		76-85	Options as above	Options as above; depending on patient history, preferences, and life expectancy
Lung	Current or former smokers, ≥30-pack-year history	55-74	Low-dose helical CT	Annual[c]
Prostate	Individuals with a prostate	≥50	Prostate-specific antigen test with or without digital rectal examination	Option if at least a 10-year life expectancy to make informed decision with their healthcare provider whether to be screened

[a]Use an FDA-approved HPV test for primary screening.

[b]Adequate negative prior screening is two consecutive negative primary HPV tests, or two negative cotests, or three negative cytology tests within the last 10 years, with the most recent occurring within the last 3-5 years.

[c]In adults who currently smoke or have quit within the last 15 years and have at least a 30-pack-year history and receive evidence-based smoking cessation counseling if they are current smokers and have undergone a process of informed/shared decision making that included information about the potential benefits, limitations, and harms of screening with low-dose CT and have access to a high-volume, high-quality lung cancer screening and treatment center.

Data from References 11 and 12.

Clinical Presentation

4 The presenting signs and symptoms vary widely and depend on the type of cancer. The presentation in adults may include any of the seven warning signs listed in Table 149-5, as well as headaches, weight loss, chronic pain, fatigue, or anorexia.[13] The warning signs of cancer in pediatrics are different and reflect the cancers more common in this population (see Table 149-6). The definitive diagnosis of cancer relies on procuring a tissue sample and pathologic assessment of this sample. This sample can be obtained by numerous methods, including an excisional, core, or needle aspiration biopsy. A tissue diagnosis is essential because many benign tumors can masquerade as cancers and most tumors are not cancer. Depending on the tumor type, the diagnosis may include evaluating genetic alterations such as hormone receptor status in breast cancer or epidermal growth factor receptor (EGFR) status in NSCLC. Multiple companion or complementary tests are available and are indicated to detect a select mutation associated with a specific tumor type or identify hundreds of genetic mutations in any solid tumor.

TABLE 149-5

Cancer's Seven Warning Signs

Change in bowel or bladder habits
A sore that does not heal
Unusual bleeding or discharge
Thickening or lump in the breast or elsewhere
Indigestion or difficulty in swallowing
Obvious change in wart or mole
Nagging cough or hoarseness
If YOU have a warning signal, see your doctor!

Data from Reference 13.

TABLE 149-6

Cancer's Warning Signs in Children

Continued, unexplained weight loss
Headaches with vomiting in the morning
Increased swelling or persistent pain in bones or joints
Lump or mass in abdomen, neck, or elsewhere
Development of a whitish appearance in the pupil of the eye
Recurrent fevers not caused by infections
Excessive bruising or bleeding
Noticeable paleness or prolonged tiredness

Staging

Following a pathologic diagnosis, cancers should be staged to determine the extent of the disease (ie, tumor location and size) before starting treatment. Staging provides information on prognosis and guides treatment selection. A staging workup may involve physical examination, biopsy, imaging tests (ie, computed tomography [CT] scans, magnetic resonance imaging [MRI], and positron emission tomography [PET] scans), and laboratory tests. The laboratory tests may include tumor markers, antigens, or other substances produced by cancer. However, tumor markers are often nonspecific and may be elevated in many different cancers or patients with nonmalignant conditions. As a result, tumor markers are generally more useful for monitoring response and detecting recurrence than diagnostic tools. For example, human chorionic gonadotropin, or hCG, and alpha-fetoprotein, or AFP, in testicular cancer or prostate-specific antigen, or PSA, in prostate cancer are useful markers to monitor response or recurrence. After starting treatment, the staging workup is usually repeated at regular intervals to evaluate the effectiveness of the treatment.

The most common staging system for solid tumors is the TNM system that describes the tumor (T), nodes (N), and metastases (M). A numerical value is assigned to each letter to indicate the size or extent of disease. The T describes the size of the primary tumor and spread to adjacent tissues; the N specifies the size, location, and number of regional lymph nodes affected by cancer; and the M describes the presence or absence of metastases. Each letter is followed by an Arabic number that uniquely describes that tumor, node, or metastases. After the individual T, N, and M are determined, their values are combined to provide an overall stage identified using Roman numerals ranging from stage I to stage IV. For example, stage $T_3N_1M_0$, which describes a moderate-to-large primary mass with regional lymph node involvement and no distant metastases, is typically a stage III cancer. This simplified staging system allows healthcare professionals to identify the extent of disease easily. For example, stage I usually indicates localized cancer, stages II and III typically indicate local and regional disease, and stage IV typically indicates distant metastases. The criteria for classifying disease extent are quite specific for each different cancer. Alternative staging systems are used in clinical practice for leukemias and lymphomas, as discussed in subsequent chapters.

TREATMENT MODALITIES

Three main modalities are used to treat cancer: surgery, radiation, and systemic anticancer agents. These modalities may be used alone but are typically given sequentially or concurrently to treat a specific cancer. The timing of the different modalities relative to one another is based on the outcomes of a clinical trial.

Surgery is the oldest treatment modality, and it plays a major role in diagnosis and treatment. It may be curative if the primary cancer has not metastasized. Surgery remains the treatment of choice for most early stage cancers, such as breast and colon cancers. Surgery typically involves the removal of the primary tumor and adjacent lymph nodes. This modality may also be used to remove isolated metastases and relieve symptoms associated with metastatic disease. For example, hepatic metastases may be removed for patients with colon cancer.

Radiation therapy can be used alone for localized cancer or cancer that may encompass a single radiation field. It was first used to treat cancer in the late 1800s and remains a mainstay of treatment for some cancers. Radiation therapy may also be used to alleviate symptoms associated with vena cava syndrome, bone metastases, spinal cord compression, and brain tumors. This modality typically damages normal tissue surrounding the cancer, but the normal tissue typically repairs itself more readily than the cancer cells. Several different types of radiation therapy are available, including external beam radiation therapy, stereotactic radiation, brachytherapy, and radioisotopes. Both early and late toxicities associated with radiation therapy are dependent on the organs within the radiation field. For example, mucositis is commonly observed in patients receiving radiation for head-and-neck cancer. Secondary cancers are a devastating late toxicity that can occur following radiation therapy.

Systemic anticancer agents include chemotherapy, targeted therapy, and immunotherapy. Hormonal therapy is used for the treatment of cancer and is discussed in other chapters. Multiple radiopharmaceuticals are also now available. In general, systemic anticancer agents are developed to destroy cancer cells while minimizing effects on healthy cells. Specific agents will be discussed later in this chapter.

Combined Modality Treatment

As stated earlier in the chapter, a cancer may be treated with multiple modalities. For example, systemic anticancer agents are often administered to patients with local disease (ie, early stage) following surgery or radiation therapy. Because many patients with local disease have undetectable metastatic disease (ie, micrometastases) at diagnosis, localized anticancer treatment alone may fail to eliminate the cancer completely. *Adjuvant* therapy is systemic therapy administered to eradicate micrometastatic disease after surgery or radiation. The goal of adjuvant therapy is to reduce recurrence rates and prolong long-term survival. Thus, adjuvant therapy is given to patients with potentially curable cancers who have no clinically detectable disease after surgery or radiation. Because adjuvant therapy is given when the cancer is undetectable (ie, no measurable disease), its

effectiveness is evaluated by recurrence rates and survival. *Neoadjuvant* (ie, preoperative or preradiation) therapy may be given to patients before surgery or radiation therapy to reduce tumor burden and destroy micrometastases. For example, neoadjuvant therapy has been given to patients with breast cancer to reduce the primary tumor size and allow for a less invasive surgical procedure.

The management of hematologic malignancies typically involves systemic anticancer therapies and radiation therapy since these cancers are systemic diseases that cannot be effectively treated with localized modalities. Systemic therapy that is administered to eradicate the cancer cells is called *induction* therapy. When a complete remission (the disappearance of all signs of cancer) is documented, postremission, or *consolidation*, therapy is administered. These therapies are designed to eradicate any remaining disease, similar to adjuvant therapy for solid tumors, and can include systemic therapy, a hematopoietic stem cell transplant (HSCT), or radiation therapy. *Maintenance* therapy is sometimes administered after consolidation therapy. The goal of this therapy is to prevent cancer from recurring or to maintain a response. Not all treatment phases are employed for all hematologic malignancies.

Goals of Care

The goals of care depend on the cancer stage and patient factors, such as comorbidities. When an anticancer agent is administered to patients with local or regional disease, the treatment (eg, adjuvant therapy) is often administered to cure the patient and may be labeled as *curative* therapy. When cancer has metastasized to distant sites, a cure is usually not possible, with rare exceptions, including testicular cancer. Anticancer therapy may be administered to patients with metastatic disease to slow cancer progression and prolong survival by months to years. If anticancer therapy is given to patients with the goal of reducing symptoms, the treatment is often called *palliative* therapy.

SYSTEMIC THERAPY

Chemotherapy

Chemotherapy was first administered in 1941 when Goodman and Gilman gave nitrogen mustard to patients with lymphoma. As discussed later in the chapter, a chemotherapy agent is typically given as part of a combination regimen, in which multiple anticancer agents with different mechanisms of action and toxicities are given together. Most chemotherapy agents target rapidly proliferating cells (both normal and cancer cells), and these agents might act at one or more phases of the cell cycle. A chemotherapy agent that demonstrates major activity in a particular phase of the cell cycle is known as a cell-cycle phase-specific agent. For example, antimetabolites exert their effect during the S phase. Cell-cycle phase-specific agents may be less active in other phases of the cell cycle. A cell-cycle phase-nonspecific agent has significant activity in multiple phases. Alkylating agents, such as nitrogen mustards, are examples of cell-cycle phase-nonspecific agents. Despite this classification, it is believed that most chemotherapy agents provide cytotoxic effects following interactions with other intracellular activities, not just specific cell-cycle events. Knowledge of cell-cycle specificity has been used to optimize treatment schedules. For example, a cell-cycle phase-specific chemotherapy agent is typically administered as a continuous infusion or in multiple repeated fractions to maximize the number of cancer cells in the sensitive cell-cycle phase. Thus, a cell-cycle phase-specific chemotherapy agent is also termed “schedule dependent.” In contrast, cell-cycle phase-nonspecific chemotherapy is active in many phases, and consequently, these agents are not schedule dependent. The activity of these chemotherapy agents depends on the dose, so these chemotherapies are termed “dose-dependent.” Chemotherapy agents are typically given in a defined repeating schedule called a cycle. The cycle length typically depends on the toxicities associated with the chemotherapy agent, such that sufficient time elapses between doses to allow a patient to adequately recover from a serious adverse drug reaction (eg, neutropenia). The number of cycles depends, in part, on the treatment goals. The number of cycles is typically defined by prior clinical trials for early stage disease. In contrast, the number of cycles is generally determined by individualized treatment response and tolerability for locally advanced or metastatic disease.

Targeted Agents

Targeted anticancer agents, including small-molecule inhibitors and mAbs, stop cancer progression by blocking aberrant intracellular signaling pathways that govern cell responses, movement, and division. Some of these agents can cause cancer cell death by inducing apoptosis or stimulating the immune system to destroy the cancer cells.

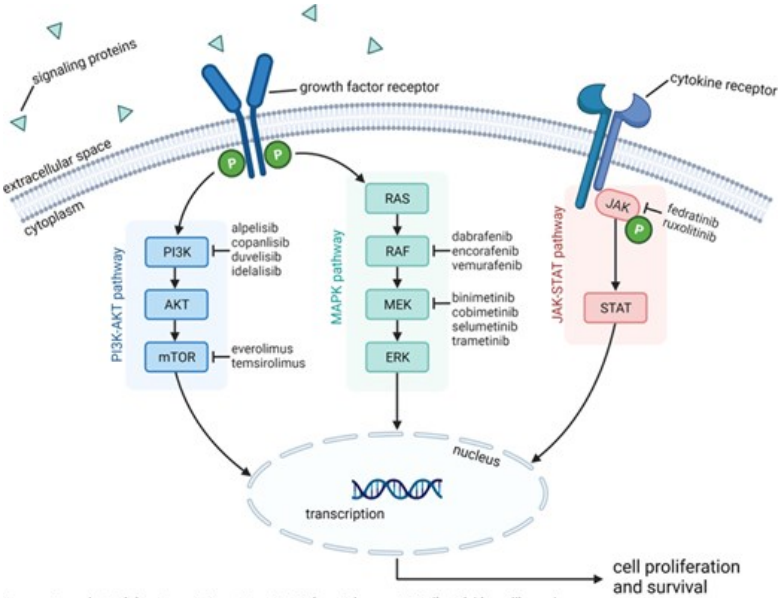
The first small-molecular targeted agent was developed in the late 1980s. Small-molecule targeted agents have a low molecular weight (less than 1,000 Da) and have been specifically designed to interfere with intracellular signaling pathways. These agents are typically given orally once or twice daily until disease progression or unacceptable toxicity occurs. Since resistance commonly develops with small-molecule targeted agents, they may be

administered concurrently with other anticancer agents.

Similar to small-molecule targeted agents, most mAbs are administered with other anticancer treatments. Both mAbs and targeted agents have been developed to interfere with intracellular signaling. Although small-molecule targeted agents typically inhibit intracellular kinases, mAbs target the extracellular receptors or their natural ligands and prevent ligand binding to the receptor. The net effect of both strategies is to interfere with intracellular signal transduction and decrease cell proliferation (see Fig. 149-6). Some common receptors and pathways affected by available small-molecule targeted agents and mAbs include ErbB2 family, mitogen-activated protein kinase (MAPK) pathway, and phosphatidylinositide 3-kinase (PI3K) pathway.

FIGURE 149-6

Common intracellular signaling pathways and targeted therapies that inhibit these pathways. Activation of the PI3K-AKT pathway, the MAPK pathway, or the JAK/STAT pathway leads to downstream signaling and ultimately cell proliferation and survival. (*Image created with BioRender.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The ErbB family of receptors contains four known members: ErbB1 (also known as EGFR), ErbB2 (human EGFR 2 [HER2]), ErbB3, and ErbB4. EGFR and HER2 are overexpressed in several cancers, including breast, lung, gastric, and colon cancers. The roles of the other receptors in cancer growth and proliferation are still under investigation. Members of this family are inactive by themselves and must form a dimer (a molecule composed of two subunits) either with a member of the same family (homodimer) or with a member of a different ErbB family (heterodimer). Dimerization of the receptor leads to kinase phosphorylation and subsequent activation of downstream pathways required to activate signal transduction and cell growth.

Well-described intracellular signaling pathways include PI3K, Janus kinase–signal transducers (JAK) and activators of transcription (STAT), and MAPK. When these pathways are activated, they promote cell proliferation and survival. These pathways consist of a chain of proteins that ultimately communicate a signal from a cell surface receptor to the DNA found in the nucleus. A protein within a signaling pathway communicates by adding a phosphate group to its neighboring protein; the phosphate groups act as an “on” or “off” switch for the pathway. In cancer, a mutated protein permits the pathway to remain in the “on” or “off” position. The downstream effectors of these pathways also initiate cell-cycle progression by promoting the expression of cyclins and repressing the expression of CDK inhibitors.

The MAPK signaling pathway regulates many fundamental cellular processes, including cell differentiation, proliferation, and senescence. These pathways relay the intracellular signals through a series of ras, raf, MEK (MAPK-extracellular signal-regulated kinase), and extracellular signal-regulated kinase (ERK) proteins that subsequently phosphorylate and regulate nuclear and cytoplasmic structures. Some of these proteins are commonly altered in pancreatic, melanoma, colorectal, hepatocellular, and other solid tumors.

The PI3K signaling pathway also regulates cell proliferation, growth, survival, and mobility. PI3K becomes activated in response to growth hormones. It

ultimately activates protein kinase B (known as AKT), a serine-threonine kinase that serves as a master switch for the cell-cycle progression. Fully activated protein kinase B translocates to the nucleus, inhibiting proapoptotic signals and activating antiapoptotic substrates. It can also phosphorylate mammalian target of rapamycin (mTOR). After being activated, mTOR stimulates protein synthesis by phosphorylating translation regulators. mTOR also contributes to protein degradation and angiogenesis. Phosphatase and tensin homolog, or *PTEN* is a tumor suppressor gene that blocks intracellular signaling through this pathway and is frequently inactivated in several solid tumors.

The JAK-STAT signaling pathway helps regulate the immune system. This pathway contains three main components: extracellular receptors, JAKs, and STAT. The pathway is initiated when cytokines or growth factors bind to the receptor, activate JAK, and subsequently recruit STAT. The STAT proteins then translocate to the nucleus and modify gene expression. Altered JAK signaling has been associated with JAK mutations in patients with myelofibrosis.

Immunotherapy

Immunotherapy works by boosting the natural defenses of the host immune system to eradicate tumor cells. These agents work in two main ways: training the individual's immune system to attack cancer directly or by administering immune components that result in a more general stimulation of the immune system. Agents classified as immunotherapies include cytokines, CAR T-cell therapies, immune checkpoint inhibitors, and therapeutic vaccines.

Combination Therapy

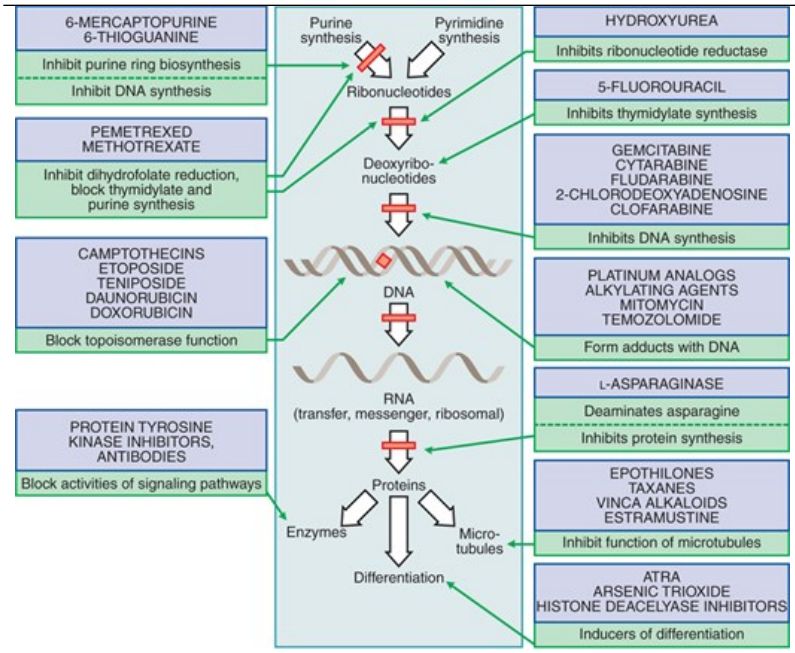
Although a single anticancer agent may be administered to a patient, the more common approach to systemic therapy is to administer multiple agents known as a regimen. Initially, this approach was based on the Goldie-Coldman hypothesis, which addresses cancer cell heterogeneity and the inevitable development of drug resistance. The individual agents selected for combination therapy should have different mechanisms of action and adverse drug reaction profiles. For example, myelosuppressive agents may be combined with non-myelosuppressive agents to minimize myelosuppression. The individual agents should each have significant activity against the cancer, and the combination therapy should have known clinical benefit in the cancer to be treated. Combination regimens that include multiple chemotherapy agents with or without a targeted agent or immunotherapy have been used to successfully manage many cancers for decades. Predictive biomarkers, such as HER2 and BRAF, may be used to identify which patients may benefit from targeted therapy.

CHEMOTHERAPY

5 Since all chemotherapy agents interfere with the cellular synthesis of DNA, ribonucleic acid (RNA), or proteins, chemotherapy agents are commonly categorized by their mechanism of action. For example, alkylators exert their effects on DNA and protein synthesis by binding to DNA and preventing the unwinding of the DNA molecule. As another example, antimetabolites resemble nucleotide bases or inhibit enzymes involved in synthesizing DNA and proteins. Figure 149-7 shows the sites of action of common categories of anticancer agents.

FIGURE 149-7

Mechanisms of action of commonly used anticancer agents (all-trans-retinoic acid). *(Reproduced, with permission, from Chabner BA. General principles of chemotherapy. In: Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's The Pharmacologic Basis of Therapeutics. 12th ed. New York, NY: McGraw Hill; 2010.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The following sections discuss the biochemical classification system and the individual agents within each classification. The clinical uses, mechanisms of action, common adverse drug reactions, and practical patient management for most available chemotherapy agents are also discussed. Table 149-7 summarizes monitoring parameters of individual anticancer agents.

TABLE 149-7

Monitoring of Anticancer Drugs[a]

Agent	Notable Adverse Drug Reactions	Monitoring Parameters	Comments
Chemotherapeutic Agents			
Antimetabolites			
Capecitabine	Diarrhea, PPE, mild nausea and vomiting, mucositis	Stool count, hands and feet for early signs of skin breakdown, CBC, liver function, renal function	Adjust dose for renal impairment Oral prodrug of fluorouracil Warfarin results in increased anticoagulant effects May require phenytoin dose reduction Deficiency of DPD correlates with increased toxicity
Cladribine	Myelosuppression, fever, immunosuppression, severe opportunistic infections occur	CBC, signs of infection	Risk of opportunistic infections necessitates prophylactic antibiotics for PJP and other infections
Cytarabine	*General toxicities:* myelosuppression, nausea and vomiting, diarrhea, mucositis, TLS, flu-like syndrome, rash *High-dose toxicities:* worsening of	CBC, uric acid, signs of infection, renal function, neurologic examinations (signs	High-dose infusions should be administered over 2-3 hours to decrease risk of CNS toxicity Use corticosteroid eye drops during treatment and for 48 hours after treatment to prevent conjunctivitis

	above, cerebellar toxicity, conjunctivitis	of confusion)	with high-dose cytarabine Increased risk of neurotoxicity with high-dose cytarabine in setting of renal impairment Use preservative-free preparations for IT preparations: occasionally combined with hydrocortisone & methotrexate
Fludarabine	Myelosuppression, immunosuppression, diarrhea, rare CNS toxicity (somnolence, seizures, altered mental status), hearing and visual changes, pulmonary toxicity, TLS	CBC, uric acid, signs of infection, renal function, neurologic examinations	Adjust dose for renal impairment Risk of opportunistic infections necessitate prophylactic antibiotics for PJP and HSV
Fluorouracil	Mucositis, diarrhea, PPE, myelosuppression, hyperpigmentation, photosensitivity, ocular toxicity, myocardial ischemic symptoms	CBC, stool count, hands and feet for early signs of skin breakdown	Deficiency of DPD correlates with increased toxicity Drug interaction with warfarin: increased anticoagulant effect
Gemcitabine	Myelosuppression, flu-like syndrome, rash, elevations in liver transaminases	CBC, liver function	Fixed dose rate (10 mg/m^2/minute) may be used in lymphoma and sarcoma settings, associated with increased myelosuppression
Mercaptopurine	Myelosuppression, dry skin, rash, hepatotoxicity, hyperbilirubinemia	CBC, liver function	Allopurinol increases the toxicity of mercaptopurine by interfering with metabolism Mercaptopurine reduces anticoagulant effects of warfarin Consider pharmacogenomic testing for TPMT and NUDT15
Methotrexate	Myelosuppression, mucositis, renal failure at high doses, nausea and vomiting, CNS toxicity (more severe with IT administration), hepatotoxicity	CBC, liver function, renal function, urine pH, methotrexate drug levels with high-dose therapy	Adjust dose or avoid use with renal impairment, avoid drugs that decrease renal excretion of methotrexate (eg, NSAIDs, PPIs, sulfas, penicillins) Distributes readily into third-space fluids (ascites, pleural effusions), prolonging exposure and increasing toxicity; may be contraindication for use Monitor methotrexate levels with high-dose administration; these must include leucovorin rescue to prevent excessive myelosuppression; sodium bicarbonate given for high-dose therapy to prevent nephrotoxicity (maintain urine pH >7) Use preservative-free preparations for IT and high-dose administration; occasionally combined with hydrocortisone & cytarabine IT

Pemetrexed	Myelosuppression, stomatitis, pharyngitis, rash, desquamation, fatigue	CBC, renal function, skin examinations	Avoid with renal impairment Avoid NSAIDs during administration Supplement with folic acid (400-1,000 mcg PO daily starting 1 week before first dose, continued 21 days after last dose) and vitamin B_{12} (1,000 mcg IM 7 days prior to first dose and every 3 cycles thereafter) to decrease myelosuppression Premedicate with dexamethasone (day before, the day of, and day after) to decrease incidence of rash
Pentostatin	Myelosuppression, rash, renal toxicity, hepatic toxicity, pulmonary toxicity, CNS toxicity	CBC, renal function, hepatic function, lung function, sign of neurotoxicity	Hydration pre/post pentostatin administration Risk of opportunistic infections necessitate prophylactic antibiotics for PJP and HSV
Trifluridine and tipiracil	Myelosuppression, asthenia/fatigue, decreased appetite, diarrhea, nausea and vomiting, abdominal pain, pyrexia	CBC, renal function	Adjust dose for moderate renal impairment
Microtubule-Targeting Drugs			
Cabazitaxel	Myelosuppression, hypersensitivity reactions, diarrhea, asthenia, nausea and vomiting, peripheral neuropathy, alopecia	CBC, signs of infection, stool count, signs of hypersensitivity reactions, liver function	Avoid with hepatic impairment Premedicate with H_1 and H_2 antagonist plus dexamethasone to decrease risk of hypersensitivity
Docetaxel	Myelosuppression, fluid retention (edema, pleural effusions, ascites), alopecia, rash, peripheral neuropathy, hypersensitivity reactions, nail toxicity	CBC, liver function, signs/symptoms of fluid retention	Contraindicated with hepatic impairment (hyperbilirubinemia, elevated transaminases, or elevated alkaline phosphatase) Premedicate with dexamethasone to lower risk of fluid retention
Eribulin	Myelosuppression, peripheral neuropathy, asthenia, alopecia, nausea, constipation	CBC, liver function, renal function, potassium and magnesium levels	Dose reduce for Child-Pugh class A or B hepatic impairment and moderate renal impairment May cause QTc prolongation in patients with electrolyte or congenital abnormalities (avoid other drugs that may prolong QTc interval)
Ixabepilone	Myelosuppression, peripheral neuropathy, hypersensitivity reactions, asthenia, arthralgias, alopecia	CBC, signs of hypersensitivity reactions, liver function	Avoid or adjust dose with hepatic impairment CYP3A4 substrate, levels may be effected by inducers or inhibitors, avoid use or dose adjustment to ixabepilone may be necessary Premedicate with H_1 and H_2 antagonist
Paclitaxel and nab-	Myelosuppression, hypersensitivity	CBC, signs of	Avoid or adjust dose with hepatic impairment

paclitaxel	reactions, peripheral neuropathy, myalgias or arthralgias, mucositis, cardiac arrhythmias, alopecia	hypersensitivity reactions, liver function	Premedicate with dexamethasone, H1 and H2 antagonist before paclitaxel; nab-paclitaxel is associated with minimal risk of hypersensitivity reactions and does not require premedication Neurotoxicity may require discontinuation or dose reduction Products are not interchangeable
Vinblastine and vinorelbine	Myelosuppression, mucositis, neurotoxicity (less common than with vincristine), myalgias, SIADH (rarely), vesicant	CBC, liver function	Adjust dose with elevated bilirubin Treat extravasation injury with warm soaks and injection of hyaluronidase
Vincristine	Peripheral neuropathy (highest of vinca alkaloids); motor, sensory, autonomic, and cranial nerves may be affected (paresthesias, ileus, urinary retention, facial palsies) and can be irreversible; SIADH; vesicant	Signs of neurotoxicity (tingling in extremities, constipation, CNS toxicity), liver function	Adjust dose with elevated bilirubin Treat constipation aggressively to prevent ileus Doses are commonly capped at 2 mg to minimize neurotoxicity LETHAL if administered IT Treat extravasation similar to vinblastine
Topoisomerase Inhibitors			
Irinotecan and liposomal irinotecan	Diarrhea: acute (during or immediately after infusion, related to cholinergic effects) and delayed (>24 hours after administration) Nausea and vomiting, myelosuppression, alopecia, fatigue, increased liver enzymes, pulmonary toxicity	CBC, liver function, stool count, fluid status, electrolytes	Acute diarrhea is treated or prevented with atropine, delayed diarrhea is managed with antimotility agents Consider dose adjustment with elevated total bilirubin or UGT1A1 deficiency Products are not interchangeable and have different indications
Topotecan	Myelosuppression, alopecia, diarrhea	CBC, renal function	Adjust dose for renal impairment
Daunorubicin	Myelosuppression, mucositis, nausea and vomiting, alopecia, vesicant Cardiac toxicities: acute (not related to cumulative dose, arrhythmias, pericarditis); chronic (cumulative injury to myocardium with total dose >250 mg/m^2)	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely Extravasation managed with dexrazoxane
Doxorubicin and liposomal doxorubicin	Similar to daunorubicin, cardiac toxicity associated with cumulative doses >250 mg/m^2, radiation recall reactions	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely May discolor urine (red-orange) Liposomal form: decreased risk of cardiac and vesicant toxicities

Epirubicin	Similar to daunorubicin, cardiac toxicity associated with cumulative doses >450 mg/m^2	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely
Etoposide	Myelosuppression, nausea and vomiting (may be worse with oral and high-dose regimens), alopecia, mucositis, hypotension (infusion rate–related), hypersensitivity reactions	CBC, blood pressure	Adjust dose for renal impairment Requires large volumes of fluid for IV administration because of limited solubility (maximum concentration 0.4 mg/mL) Available orally in liquid-filled gelatin capsules; ~50% bioavailability but absorption is variable and greater at lower oral doses
Idarubicin	Similar to daunorubicin, total cumulative dose not well established; >150 mg/m^2 reported to be associated with decreased LVEF	CBC, LVEF, liver function	Adjust dose for elevated bilirubin LVEF should be >50% to administer safely
Mitoxantrone	Myelosuppression, nausea and vomiting, mucositis, alopecia, less cardiotoxic than the anthracyclines	CBC, LVEF, liver function	Not a vesicant (may cause vein irritation but not associated with severe tissue injury such as anthracyclines) May discolor urine blue-green
Alkylating Agents			
Bendamustine	Myelosuppression, infection, dermatologic reactions including Stevens-Johnson syndrome, TLS, infusion reactions	CBC, signs of infection, signs of dermatologic toxicity, uric acid	Allopurinol may increase risk for Stevens-Johnson syndrome
Busulfan	General toxicities: myelosuppression, skin hyperpigmentation, pulmonary fibrosis, gynecomastia, adrenal insufficiency High (HSCT) dose toxicities: seizures, hepatic veno-occlusive disease, severe nausea and vomiting	CBC, pulmonary status, liver function, signs of edema (weight gain, fluid status)	Bone marrow recovery may be delayed (3-6 weeks), pulmonary fibrosis associated with >3-year exposure and/or prior chest radiation Seizure prophylaxis with HSCT doses Pharmacokinetic monitoring is required with IV busulfan IV and oral preparations are not interchangeable Put tablets in gelatin capsules for easier administration with high doses
Carboplatin	Myelosuppression (thrombocytopenia), nausea and vomiting (acute and delayed), risk of hypersensitivity reactions at higher cumulative doses (frequently results in cross-hypersensitivity to cisplatin)	CBC, renal function	Calvert formula used to dose carboplatin Lower incidence of nephrotoxicity, neurotoxicity, nausea and vomiting than cisplatin

Chlorambucil	Myelosuppression, increased liver enzymes, skin rash, menstrual irregularities, pulmonary toxicity, risk of secondary malignancies, infertility and sterility, teratogenic	CBC, liver function, pulmonary function	Administer on an empty stomach, food decreases absorption May be dosed in low daily-dosing regimens, higher dose (ie, pulse), or intermittent dosing schedules administered biweekly or monthly; pulse dosing may require patients to take several tablets (eg, 10-20 tablets) per dose
Cisplatin	Nephrotoxicity, potassium and magnesium wasting, severe nausea and vomiting (acute or delayed onset), peripheral neuropathy that is cumulative and dose related, ototoxicity, anemia seen with chronic dosing	Renal function, potassium and magnesium levels, GI symptoms (nausea and vomiting)	Avoid with renal impairment IV hydration required before and after administration; ensure good urine output; potassium and magnesium sulfate in IV fluid to replace losses; consider carboplatin with impaired renal function Aggressive antiemetics required pretreatment and after treatment to prevent delayed nausea and vomiting Doses should not exceed 100 mg/m^2 (maximum single dose and per-cycle dose)
Cyclophosphamide	Hemorrhagic cystitis, nausea and vomiting (acute and delayed), myelosuppression, alopecia, SIADH (typically with high doses of >2 g/m^2), risk of secondary malignancies, infertility and sterility	CBC, renal function, urinalysis	Adjust dose for renal impairment Hydration needed to prevent hemorrhagic cystitis (PO or IV); mesna may be required with high-dose regimens (see ifosfamide) Instruct patients to take oral tablets in the morning to allow for elimination of toxic metabolite Absorbed through skin: avoid spills Drug interactions: CYP450 inducers (eg, barbiturates) may increase formation of toxic metabolites; CYP450 inhibitors may increase myelosuppression
Ifosfamide	Hemorrhagic cystitis, nephrotoxicity, myelosuppression, CNS effects (somnolence, confusion, disorientation, cerebellar symptoms that are dose related), nausea and vomiting (acute and delayed), alopecia	CBC, urinalysis, renal function	Adjust dose for renal impairment 3-4 L/day fluid for hydration; potassium, magnesium, and phosphate may be required to replace losses Mesna is always given (typically 60%-100% of ifosfamide dose); may be delivered in same IV bag CNS toxicity, nausea, and vomiting may be more severe with rapid infusion Methylene blue is controversial for CNS toxicity
Lurbinectedin	Myelosuppression, nausea and vomiting, hepatotoxicity	CBC, liver function, magnesium	Avoid coadministration with strong or moderate CYP3A inducers or inhibitors
Mechlorethamine	Myelosuppression, severe nausea and vomiting, vesicant, secondary malignancies, sterility and infertility	CBC, GI symptoms (nausea and vomiting)	Antidote for extravasation is sodium thiosulfate

Melphalan	Myelosuppression, nausea and vomiting, diarrhea, mucositis, secondary malignancies, hypersensitivity reactions	CBC, renal function, electrolytes, liver function	Complete administration of IV dose should occur within 60 min of reconstitution for Alkeran formulation
Nitrosoureas (carmustine and lomustine)	Myelosuppression, severe nausea and vomiting, cumulative nephrotoxicity, pulmonary fibrosis, facial flushing during infusion	CBC, renal function, pulmonary function	Bone marrow recovery may require 6-8 weeks Carmustine is a vein irritant Facial flushing may be related to alcohol vehicle Also available in wafer form for implantation into brain tumor cavities after resection Lomustine is administered orally
Oxaliplatin	Pharyngolaryngeal dysesthesias, nausea and vomiting, anaphylaxis risk Peripheral neuropathy >50% patients: acute form (<14 days, rapid onset, reversible, exacerbated by cold); chronic form (onset >14 days and may be permanent)	CBC, renal function, acute and chronic neuropathies	Adjust dose for renal impairment Avoid exposure to cold
Procarbazine	Myelosuppression, diarrhea, neurotoxicity, neuropathy, flu-like syndrome, infertility and sterility, secondary malignancies	CBC	Administer as a single daily dose on an empty stomach Drug interactions: MAOIs that interact with tyramine-rich foods and may precipitate hypertensive crisis; TCAs and SSRIs; sympathomimetics; disulfiram-like reaction with alcohol
Thiotepa	Myelosuppression, nausea and vomiting, mucositis, pruritus and dermatitis	CBC, dermatologic toxicities	Most commonly used in HSCT preparative regimens
Trabectedin	Myelosuppression, rhabdomyolysis, hepatotoxicity, nausea and vomiting, diarrhea or constipation, cardiomyopathy	CBC, CPK, liver function	Extravasation may lead to tissue necrosis
Triazenes (dacarbazine and temozolomide)	Myelosuppression, severe nausea and vomiting, increased liver enzymes, flu-like syndrome (may last for several days after dacarbazine administration), facial flushing, photosensitivity	CBC, liver function	Dispense in a light-proof bag Temozolomide crosses the blood-brain barrier, may cause lymphosuppression and requires PJP prophylaxis when given with radiation therapy
DNA Methyltransferase Inhibitors			
Azacitidine and	Myelosuppression and infection,	CBC, infection	Oral formulation decitabine/cedazuridine available

decitabine	constitutional symptoms, musculoskeletal symptoms (arthralgias), cough, dyspnea		
Immunomodulatory Imide Drugs			
Lenalidomide	Teratogen, fatigue, peripheral neuropathy, neutropenia and thrombocytopenia, thromboembolic events	CBC, signs of thrombosis, signs of peripheral neuropathies, pregnancy status	REMS program for fetal toxicity Adjust dose for renal impairment Prophylactic anticoagulation may be required
Pomalidomide	Teratogen, neutropenia, hepatotoxicity, thromboembolic events	Same as for lenalidomide	REMS program for fetal toxicity Adjust dose for renal and hepatic impairment Prophylactic anticoagulation may be required
Thalidomide	Teratogen, somnolence, constipation, dizziness or orthostatic hypotension, rash, peripheral neuropathy, thromboembolic events, increased HIV viral load	Same as for lenalidomide	REMS program for fetal toxicity Prophylactic anticoagulation may be required
Retinoids			
Bexarotene	Peripheral edema, insomnia, headache, fever, increased triglycerides and cholesterol, hypothyroidism, leukopenia and anemia, dry skin, increased liver enzymes, pancreatitis, photosensitivity	CBC, liver function, cholesterol and triglyceride levels, thyroid function	Avoid gemfibrozil to treat elevated triglycerides Limit vitamin A supplements May cause hypoglycemia in patients receiving insulin, sulfonylureas, or metformin Teratogenic, contraindicated in pregnancy, patients should be educated about proper contraceptive measures
Tretinoin	Headache, differentiation syndrome (consisting of pulmonary symptoms, fever, hypotension, and pleural effusions), dry skin and mucous membranes, mucositis, increases in liver enzymes and bilirubin	CBC, liver function, signs of differentiation syndrome	Differentiation syndrome must be treated promptly with corticosteroids Teratogenic, contraindicated in pregnancy, patients should be educated about proper contraceptive measures
Miscellaneous Agents			
Arsenic trioxide	Differentiation syndrome (pulmonary infiltrates, respiratory distress, fever, and hypotension), QTc prolongation, electrolyte abnormalities (hypokalemia, hyperkalemia, hypomagnesemia), hyperglycemia,	ECG, serum electrolytes (calcium, magnesium, potassium), renal function	Differentiation syndrome must be treated promptly with corticosteroids Do not give if QTc >500 msec Replace electrolytes before therapy

	rash, lightheadedness, fatigue, musculoskeletal pain		
Asparaginase	Anaphylaxis, thrombosis, pancreatitis, glucose intolerance, hemorrhage, hepatotoxicity	Pancreatic enzymes, liver function, glucose, coagulation parameters (fibrinogen, PT, PTT), hypersensitivity reactions, blood glucose, CBC	FDA-approved products include L-asparaginase, recombinant asparaginase (*Erwinia*), pegaspargase, and calaspargase pegol
Bleomycin	Anaphylaxis and hypersensitivity reactions, fever and flu-like symptoms, mucositis, pulmonary fibrosis	Obtain PFTs before use and if signs of pulmonary toxicity develop, monitor for anaphylactic reactions	Adjust dose for renal impairment Test dose (1 unit) is recommended but controversial; premedicate for subsequent doses with acetaminophen Pulmonary toxicity associated with cumulative dose >400 units and preexisting pulmonary disease
Hydroxyurea	Myelosuppression, rash, skin hyperpigmentation, TLS, secondary leukemias	CBC, uric acid	Dose may need to be adjusted with renal impairment (use with caution) Used to decrease white blood cell counts rapidly to prevent adverse effects of leukocytosis
Lanreotide	Abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hypertension, glucose abnormalities	Glucose, thyroid function, heart rate	Cholelithiasis and complications of cholelithiasis May need to adjust anti-diabetic medications in diabetic patients May decrease heart rate, use with caution in at-risk patients
Mitomycin	Myelosuppression (delayed and prolonged), mucositis, nausea and vomiting, vesicant, pulmonary fibrosis, hemolytic anemia and uremic syndrome	CBC, renal function, pulmonary function	Apply ice or cold packs to site for extravasation May be given intravenously or by intravesical administration; also available as a ureteral gel formulation
Omacetaxine	Myelosuppression (thrombocytopenia including increased risk of hemorrhage, anemia, neutropenia), diarrhea, nausea, fatigue, asthenia, injection site reaction, pyrexia, infection, lymphopenia, hyperglycemia	CBC, blood glucose	
Targeted Agents: Small Molecules			
Anaplastic Lymphoma Kinase (ALK) Inhibitors			

Alectinib	Fatigue, bradycardia, hepatotoxicity, anemia, constipation, edema, myalgia, visual disturbances	CBC, liver function, heart rate, CPK	Administer with food
Brigatinib	ILD and pneumonitis, hypertension, bradycardia, visual disturbances, CPK elevation, pancreatic enzyme elevation, hyperglycemia	HR, BP, pulmonary symptoms, CPK, pancreatic enzymes	Dose escalation required to decrease early-onset pulmonary symptoms Avoid strong CYP3A inhibitors and inducers; may affect hormonal contraceptives
Ceritinib	Gastrointestinal toxicity, increases in liver enzymes, fatigue, visual disturbances, QTc prolongation, bradycardia, hyperglycemia	CBC, renal function, liver function, blood glucose, pancreatic enzymes, cardiac monitoring, electrolytes	Administer on an empty stomach
Crizotinib	Nausea and vomiting, diarrhea, constipation, fatigue, increases in liver enzymes, visual disorders, edema, ILD, QTc prolongation, bradycardia	CBC, renal function, liver function, HR, BP, cardiac monitoring, electrolytes, pulmonary symptoms	Visual disorders (visual impairment, blurred vision, and photopsia) occur in approximately 50% of patients
Lorlatinib	Hepatotoxicity, CNS toxicity, hyperlipidemia, atrioventricular block, ILD and pneumonitis	Liver function, lipids, ECG	Strong CYP3A inducers are contraindicated, avoid strong CYP3A4 inhibitors and CYP3A4 substrates
B-Cell Lymphoma 2 (BCL-2) Inhibitors			
Venetoclax	TLS, myelosuppression, diarrhea, upper respiratory tract infection	CBC, uric acid, electrolytes	Ramp-up dose required Premedicate with anti-hyperuricemics and ensure adequate hydration Contraindicated with strong CYP3A inhibitors during initiation and ramp-up Avoid strong and moderate CYP3A inhibitors, strong or moderate CYP3A inducers, P-gp inhibitors, or narrow therapeutic substrates Avoid live-attenuated vaccines Administer with a meal
Breakpoint Cluster Region-Abelson (BCR-ABL) Inhibitors & Specifically Targeting the ABL Myristoyl Pocket (STAMP) INhibitor			
Asciminib	Myelosuppression, pancreatic toxicity, hypertension, hypersensitivity, infections, musculoskeletal pain, headache, fatigue, nausea, rash, diarrhea	CBC, liver function, lipase, amylase, uric acid, CPK, blood pressure	STAMP inhibitor demonstrating activity in patients with T315I mutation Avoid concomitant use of itraconazole oral solution containing hydroxypropyl-β-cyclodextran and CYP2C9 substrate drugs

			Close monitoring required with strong CYP3A4 inhibitors, select CYP3A4 substrates, and certain P-gp substrates Take on an empty stomach
Bosutinib	Nausea and vomiting, edema, pleural effusions and ascites, myelosuppression, CHF, arthralgias, rash, diarrhea, increased liver enzymes, hypophosphatemia	CBC, liver function, electrolytes, Philadelphia chromosome levels, signs of edema	Adjust dose for hepatic impairment Avoid antacids and PPIs Maintenance dose based on CBC Administer with food
Dasatinib	Nausea and vomiting, edema, pleural effusions and ascites, myelosuppression, CHF, arthralgias, fatigue, rash, diarrhea, increased liver enzymes, QTc prolongation, hypophosphatemia, hypocalcemia	CBC, liver function, electrolytes, signs of edema, Philadelphia chromosome levels	Avoid antacids, H_2 antagonists, and PPIs Maintenance dose based on CBC
Imatinib	Nausea and vomiting, edema, pleural effusions and ascites, myelosuppression, CHF, arthralgias, rash, diarrhea, increased liver enzymes, hypophosphatemia	CBC, liver function, electrolytes, Philadelphia chromosome levels, signs of edema	Dose adjustments should be considered with severe liver and moderate renal impairment May increase warfarin effects Maintenance dose based on CBC Take with meals and a full glass of water
Nilotinib	Nausea and vomiting, edema, myelosuppression, increased lipase, hyperglycemia, arthralgias, rash, diarrhea, increased liver enzymes, QTc prolongation	CBC, liver function, serum lipase, serum glucose, electrolytes, Philadelphia chromosome levels	Adjust dose for hepatic impairment Take on an empty stomach CYP3A4 substrate: avoid inhibitors Maintenance dose based on CBC Avoid PPIs, stagger administration with H_2 antagonists and antacids if use is necessary
Ponatinib	Myelosuppression, hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, pyrexia, thromboembolic events, hepatotoxicity, CHF, pancreatitis, hemorrhage (secondary to thrombocytopenia), fluid retention	Cardiac monitoring (CHF, arrhythmias), BP, pancreatic enzymes, fluid retention, CBC, liver function	May need to decrease dose or hold therapy if hepatotoxicity develops Avoid antacids and drugs that decrease gastric pH
BRAF Inhibitors			
Dabrafenib	Papilloma, arthralgia, alopecia, fatigue, headache, PPE, pyrexia	CBC, serum glucose, electrolytes, renal function, dermatologic evaluations	Take on an empty stomach
Encorafenib	Cutaneous and noncutaneous	Visual symptoms,	Avoid strong and moderate CYP3A inhibitors, strong

	malignancies, hemorrhage, uveitis, QTc prolongation	ophthalmologic evaluations, ECG, electrolytes	inducers, and sensitive CYP3A substrates Use nonhormonal contraceptives
Vemurafenib	Papilloma, arthralgia, alopecia, fatigue, headache, photosensitivity reaction, hypersensitivity reactions, QTc prolongation	Liver function, electrolytes, cardiac monitoring, dermatologic evaluations	Radiation sensitization/recall
Bruton's Tyrosine Kinase (BTK) Inhibitors			
Acalabrutinib	Infections, secondary primary malignancies, atrial flutter and fibrillation	CBC, cardiac monitoring	Avoid strong CYP3A inhibitors, strong CYP3A inducers Avoid PPIs, stagger administration with H_2 antagonists and antacids if use is necessary
Ibrutinib	Diarrhea, fatigue, musculoskeletal pain, nausea, rash, atrial fibrillation, hemorrhage, TLS, myelosuppression	CBC, renal function, liver function, uric acid levels, electrolytes, cardiac monitoring	Reduce dose with hepatic impairment Dose modifications for use with CYP3A inhibitors or inducers
Pirtobrutinib	Infections, secondary primary malignancies, atrial flutter and fibrillation	CBC, cardiac monitoring	Dose modifications for use with CYP3A inhibitors or inducers
Zanubrutinib	Myelosuppression, infections, secondary malignancies, cardiac arrhythmias, hemorrhage, rash, bruising, diarrhea, cough	CBC, liver function	Dose modifications for use with CYP3A inhibitors or inducers
Cyclin-Dependent Kinase (CDK) Inhibitors			
Abemaciclib	Diarrhea, neutropenia, hepatotoxicity, venous thromboembolism	CBC, electrolytes, liver function	Avoid moderate and strong CY3A inducers Dose reduce with moderate and strong CYP3A inhibitors Reduce dose with severe hepatic impairment
Palbociclib	Thromboembolic events, infection, bone marrow suppression, gastrointestinal toxicity	CBC, infection	Administer with food
Ribociclib	QTc prolongation, hepatobiliary toxicity, neutropenia	ECG, electrolytes, liver function, CBC	Avoid drugs known to prolong QTc interval, strong CYP3A inhibitors, strong CYP3A inducers, sensitive CYP3A substrates
Colony-Stimulating Factor-1 Receptor (CSF-1R) Inhibitors			
Pexidartinib	Hepatotoxicity, hair color change, rash,	Liver function,	REMS program for liver toxicity

	dysgeusia, edema of eyelid, fatigue	creatinine clearance	Dose adjustment for renal and hepatic impairment Administer with a low-fat meal (~11 to 14 grams total fat) Acid-reducing agents: Administer pexidartinib 2 hours before or 2 hours after locally-acting antacids; administer pexidartinib ≥2 hours before or 10 hours after a H2-receptor antagonist; avoid concomitant administration of pexidartinib with PPIs
Epidermal Growth Factor Receptor (EGFR) Inhibitors			
Afatinib	Rash, diarrhea, ILD, keratitis, stomatitis	Liver function, renal function, dermatologic evaluations, electrolytes, LVEF in patients with cardiac risk factors, pulmonary symptoms	Administer on an empty stomach
Dacomitinib	ILD, diarrhea, dermatologic toxicity	Pulmonary symptoms, skin	Avoid PPIs and sensitive CYP2D6 inhibitors Initiate use of moisturizers and appropriate measures to limit sun exposure
Erlotinib	Rash, diarrhea, ILD, hepatic and renal failure reported	Liver function, renal function, electrolytes, pulmonary symptoms, dermatologic evaluations	Dose reductions or delays may be required for rash but supportive care should be attempted first Major interaction with warfarin (may lead to increased bleeding risk) H_2 antagonists, PPIs, and antacids may decrease drug levels Administer on an empty stomach as food increases absorption and possibly toxicity
Gefitinib	Similar to erlotinib	Liver function, renal function, electrolytes, pulmonary symptoms, dermatologic evaluations	Similar precautions and drug interactions as with erlotinib
Mobocertinib	QTc prolongation, diarrhea, ILD/pneumonitis, decreases in LVEF	ECG, CBC, chemistries, amylase, lipase	Avoid strong CYP3A4 inhibitors and inducers Avoid drugs that prolong QTc
Osimertinib	Gastrointestinal toxicity, dermatologic toxicity, ILD/pneumonitis, pneumonia,	Cardiac monitoring (LVEF, QTc),	Avoid strong CYP3A4 inhibitors and inducers Avoid drugs that prolong QTc

	pulmonary embolism, cardiomyopathy, QTc prolongation	pulmonary symptoms, dermatologic evaluations	
Enhancer of Zeste Homolog 2 (EZH2) Inhibitors			
Tazemetostat	Myelosuppression, fatigue, nausea and vomiting, secondary malignancies	CBC	Avoid moderate/strong CYP3A4 inhibitors or inducers
Fibroblast Growth Factor Receptor (FGFR) Inhibitors			
Erdafitinib, Futibatinib, and Pemigatinib	Ocular disorders, hyperphosphatemia, stomatitis, creatinine increased, PPE, elevated liver enzymes	Ophthalmological exams, phosphate levels	Avoid moderate/strong CYP2C9 or inhibitors and inducers (erdafitinib), CYP3A4 inhibitors and inducers (erdafitinib and pemigatinib), and dual P-gp and CYP3A inhibitors and inducers (futibatinib) Increased phosphate levels are a pharmacodynamic effect
FMS-Like Tyrosine Kinase-3 (FLT3) Inhibitors			
Gilteritinib	PRES, QTc prolongation, pancreatitis, hypersensitivity	ECG, electrolytes	Avoid dual P-gp and CYP3A inducers and strong CYP3A inhibitors
Midostaurin	Pulmonary toxicity	ECG	Administer with food Avoid strong CYP3A inducers
Hedgehog Inhibitors			
Glasdegib	QTc prolongation, teratogenic effects	Pregnancy status, ECG	Boxed warning for severe birth defects and embryo-fetal death; advise females to use contraception during treatment and for 20 months after the last dose; advise males to use condoms during treatment and for at least 8 months after the last dose; do not donate blood during treatment and for 30 months after the last dose; do not donate sperm during treatment and for 8 months after the last dose
Sonidegib	Fatigue, alopecia, amenorrhea, musculoskeletal toxicity, teratogenic effects	Pregnancy status, CPK, renal function, liver function	Boxed warning for severe birth defects and embryo-fetal death; advise females to use contraception during treatment and for 20 months after the last dose; advise males to use condoms during treatment and for at least 8 months after the last dose; do not donate blood during treatment and for 20 months after the last dose; do not donate sperm during treatment and for 8 months after the last dose Avoid strong and moderate CYP3A modulators; moderate CYP3A inhibitors may be used for short

			term
Vismodegib	Muscle spasms, alopecia, dysgeusia, fatigue, nausea and vomiting, diarrhea, decreased appetite, constipation, arthralgias, teratogenic effects	Pregnancy status	Boxed warning for severe birth defects and embryo-fetal death; patients should not donate blood or blood products while receiving vismodegib and for at least 7 months after the last dose; verify pregnancy status within 7 days prior to treatment initiation; do not donate sperm during treatment and for 3 months after the last dose
Human Epidermal Growth Factor Receptor 2 (HER2) Inhibitors			
Lapatinib	Diarrhea, rash, nausea, vomiting, fatigue, decreases in LVEF, hepatotoxicity, QTc prolongation, ILD	Liver function, cardiac monitoring (LVEF, QTc), electrolytes, pulmonary symptoms	Adjust dose for severe hepatic impairment Administer on empty stomach Avoid strong CYP3A4 inhibitors (if unavoidable, consider dose reduction), avoid strong CYP3A4 inducers (if unavoidable, consider gradual dose increases)
Neratinib	Diarrhea, hepatotoxicity	Liver function, electrolytes	Use prophylactic antidiarrheals Lower starting dose for hepatic impairment Avoid PPIs, strong and moderate CYP3A inhibitors, strong and moderate CYP3A inducers, and sensitive P-gp substrates
Tucatinib	Diarrhea, hepatotoxicity	Liver function, Child-Pugh score, stool count	Dose adjustment recommended for hepatic impairment
Histone Deacetylase (HDAC) Inhibitors			
Belinostat	Pyrexia, nausea, fatigue, anemia, hepatotoxicity, infection, TLS	Liver function, renal function, CBC, uric acid levels	Empiric dose reduction in patients known to be homozygous for UGT1A1*28 allele
Romidepsin	Myelosuppression, infection, nausea and vomiting, fatigue, anorexia, ECG T-wave changes	CBC, cardiac monitoring (ECG), electrolytes	Monitor INR with concurrent use of warfarin
Vorinostat	Diarrhea, fatigue, nausea, thrombocytopenia, anorexia, dysgeusia, thromboembolic events, hyperglycemia	CBC, electrolytes, serum glucose, renal function	Avoid or adjust dose for hepatic impairment Increase in INR with concomitant warfarin Severe thrombocytopenia and GI bleeding have been reported with concomitant use with vorinostat and other HDAC inhibitors (eg, valproic acid)
Hypoxia-inducible Factor 2 Alpha (HIF-2α)			

Belzutifan	Anemia, hypoxia, nausea, increased glucose, fatigue, increased creatinine, headache	CBC, oxygen saturation, creatinine, liver function	Drug interactions with UGT2B17 or CYP2C19 inhibitors Monitor for signs/symptoms of anemia or hypoxia and reduce dose
Isocitrate Dehydrogenase (IDH) Inhibitors			
Enasidenib	Differentiation syndrome, TLS, myelosuppression, hepatotoxicity, nausea and vomiting	CBC, electrolytes, signs of differentiation syndrome	Differentiation syndrome may be life-threatening. If suspected, initiate oral or intravenous corticosteroids and hemodynamic monitoring until improvement Decrease dosage of OATP1B1, OATP1B3, BCRP, and P-gp substrates with coadministration
Ivosidenib	Differentiation syndrome, QTc prolongation, Guillain-Barré Syndrome, TLS	CBC, chemistries, CPK, ECG, electrolytes, signs of differentiation syndrome	Differentiation syndrome may be life-threatening. If suspected, initiate oral or intravenous corticosteroids and hemodynamic monitoring until improvement Reduce ivosidenib dose with strong CYP3A4 inhibitors Avoid strong CYP3A inducers; sensitive CYP3A substrates; drugs that prolong QTc interval Avoid high-fat meal
Olutasidenib	Differentiation syndrome, hepatotoxicity, nausea and vomiting	CBC, chemistries, liver function, signs of differentiation syndrome	Differentiation syndrome may be life-threatening. If suspected, initiate oral or intravenous corticosteroids and hemodynamic monitoring until improvement Avoid strong and moderate CYP3A inducers and sensitive CYP3A substrates Take on an empty stomach
Janus Kinase (JAK) Inhibitors			
Fedratinib	Encephalopathy, thrombocytopenia, anemia, nausea and vomiting, diarrhea, hepatotoxicity, amylase/lipase elevations	CBC, liver function, thiamine, symptoms of encephalopathy, pancreatic enzymes	Assess and replete thiamine at baseline and periodically Avoid coadministration with strong and moderate CYP3A4 inducers; avoid dual CYP3A4 and CYP2C19 inhibitors; and reduce fedratinib dose with strong CYP3A4 inhibitors Reduce dose for severe renal impairment, avoid use with severe hepatic impairment
Ruxolitinib	Thrombocytopenia, anemia, bruising, dizziness, headache, infections, cardiovascular abnormalities	CBC, renal function, liver function, cardiac monitoring	Consider dose adjustment for renal and hepatic impairment
Mitogen-Activated Protein Kinase-Extracellular Signal-Regulated Kinase (MEK) Inhibitors			
Binimetinib	Cardiomyopathy, venous thromboembolism, ILD, hepatotoxicity, rhabdomyolysis,	LVEF, ophthalmologic evaluation, liver	Reduce dose for moderate and severe hepatic impairment

	hemorrhage, ophthalmic events	function, CPK, renal function	
Cobimetinib and Selumetinib	Dermatologic toxicity, nausea and vomiting, pyrexia, hemorrhage, new primary malignancies, cardiomyopathy, ophthalmic events, hepatotoxicity, rhabdomyolysis	CBC, liver function, dermatologic evaluation, ophthalmologic evaluation, LVEF, CPK, electrolytes	Avoid coadministration with strong or moderate CYP3A inducers or inhibitors Selumetinib capsules contain vitamin E which may result in increased vitamin E levels and risk of bleeding
Trametinib	Diarrhea, lymphedema, hemorrhage, venous thromboembolism, febrile reactions, cardiomyopathy, dermatologic toxicity, hyperglycemia, hypertension, ophthalmic events	CBC, liver function, LVEF, ophthalmologic evaluation, dermatologic evaluation, BP	Capsules are stored refrigerated Administer on an empty stomach
Mesenchymal-Epithelial Transition (MET) Inhibitors			
Tepotinib and Capmatinib	Edema, fatigue, hepatotoxicity, dyspnea, musculoskeletal pain	Liver function, pulmonary symptoms	Modify dose for hepatotoxicity during treatment Take tepotinib with food
Mammalian Target of Rapamycin (mTOR) Inhibitors			
Everolimus	Rash, asthenia, stomatitis, nausea, edema, anorexia, anemia, pneumonitis, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypophosphatemia, elevated liver enzymes, elevated creatinine, lymphopenia, thrombocytopenia, leukopenia, infection	Metabolic toxicities, CBC, renal function, liver function, electrolytes, pulmonary symptoms	Adjust dose for hepatic impairment Cholesterol or diabetic medications may need to be initiated or dosages increased CYP3A4 and P-gp substrate; may require dose adjustment based on concurrent medication
Temsirolimus	Similar to everolimus with addition of infusion-related reactions	Similar to everolimus, infusion reactions	Adjust dose for hepatic impairment Requires diphenhydramine premedication
Nuclear Export Inhibitors			
Selinexor	Myelosuppression, nausea and vomiting, hyponatremia, diarrhea, weight loss, loss of appetite, neurotoxicity	CBC, electrolytes, volume status, weight	Dose adjustment for hyponatremia Maintain adequate fluid and caloric intake throughout treatment and consider IV hydration in patients at risk of dehydration
Poly ADP Ribose Polymerase (PARP) Inhibitors			
Niraparib	MDS/AML, myelosuppression, cardiovascular toxicity	CBC, liver function, BP, HR	Dose adjust for hepatic impairment and myelosuppression

Olaparib	MDS/AML, fatigue, musculoskeletal pain, dermatitis, nausea and vomiting, upper respiratory infections, anemia, pneumonitis	CBC, pulmonary symptoms	Reduce dose for renal impairment
Rucaparib	MDS/AML, nausea and vomiting	CBC	Adjust dose of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, if clinically indicated. If coadministration with warfarin cannot be avoided, consider increasing the frequency of INR monitoring
Talazoparib	MDS/AML, myelosuppression	CBC, renal function	Reduce starting dose for renal impairment Reduce dose with certain P-gp inhibitors
Platelet-Derived Growth Factor Receptor-alpha (PDGFR-α) Inhibitors			
Avapritinib	Edema, hair color change, rash, abdominal pain, fatigue, excessive tear production, anemia, CNS toxicity	Liver function, CBC	Dose adjustment for hepatic impairment Dose adjustment for concomitant CYP3A4 inhibitors Take on empty stomach
Ripretinib	Arthralgia/myalgia, hypertension, LV dysfunction, dermatologic toxicity, alopecia, abdominal pain, constipation, diarrhea, nausea and vomiting	LVEF, BP, dermatologic evaluation	Withhold for at least 1 week prior to elective surgery; do not administer for at least 2 weeks following major surgery and until adequate wound healing
Phosphatidylinositide 3-Kinase (PI3K) Inhibitors			
Alpelisib	Dermatologic reactions, severe diarrhea, pneumonitis, hyperglycemia, severe hypersensitivity reactions	Blood glucose, dermatologic evaluation, pulmonary symptoms	Avoid strong CYP3A inducers, closely monitor with concurrent CYP2C9 substrates (eg, warfarin)
Copanlisib	Infections, hyperglycemia, hypertension, pneumonitis, neutropenia, dermatologic reactions	CBC, blood glucose, BP	Reduce dose with strong CYP3A inhibitors; avoid strong CYP3A inducers Consider PJP prophylaxis
Duvelisib	Infections, neutropenia, fatal/serious diarrhea, dermatologic reactions, pneumonitis, hepatotoxicity	CBC, liver function, dermatologic evaluation, pulmonary symptoms, GI symptoms	REMS program for infections, diarrhea/colitis, cutaneous reactions, and pneumonitis Avoid strong CYP3A inducers; reduce moderate and strong CYP3A inhibitors PJP prophylaxis required; consider antiviral prophylaxis for CMV
Idelalisib	Fatal/serious diarrhea, intestinal	Liver function, CBC,	REMS program for hepatoxicity, diarrhea/colitis,

	perforation, hepatotoxicity, pneumonitis, infections, neutropenia, dermatologic reactions, anaphylaxis	dermatologic evaluation, pulmonary symptoms, GI symptoms	pneumonitis, infections, intestinal perforation PJP prophylaxis required
Proteasome Inhibitors			
Bortezomib	Fatigue or malaise, nausea and vomiting, diarrhea, anorexia, constipation, myelosuppression (especially thrombocytopenia), hyponatremia, hypokalemia, peripheral neuropathy (cumulative and dose-related), fever	CBC, thyroid function, symptoms of neuropathy, electrolytes	Adjust dose for hepatic impairment Administer IV or subcutaneous (subcutaneous administration has been shown to decrease neuropathies); increased risk of severe neuropathy with preexisting neuropathy Coadministration with strong CYP3A4 inhibitors can increase bortezomib concentrations
Carfilzomib	Fatigue, anemia, thrombocytopenia, nausea, diarrhea, dyspnea, pyrexia, infusion-related reactions, rare reports of cardiac arrest, CHF, and MI	Pulmonary symptoms, CBC, liver function, cardiac monitoring, infusion reactions	Premedicate with dexamethasone before all cycle 1 doses then as needed for future cycles to reduce the incidence of infusion reactions
Ixazomib	Gastrointestinal toxicity, thrombocytopenia, peripheral neuropathy, edema, cutaneous reactions, hepatotoxicity	CBC, liver function, dermatologic evaluation	Administer on an empty stomach Reduce starting dose for hepatic or renal impairment Avoid use with strong CYP3A4 inducers Consider antiviral prophylaxis
Ras Inhibitors			
Adagrasib	QTc prolongation, nausea and vomiting, diarrhea, musculoskeletal pain, hepatotoxicity, renal impairment, edema, dyspnea, ILD/pneumonitis	ECG, electrolytes, liver function, pulmonary symptoms	Avoid concurrent use with the following: strong CYP3A4 inducers and inhibitors; sensitive substrates of CYP3A4, CYP2C9, CYP2D6, and P-gp; and drugs that prolong the QTc interval Antiemetic and antidiarrheals may be necessary
Sotorasib	Hepatotoxicity, ILD, diarrhea, musculoskeletal pain, fatigue, cough	Pulmonary symptoms, liver function	Avoid coadministration with PPIs and H2 antagonists Avoid coadministration with strong CYP3A4 inducers, CYP3A4 substrates, and P-gp substrates
Rearranged during Transfection (RET) Inhibitors			
Pralsetinib	Edema, constipation, diarrhea, hepatoxicity, musculoskeletal pain, cough, fatigue, hypertension	Liver function, BP	Take on empty stomach Avoid use with strong CYP3A4 inducers and inhibitors Withhold at least 5 days prior to elective surgery. Do not administer for at least 2 weeks after surgery and until adequate wound healing
Selpercatinib	Thrombocytopenia, hemorrhage, hypertension, QTc prolongation, rash,	CBC, liver function, BP, QTc	Avoid moderate/strong CYP3A inhibitors Avoid PPIs, H2 antagonists, and antacids

	constipation, diarrhea, xerostomia, impaired wound healing		Dose adjustment with hepatic impairment Withhold for at least 1 week prior to elective surgery; do not administer for at least 2 weeks following major surgery and until adequate wound healing
Tropomyosin Receptor Kinase (TRK) Inhibitors			
Entrectinib	Cardiotoxicity, CNS toxicity, hepatoxicity, vision disorders, skeletal fractures	CBC, liver function, uric acid, ECG, electrolytes	Avoid strong CYP3A inhibitors, if coadministration cannot be avoided, dose adjust entrectinib
Larotrectinib	Neurotoxicity, hepatotoxicity	Liver function	Avoid strong CYP3A inhibitors and inducers; avoid sensitive CYP3A substrates Reduce starting dose in moderate or severe hepatic impairment
Vascular Endothelial Growth Factor Receptor (VEGFR) Multikinase Inhibitors			
Axitinib	Diarrhea, rash, PPE, bleeding, thrombotic events, hypertension, hepatotoxicity, hypothyroidism, proteinuria, GI perforation, fatigue, rare reports of RPLS	CBC, liver function, BP, thyroid function, urine protein, neurologic evaluation, dermatologic evaluation	Blood pressure should be well-controlled prior to administration Hold for at least 2 days prior to elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing Adjust dose for hepatic impairment Substrate of CYP3A4, may require dose adjustment based on concurrently administered medication
Cabozantinib	Diarrhea, stomatitis, PPE, decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, constipation, increased liver enzymes, proteinuria, lymphopenia, neutropenia, thrombocytopenia, hypocalcemia, hypophosphatemia, GI perforations and fistulas, hemorrhage	BP, urine protein, CBC, liver function, thyroid function, electrolytes, dermatologic evaluation	Blood pressure should be well-controlled prior to administration Hold for at least 3 weeks prior to elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing Adjust dose for hepatic impairment Substrate of CYP3A4, may require dose adjustment based on concurrently administered medication
Lenvatinib	Hypertension, fatigue, diarrhea, proteinuria, stomatitis, PPE, hypothyroidism, hepatotoxicity, thromboembolic events, renal toxicity, hypocalcemia, GI perforation	Liver function, renal function, thyroid function, BP, electrolytes	Blood pressure should be well-controlled prior to administration Hold for at least 1 week prior to elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing Adjust dose for severe hepatic and renal impairment Weight-based dosing for HCC
Pazopanib	Diarrhea, hypertension, hair/skin hypopigmentation, nausea, anorexia,	Liver function, cardiac monitoring	Blood pressure should be well-controlled prior to administration

	vomiting, decreased weight, fatigue, musculoskeletal pain, dysgeusia, dyspnea, hypothyroidism, proteinuria, fatal hepatotoxicity, thromboembolic events	(ECG), BP, thyroid function, urine protein, dermatologic evaluation	Hold for at least 1 week prior to elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing Adjust dose for hepatic impairment Take on empty stomach Reduce dose when administered with strong CYP3A4 inhibitors, avoid CYP3A4 inducers, concomitant use with simvastatin increases liver enzymes
Regorafenib	Asthenia, fatigue, decreased appetite, PPE, diarrhea, mucositis, weight loss, infection, hypertension, dysphonia, hepatotoxicity, hemorrhage	Liver function, BP, dermatologic evaluation	Blood pressure should be well-controlled prior to administration Hold for at least 2 weeks prior to elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing Administer with food (low-fat breakfast that contains <30% fat) Monitor INR closely with concomitant warfarin because of an increased risk of hemorrhage
Sorafenib	Diarrhea, rash, PPE, fatigue, hypertension, prolonged QTc interval, cardiac events (including MI), hepatitis	BP, liver function, cardiac monitoring, electrolytes, dermatologic evaluation	Blood pressure should be well-controlled prior to administration Hold for at least 10 days prior to elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing Administer on an empty stomach May increase the anticoagulation effects of warfarin
Sunitinib	Diarrhea, rash, bleeding, CHF and cardiac effects, QTc prolongation, fatigue, hypertension, hepatotoxicity, thyroid dysfunction	CBC, liver function, BP, thyroid function, cardiac monitoring (CHF, ECG), electrolytes	Blood pressure should be well-controlled prior to administration Hold for at least 3 weeks prior to elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing CYP3A4 substrate, may require dose adjustment based on concurrent medications
Tivozanib	Diarrhea, hypertension, decrease appetite, stomatitis, thyroid dysfunction, proteinuria, thromboembolic events	BP, liver function, proteinuria, thyroid function	Blood pressure should be well-controlled prior to administration Hold for at least 24 days prior to elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing Avoid strong CYP3A4 inducers Dose adjustment for hepatic impairment
Vandetanib	Diarrhea, rash, acne, nausea, hypertension, headache, fatigue, upper respiratory tract infections, decreased appetite, abdominal pain,	Liver function, electrolytes, cardiac monitoring (ECG), BP, pulmonary	Hold for at least 1 month prior to elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing REMS program for QTc prolongation and sudden

	QTc prolongation, torsades de pointes and sudden death, ILD, hemorrhage, increased liver enzymes	symptoms, dermatologic evaluation	death; avoid other medications that prolong the QTc interval Adjust dose for renal impairment Advise patients to wear sunscreen and protective clothing when exposed to sun
Targeted Agents: mAbs & ADCs			
Antibodies That Target CD19			
Loncastuximab tesirine	Myelosuppression, edema, dermatologic toxicity, musculoskeletal pain	CBC, infection, skin evaluation	ADC with payload SG3199 (an alkylating agent) Premedicate with dexamethasone
Tafasitamab	Myelosuppression, infusion-related reactions, edema, decrease appetite, diarrhea, fatigue, fever	CBC, infusion-related reactions, infection	Premedication (may include acetaminophen, an H1 receptor antagonist, an H2 receptor antagonist, and/or glucocorticoids) for initial infusion, may discontinue for subsequent infusions
Antibodies That Target CD20			
Obinutuzumab	Infusion-related reactions, myelosuppression, nausea, diarrhea, PML, HBV reactivation	CBC, hepatitis B screening at baseline, renal function, electrolytes, infusion-related reactions, fluid status	Patients should be screened for hepatitis B before therapy initiation Antimicrobial, antiviral, and antifungal prophylaxis in select patients Anti-hyperuricemic prophylaxis and hydration if risk for TLS Premedicate with acetaminophen, an antihistamine, and a glucocorticoid
Ofatumumab	Neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, upper respiratory infection	Infusion-related reactions, CBC, hepatitis B screening at baseline	Restricted distribution program allows access for select patients Patients should be screened for hepatitis B before therapy initiation Premedicate with acetaminophen, antihistamine, and corticosteroid Infusion rate-escalation required
Rituximab	Hypersensitivity reactions and infusion-related reactions, TLS (especially with large tumor burden), myelosuppression and infection, rare reports of PML, severe skin reactions, myalgias, tachycardia	Infusion-related reactions, CBC, neurologic examination, hepatitis B screening at baseline, electrolytes, HR, BP	Patients should be screened for hepatitis B before therapy initiation Infusion-related reactions may be severe; increase rate of infusion gradually and premedicate with acetaminophen and diphenhydramine Rituximab and hyaluronidase available for subcutaneous injection after 1 full dose of IV rituximab

Antibodies That Target CD22			
Inotuzumab ozogamicin	Myelosuppression, infusion-related reactions, QTc interval prolongation, hepatotoxicity	CBC, ECG, infusion-related reactions, liver function	ADC with a calicheamicin derivative payload Premedicate with a corticosteroid, antipyretic, and antihistamine
Antibodies That Target CD30			
Brentuximab vedotin	Neutropenia, peripheral neuropathy, fatigue, nausea and vomiting, anemia, diarrhea, rash, thrombocytopenia, infusion-related reactions, TLS, rare reports of PML	CBC, symptoms of neuropathy, infusion-related reactions, uric acid levels, electrolytes	ADC with payload MMAE (a microtubule disrupting agent) Adjust dose for renal and hepatic impairment
Antibodies That Target CD33			
Gemtuzumab ozogamicin	Hypersensitivity and infusion-related reactions, hemorrhage	Infusion-related reactions	ADC with a calicheamicin derivative payload Premedicate with a corticosteroid, antihistamine, and acetaminophen
Antibodies That Target CD38			
Daratumumab	Infusion-related reactions, pyrexia, fatigue, upper respiratory tract infection, nausea, myelosuppression	CBC, acute or delayed infusion-related reactions	Type and screen patients prior to starting treatment as daratumumab may interfere with cross-matching and red blood cell antibody screening Premedicate with corticosteroids, antipyretics, and antihistamines; administer post-infusion medications Available as subcutaneous injection in combination with hyaluronidase
Isatuximab	Myelosuppression, infusion-related reactions, hypertension, diarrhea, infection, secondary malignancies	CBC, infusion-related reactions, BP	Premedicate with acetaminophen, H1 and H2 antagonist; also administer dexamethasone prior to administration Antiviral prophylaxis recommended
Antibodies That Target CD52			
Alemtuzumab	Myelosuppression and immunosuppression, autoimmune conditions, infection, infusion-related reactions, nausea and vomiting, fever, hypotension, rash, headache, fatigue, secondary malignancies	CBC, infusion-related reactions, CMV, $CD4^+$ counts, HR, BP, autoimmune symptoms, symptoms of infection	Restricted distribution program allows access for select patients Patients should be started on antiviral and PJP prophylaxis during and for 6 months post-treatment
Antibodies That Target CD79B			
Polatuzumab	Peripheral neuropathy, infusion-	CBC, symptoms of	ADC with payload MMAE (a microtubule disrupting

vedotin	related reactions, myelosuppression, infections, TLS, hepatotoxicity	neuropathy, infusion-related reactions, uric acid levels, electrolytes, liver function	agent) Premedicate with an antihistamine and antipyretic
Antibodies That Target Chemokine Receptor			
Mogamulizumab	Dermatologic reactions, infusion-related reactions, infections, autoimmune complications, complications of allogeneic HSCT	Infusion-related reactions	Administer diphenhydramine and acetaminophen for the first infusion
Antibodies That Target Folate Receptor Alpha			
Mirvetuximab soravtansine	Ocular toxicity, pneumonitis, peripheral neuropathy, nausea, fatigue	CBC, chemistries, liver function, ophthalmic exam	ADC with payload DM4 (an anti-tubulin agent) Premedicate with corticosteroid, antihistamine, antipyretic, and antiemetic Administer prophylactic artificial tears and ophthalmic topical steroids Dose is based on adjusted body weight
Antibodies That Target GD2 Receptor			
Dinutuximab	Infections, infusion-related reactions, hypokalemia, hypotension, capillary leak syndrome, neurological ocular toxicity, pain, bone marrow suppression, hemolytic uremic syndrome	CBC, electrolytes, renal function, BP, infusion-related reactions	Premedicate with IV analgesics (such as morphine), an antihistamine, acetaminophen, antiemetics, and IV hydration
Naxitamab	Edema, hypertension, tachycardia, dermatologic toxicity, diarrhea, nausea and vomiting, headache, peripheral neuropathy, anxiety, irritability, cough, fever, infusion-related reactions	BP, HR, infusion-related reactions	Premedications and supportive medications (pain management): 5 days prior to the first infusion in each cycle, initiate a 12-day course (day 4 through day 7) of prophylactic medication for neuropathic pain (eg, gabapentin); give oral opioids 45 to 60 minutes prior to initiation of each infusion with additional IV opioids as needed for breakthrough pain during infusion; consider ketamine for pain not adequately controlled by opioids
Antibodies That Target Nectin-4			
Enfortumab vedotin	Myelosuppression, peripheral neuropathy, ocular toxicity, dermatologic toxicity, alopecia, diarrhea, dysgeusia, decreased appetite, hyperglycemia	CBC, blood glucose, liver function, Child-Pugh score	ADC with payload MMAE (a microtubule disrupting agent) Dose capped at 125 mg Avoid use in Child-Pugh classes B and C

Antibodies That Target EGFR			
Cetuximab, necitumumab, and panitumumab	Rash, paronychial cracking in fingers or toes, asthenia, abdominal pain, nausea, constipation, diarrhea, infusion and hypersensitivity reactions, electrolyte wasting, cardiopulmonary arrest	Electrolytes, infusion-related reactions, dermatologic evaluation	Dose reductions or delays may be required for rash but supportive care should be attempted first Decreased risk of infusion-related reactions with panitumumab and does not appear to be cross-reactive (ie, a patient may receive panitumumab if they react to cetuximab) Monitor patients during treatment for hypomagnesemia, hypocalcemia, and hypokalemia, and for at least 8 weeks following the completion of therapy
Antibodies That Target EGFR and MET			
Amivantamab	Pulmonary toxicity, rash, paronychia, ocular toxicity, infusion-related reactions, nausea and vomiting	Infusion-related reactions, pulmonary symptoms, dermatologic evaluations	A bispecific antibody that binds both EGFR and MET The first two infusions should be administered via peripheral line Premedication is required
Antibodies That Target HER2			
Ado-trastuzumab emtansine	Cardiac toxicity, thrombocytopenia, hemorrhage, hepatotoxicity, infusion-related reactions, peripheral neuropathy, ILD, embryo-fetal toxicity	CBC, liver function, pregnancy status, cardiac monitoring (LVEF), pulmonary symptoms	ADC with payload DM1 (a microtubule inhibitor) Ado-trastuzumab emtansine is NOT interchangeable with other antibodies that target HER2
Fam-trastuzumab deruxtecan	Myelosuppression, decrease LVEF, ILD, constipation, diarrhea, decrease appetite, nausea and vomiting	CBC, LVEF, liver function, pulmonary symptoms, fever	ADC with payload DXd (a topoisomerase I inhibitor) Fam-trastuzumab deruxtecan is NOT interchangeable with other antibodies that target HER2
Margetuximab	Alopecia, cardiac toxicity (hypertension and decrease LVEF), abdominal pain, diarrhea, nausea and vomiting, headache, fatigue, fever, infusion-related reactions	LVEF, BP, infusion-related reactions	Consider premedications (including antihistamines, corticosteroids, and antipyretics) with future cycles if a mild to moderate infusion reaction occurs
Pertuzumab	Diarrhea, nausea, alopecia, rash, neutropenia, fatigue, peripheral neuropathy, embryo-fetal toxicity, left ventricular dysfunction, infusion-related reactions	LVEF, infusion-related reactions, pregnancy status	Available in combination with trastuzumab and hyaluronidase as a single subcutaneous injection
Trastuzumab	Cardiac toxicity (congestive cardiomyopathy, usually reversible	Infusion-related reactions, cardiac	Do not administer with anthracyclines because of increased cardiotoxicity

	with medical management), infusion-related reactions, pulmonary toxicity, embryo-fetal toxicity	monitoring (LVEF)	Trastuzumab is NOT interchangeable with other antibodies that target HER2 Trastuzumab with hyaluronidase available for subcutaneous injection
Antibodies That Target SLAMF7 (Signaling Lymphocytic Activation Molecule Family 7)			
Elotuzumab	Fatigue, pyrexia, diarrhea or constipation, respiratory infections, peripheral neuropathy, hepatotoxicity, infusion-related reactions, secondary primary malignancies	Liver function, infusion-related reactions, infections	May interfere with the assay used to monitor M-protein which can impact the determination of complete response Premedicate with dexamethasone, diphenhydramine, an H2 antagonist, and acetaminophen
Antibodies That Target Tissue Factor			
Tisotumab vedotin	Ocular toxicity, peripheral neuropathy, hemorrhage, pneumonitis, alopecia, fatigue, creatinine increase, diarrhea, rash	CBC, liver function, CPK, PT/PTT/INR. chemistries, ophthalmic exam	ADC with payload MMAE (a microtubule disrupting agent) Corticosteroid eye drops, vasoconstrictor eye drops, and lubricating eye drops are recommended before, during, and after infusion Cold packs placed on eyes are recommended during infusion
Antibodies That Target TROP2 (Trophoblast Cell-Surface Antigen 2)			
Sacituzumab govitecan	Myelosuppression, nausea and vomiting, alopecia, rash, abdominal pain, fatigue, hypersensitivity reaction	CBC, infusion-related reactions	ADC with payload SN-38 (a topoisomerase I inhibitor) Premedication with corticosteroids, an H1 and H2 antagonist Patients who are homozygous for the UGT1A1*28 allele are at increased risk of toxicity
Antibodies That Target VEGFR			
Bevacizumab	GI perforation, impaired wound healing, hypertension, proteinuria, thrombotic events, hemorrhage, rare reports of RPLS	BP, urine protein, neurologic examination, signs of GI perforation, symptoms of thromboembolism	Withhold 28 days prior to elective surgery. Do not administer for at least 2 weeks following a major surgical procedure and until adequate wound healing
Ramucirumab	GI perforation, impaired wound healing, hypertension, proteinuria, thyroid dysfunction, thromboembolic events, hemorrhage	BP, urine protein, thyroid function, liver function	Withhold 28 days prior to elective surgery. Do not administer for at least 2 weeks following a major surgical procedure and until adequate wound healing
Bispecific T-Cell Engagers			
Blinatumomab	Infusion-related reactions, cytokine release syndrome, neurologic	CBC, liver function, neurological	Premedicate with dexamethasone prior to the first dose of each cycle, prior to a step dose or when

	toxicities, infections, fever, headache, peripheral edema, rash, TLS, hepatotoxicity, bone marrow suppression	examination, uric acid levels, electrolytes	restarting therapy after an interruption >4 hours Administered as a continuous intravenous infusion over 28 days
Mosunetuzumab	Cytokine release syndrome, neurotoxicity, infections, myelosuppression, tumor flare, fatigue, rash, pyrexia	CBC, uric acid, chemistries, neurologic exam	Step-up dosing to reduce cytokine release syndrome If treatment delay, recommendations for restarting therapy are available Premedicate with corticosteroid, antipyretic, antihistamine
Teclistamab	Cytokine release syndrome, neurotoxicity, infections, cardiovascular toxicity, electrolyte abnormalities, hypogammaglobulinemia	IgG, CBC, liver function, renal function, chemistries, neurologic exam	REMS to mitigate the risk of cytokine release syndrome and neurologic toxicity Step-up dosing to reduce cytokine release syndrome Premedicate with corticosteroid, antipyretic, antihistamine
Fusion Proteins			
Moxetumomab pasudotox	Renal toxicity, infusion-related reactions, electrolyte abnormalities, hemolytic uremic syndrome	Renal function, electrolytes, infusion-related reactions	Premedicate with acetaminophen, an antihistamine, and an H2 antagonist Consider low-dose aspirin on days 1-8 of each cycle
Tebentafusp	Cytokine release syndrome, edema, hypotension, dermatologic reactions, elevated liver enzymes	CBC, liver function, chemistries	Administer first 3 doses (step-up dosing) in appropriate healthcare setting with immediate access to medications to manage cytokine release syndrome
Ziv-aflibercept	Myelosuppression, diarrhea, proteinuria, increases in liver enzymes, stomatitis, fatigue, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, increased serum creatinine, headache, hemorrhage, GI perforation, compromised wound healing, arterial thromboembolic events, fistula formation	BP, urine protein, signs and symptoms of hemorrhage, CBC, liver function, renal function	Hold at least 4 weeks before elective surgery and restart at least 4 weeks after major surgery and after the surgical wound is fully healed
Immunotherapy			
Immune Checkpoint Inhibitors			
Ipilimumab and tremelimumab	Fatigue, irAEs (eg, enterocolitis, dermatitis, endocrinopathy, hepatitis), infusion-related reactions (rare)	Thyroid function, electrolytes, liver function, renal function, dermatologic evaluations, GI symptoms, consider CBC	Treat severe irAEs with corticosteroids

Atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, nivolumab, and pembrolizumab	Fatigue, irAEs (eg, pneumonitis, colitis, hepatitis, thyroid dysfunction)	Liver function, renal function, thyroid function, GI symptoms	Treat severe irAEs with corticosteroids For avelumab, premedicate with an antihistamine and acetaminophen prior to the first four infusions
Nivolumab/ relatlimab	Fatigue, irAEs (eg, pneumonitis, colitis, hepatitis, thyroid dysfunction)	Liver function, renal function, thyroid function, GI symptoms	Available as a fixed-dose combination Treat severe irAEs with corticosteroids
Cytokines			
Interleukin-2	Flu-like syndrome (fevers, chills, malaise), vascular or capillary leak syndrome (hypotension, pulmonary and peripheral edema), nausea and vomiting, diarrhea, nephrotoxicity, myelosuppression (thrombocytopenia and leukopenia), bacterial infections, CNS toxicities (somnolence and confusion), arrhythmias, rash, itching	Intense monitoring required, electrolytes, liver function, renal function, CBC, thallium stress test, pulmonary function tests, cardiac monitoring during administration, BP, HR	Vasopressor support and fluid resuscitation may be necessary during treatment because of hypotension Pulmonary edema can be managed with cautious use of diuretics; short courses of albumin may also be beneficial Itching may respond to treatment with antihistamines; emollient skin creams or occlusive agents are effective for dry, peeling skin Avoid corticosteroids because they may counteract the antitumor effects of interleukin-2 Patients on beta-blockers will need to be tapered off before initiation of interleukin-2
Therapeutic Vaccines			
Sipuleucel-T	Infusion-related reactions, chills, fatigue, back pain, nausea, joint ache, headache, thromboembolic events have occurred	Infusion-related reaction	Physicians and patients must be registered Premedicate with an antihistamine and acetaminophen For autologous use only
Talimogene laherparepvec	Fatigue, chills, pyrexia, nausea, influenza-like illness, injection-site pain, cellulitis, risk of herpetic infection	Herpetic infections, injection-site complications, immune-mediated events	Administered directly into the cutaneous, subcutaneous, and/or nodal lesion(s) Precautions for accidental exposure of healthcare workers and close contacts Acyclovir and other antiviral medications may interfere with the efficacy
Chimeric Antigen Receptor (CAR) Therapies			
Axicabtagene ciloleucel, brexucabtagene autoleucel,	Hypersensitivity, myelosuppression, hypogammaglobulinemia, secondary malignancies, neurologic toxicities, cytokine release syndrome	CBC, infection, cytokine release syndrome, neurologic	For autologous use only REMS program to mitigate the risk of cytokine release syndrome and neurological toxicities

idecabtagene vicleucel, lisocabtagene maraleucel, tisagenlecleucel		examinations	

[a]Only approximate guidelines can be given. Consult current references before dispensing as not all dose adjustments and monitoring parameters are provided in the table.

Data from Reference 4.

BP, blood pressure; CBC, complete blood count; CHF, congestive heart failure; CMV, cytomegalovirus; CPK, creatine phosphokinase; CYP, cytochrome P450 isoenzyme; DXd, DX-8951 derivative; GI, gastrointestinal; H1 and H2, histamine 1 and 2; HCC, hepatocellular carcinoma; HHV-8, human herpes virus 8; HIF-2α, hypoxia-inducible factor 2 alpha, HIV, human immunodeficiency virus; HR, heart rate; ILD, interstitial lung disease; IM, intramuscular; INR, international normalized ratio; IT, intrathecal; IV, intravenous; MAOI, monoamine oxidase inhibitor; MI, myocardial infarction; MMAE, monomethylauristatin E; PFTs, pulmonary function tests; PJP, pneumocystis jirovecii pneumonia; PML, progressive multifocal leukoencephalopathy; PPIs, proton pump inhibitors; PRES, posterior reversible encephalopathy syndrome; PT, prothrombin time; PTT, partial thromboplastin time; RPLS, reversible posterior leukoencephalopathy syndrome; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; SSRI, selective serotonin reuptake inhibitor; STAMP, specifically targeting the ABL myristoyl pocket; TCA, tricyclic antidepressant.

Antimetabolites

Antimetabolites are similar to the nucleotides that make up DNA and RNA. The body mistakes these chemotherapy agents for the naturally occurring nucleotide bases and metabolizes these agents as the natural nucleotides. These chemotherapy agents ultimately disrupt replication and cell division by interfering with the production of nucleic acids, DNA, and RNA. Unfortunately, these compounds are not selective for cancer cells, and rapidly dividing normal cells may be affected. The most common toxicities associated with the antimetabolites are secondary to their effect on rapidly dividing normal cells, such as bone marrow and gastrointestinal tract cells. The three major classes of antimetabolites include pyrimidine analogues, purine analogues, and folate antagonists. Hypomethylating agents are also considered antimetabolites.

Pyrimidine Analogues

Cytarabine

Cytarabine is a cytidine analogue commonly used to treat AML, acute lymphoblastic leukemia (ALL), and NHL. It is phosphorylated to its active phosphates within cancer cells and inhibits DNA polymerase, an enzyme responsible for strand elongation. It is also incorporated directly into DNA, where it inhibits DNA replication and acts as a chain terminator to prevent DNA elongation. Deaminase enzymes, particularly cytidine deaminase, degrade cytarabine and other cytidine analogues.

Cytarabine may be given intravenously or intrathecally. Intrathecal administration allows for cytotoxic concentrations of cytarabine to be maintained in the central nervous system (CNS) for several hours. It may be given to patients with leukemia.

The dose-limiting toxicities are leukopenia and thrombocytopenia. Other common toxicities include nausea, vomiting, mucositis, and diarrhea. Following administration of high-dose cytarabine (greater than 1 g/m^2 per dose), cerebellar syndrome may occur presenting with dysarthria, nystagmus, and ataxia. The risk of cerebellar syndrome is strongly correlated with advanced age and renal dysfunction. Renal dysfunction permits accumulation of high levels of triphosphate, which is believed to be neurotoxic. Hepatic dysfunction, high cumulative doses, and bolus dosing may also increase the risk of neurotoxicity. Conjunctivitis or keratitis is another common toxicity associated with high-dose cytarabine. Prophylactic corticosteroid or saline eye drops should be administered with high-dose cytarabine to minimize irritation. Allopurinol may be given with high-dose cytarabine to minimize the risk of tumor lysis syndrome (TLS), a group of metabolic complications that can occur following the breakdown of dying cancer cells.

Fluoropyrimidines

Fluorouracil (sometimes referred to as 5-FU) is a fluorinated uracil analogue initially synthesized in the late 1950s. It acts as a false pyrimidine and undergoes sequential phosphorylation to a mono-, di-, and triphosphate similar to natural nucleotide bases. In the presence of folates, the monophosphate binds tightly to and interferes with the function of thymidylate synthase. The triphosphate metabolite is incorporated into RNA as a false base and interferes with its function. The interference with both thymidine formation and RNA function contributes to its cytotoxic effects. Fluorouracil is commonly used to treat gastrointestinal tract and head-and-neck cancers.

The dosage and administration influence both the mechanism of action and toxicity profile. With continuous-infusion regimens, the inhibition of thymidylate synthesis plays a greater role, and dose-limiting toxicities include palmar-plantar erythrodysesthesia (PPE) and diarrhea. Comparatively, the incorporation into RNA plays a greater role with intermittent bolus schedules. The dose-limiting toxicity commonly associated with a bolus administration is myelosuppression.

Several pharmacologic strategies have been attempted to increase its cytotoxicity against cancer cells and decrease its toxicity to normal cells. The most common strategy combines fluorouracil with the reduced folate leucovorin. Folates increase the reduced folate pool, stabilize the monophosphate–thymidylate synthase complex, and prolong the inhibition of thymidylate synthase. Clinical trials suggest that combining reduced folates with fluorouracil provides greater anticancer activity and improves tolerability.

Dihydropyrimidine dehydrogenase (DPD) is a pyrimidine catabolic enzyme responsible for about 80% of the catabolism of fluorouracil. Reduced expression of this enzyme has been associated with drug accumulation and serious adverse drug reactions. DPD deficiency is an autosomal recessive genetic disorder, with genetic variation in the *DPYD* gene associated with reduced enzyme activity. DPD deficiency occurs in up to 5% of the overall population. Fluorouracil is contraindicated in patients with known DPD deficiency.

Capecitabine is an oral pyrimidine uracil analogue used to treat breast and colon cancers. Because capecitabine is enzymatically converted to fluorouracil, it shares the same mechanisms of action. Capecitabine is typically taken twice daily with food for the first 14 days of a 21-day treatment cycle. Since chronic twice-daily oral dosing produces sustained fluorouracil levels similar to those observed with continuous infusions, PPE and diarrhea are the dose-limiting toxicities.

Uridine triacetate is a pro-drug of uridine and competitively inhibits fluorouracil-mediated cell damage. It is approved for the emergency treatment of adult and pediatric patients following a fluorouracil or capecitabine overdose, regardless of symptoms. It is also indicated for patients who have received fluorouracil or capecitabine and exhibit early onset, severe, or life-threatening cardiac or CNS toxicity and/or early onset unusually severe adverse drug reactions within 96 hours following exposure. It is not recommended for nonemergent treatment of adverse drug reactions. The safety and efficacy have not been established when more than 96 hours have elapsed following the end of fluorouracil or capecitabine administration. Few adverse drug reactions have been reported, but the most common are vomiting, nausea, and diarrhea.

Gemcitabine

Gemcitabine is a fluorine-substituted deoxycytidine analogue structurally related to cytarabine and is used to treat pancreatic cancer, NSCLC, breast cancer, and urothelial cancer. Its activation and mechanism of action are similar to those of cytarabine. Gemcitabine is incorporated into DNA, where it inhibits DNA polymerase activity. It also inhibits ribonucleotide reductase, which is the enzyme required to convert ribonucleotides into the deoxyribonucleotides needed for DNA synthesis and repair. Compared with cytarabine, gemcitabine achieves intracellular concentrations about 20 times higher, secondary to increased penetration of cell membranes and greater affinity for the activating enzyme deoxycytidine kinase. Gemcitabine that is incorporated into DNA has a prolonged intracellular half-life. Its stereoconfiguration causes another normal base pair to be added next to the fraudulent gemcitabine base pair in the DNA strand. This “masked chain termination” protects the gemcitabine from excision and elimination. Flu-like symptoms, myelosuppression, liver enzyme abnormalities, and dermatologic toxicities are commonly associated with gemcitabine.

Trifluridine and Tipiracil

Trifluridine and tipiracil are combined in a molar ratio of 1:0.5 in one tablet approved for the treatment of metastatic colorectal and gastric cancers. Trifluridine is a thymidine-based nucleoside analogue, and tipiracil is a thymidine phosphorylase inhibitor. Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis, and inhibits cell proliferation. Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase. The dose-limiting toxicity is myelosuppression; patients older than 65 years of age may be at greater risk. Other common toxicities include asthenia/fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

Purine Analogues

Cladribine and Pentostatin

Cladribine and pentostatin are purine nucleoside analogues with slightly different mechanisms of action. Both agents are used to treat hairy cell leukemia. Cladribine is resistant to inactivation by adenosine deaminase and is triphosphorylated to an active form incorporated into DNA that inhibits DNA synthesis and early chain termination. Its anticancer activity is unusual for an antimetabolite, in that it affects both actively dividing and resting cancer cells. Pentostatin is a potent inhibitor of adenosine deaminase. Adenosine deaminase is an enzyme critical in purine base metabolism and is found in high concentrations in lymphatic tissue. Both agents have immunosuppressive effects that place patients at risk for serious opportunistic infections and require the administration of prophylactic antibiotics.

Fludarabine

Fludarabine is an adenine analogue used to treat chronic lymphocytic leukemia (CLL) and indolent NHL. Similar to cytarabine, fludarabine interferes with DNA polymerase, causing chain termination. Fludarabine also incorporates into RNA, resulting in inhibition of transcription. Fludarabine is immunosuppressive; it has been associated with the development of opportunistic infections, secondary to its effect on T cells and subsequent decrease in CD4 counts. It is often given as part of a conditioning regimen prior to HSCT. Prophylactic antibiotics and antiviral medications are recommended and should continue until CD4 counts normalize.

Mercaptopurine and Thioguanine

6-Mercaptopurine and its analogue thioguanine are oral antimetabolites used for the treatment of ALL. These antimetabolites are rapidly converted to ribonucleotides that inhibit purine biosynthesis or undergo purine interconversion reactions needed to supply purine precursors to synthesize nucleic acids. Clinical cross-resistance is generally observed. Both antimetabolites are metabolized by thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyl transferase to produce multiple metabolites that contribute to the observed anticancer activity, hepatotoxicity, and myelosuppression. Additionally, nucleoside diphosphate-linked moiety X (nudix)-type motif 15 (NUDT15) catalyzes the conversion of the cytotoxic metabolite into a less toxic compound. Certain genetic alterations within the *TPMT* or *NUDT15* gene can lead to a reduction or loss of enzyme activity. Therefore, patients who are homozygous or heterozygous for a genetic alteration that affects TPMT or NUDT15 activity may experience an accumulation of toxic metabolites and an increased risk of severe myelosuppression. The Clinical Pharmacogenetics Implementation Consortium provides primary dosing recommendations for patients with *TPMT* or *NUDT15* alterations.

6-Mercaptopurine depends on xanthine oxidase for an initial oxidation step. Its metabolism is markedly decreased by coadministration with a xanthine oxidase inhibitor (eg, allopurinol), which may lead to serious adverse drug reactions. If allopurinol is given concurrently with 6-mercaptopurine to minimize TLS, the dose of 6-mercaptopurine must be reduced.

Folate Antagonists

Methotrexate

Methotrexate is commonly used to treat ALL and some lymphomas. It inhibits dihydrofolate reductase (DHFR), which results in the depletion of intracellular pools of reduced folates (tetrahydrofolates) essential for thymidylate and purine synthesis. Folates are essential cofactors for DNA and RNA synthesis and, thus, lack of either thymidine or purines prevents DNA or RNA synthesis.

Chemotherapy regimens may contain low-, intermediate- or high-dose methotrexate and may incorporate methotrexate administered orally, intravenously, or intrathecally. High-dose, defined as doses greater than 500 mg/m^2/dose given intravenously as prophylaxis or treatment of CNS disease, can cause severe myelosuppression and gastrointestinal toxicity. The development of these toxicities is related to both the maximal concentrations and the time that concentrations remain above 0.02 mg/L (50 nmol/L). These effects may be neutralized by exogenously supplying reduced folates, such as leucovorin (folinic acid), which bypasses the metabolic block induced by DHFR inhibitors. Leucovorin should be administered until methotrexate levels fall below the threshold and various dosing algorithms are available. Vigorous hydration and sodium bicarbonate to alkalinize the urine should be given to decrease the risk of renal failure. Patients with third space fluids may require prolonged leucovorin rescue since these fluids influence methotrexate volume of distribution and elimination half-life.

Glucarpidase is approved for the treatment of toxic plasma methotrexate concentrations in patients with delayed methotrexate clearance because of impaired renal function. It is important to note that methotrexate concentrations within 48 hours after glucarpidase administration can only be reliably measured by chromatographic methods. Immunoassays can overestimate methotrexate concentration because of interference from metabolites.

Methotrexate is highly protein bound, and drugs such as sulfonamides, salicylates, phenytoin, and tetracyclines may displace methotrexate from albumin. Increased toxicity may be observed. Nonsteroidal anti-inflammatory drugs and vitamin C may also affect methotrexate disposition and prolong methotrexate elimination half-life. Although the exact mechanism is uncertain, proton pump inhibitors are thought to inhibit methotrexate elimination and potentially increase methotrexate toxicity.

Pemetrexed

Pemetrexed is a multitargeted antifolate that is used to treat nonsquamous NSCLC and mesothelioma. It inhibits at least three biosynthetic pathways in thymidine and purine synthesis. In addition to inhibiting DHFR, it also inhibits thymidine synthase and glycinamide ribonucleotide formyltransferase, decreasing the risk of the development of drug resistance. Severe hematologic toxicity and deaths associated with neutropenic sepsis have been reported in clinical trials: elevated baseline cystathionine or homocysteine concentrations correlate with this unexpected toxicity. Routine supplementation of folic acid and vitamin B_{12} before the initiation of pemetrexed and throughout treatment reduces levels of these substances and lowers the risk of mortality related to neutropenic sepsis. Dexamethasone should be given with pemetrexed to minimize the risk of dermatologic toxicities.

Pralatrexate

Pralatrexate is an antifolate drug approved for patients with relapsed or refractory peripheral T-cell lymphoma. It competitively inhibits DHFR and polyglutamylation by the enzyme folylpolyglutamyl synthetase. This inhibition results in the depletion of thymidine and other synthesis of biological molecules that depends on single carbon transfer. The most common adverse drug reactions resulting in dose reductions are pyrexia, mucositis, febrile neutropenia, sepsis, and thrombocytopenia.

Hypomethylating Agents

Azacitidine and decitabine are nucleoside analogues that demonstrate dose-dependent effects. These analogues exert their effects at lower doses by directly incorporating into DNA and inhibiting DNMT, which leads to cellular differentiation and apoptosis.[14] At higher doses, these agents might cause the formation of covalent adducts between DNMT and the active drug being incorporated into DNA, particularly in cells actively dividing. Hypomethylation also normalizes the function of genes that control cell differentiation and proliferation, promoting normal cell maturation.[14] Decitabine is also available in combination with cedazuridine, a cytidine deaminase inhibitor that impedes the degradation of decitabine and allows for improved systemic exposure following oral administration.

These inhibitors slow the progression of myelodysplastic syndrome (MDS) to AML, reduce transfusion requirements, and allow for the improvement of normal hematopoiesis over time. Azacitidine tablets are approved for the maintenance treatment of AML in patients who achieve complete remission following intensive induction chemotherapy and cannot complete intensive curative treatment. The primary toxicity is myelosuppression, particularly during early phases of treatment as the malignant clone driving the MDS is cleared from the bone marrow, and normal hematopoiesis is slowly restored. As a result, infections occur frequently.

Microtubule-Targeting Drugs

Microtubules are an integral part of the cytoskeleton and help maintain the shape of a cell. These structures are also involved in chromosome separation during mitosis and form the mitotic spindle responsible for separating chromosomes during cell replication. Several chemotherapy agents affect microtubule function, including taxanes, vinca alkaloids, epipodophyllotoxins, epitholones, and macrolides.

Taxanes

Paclitaxel and docetaxel are taxane plant alkaloids with antimitotic activity used to treat many different solid tumors. Paclitaxel and docetaxel both act by binding to tubulin, but they do not interfere with tubulin assembly. Instead, the taxanes promote microtubule assembly and interfere with

microtubule disassembly. They induce tubulin polymerization, resulting in formation of inappropriately stable, nonfunctional microtubules. The stability of the microtubules damages cells by disrupting the dynamics of microtubule-dependent structures required for mitosis and other cellular functions. Taxanes also have some nonmitotic actions that can promote cancer cell death, such as inhibition of angiogenesis.

Resistance to the antitumor effects of the taxanes is attributable to alterations in tubulin or tubulin-binding sites or to P-glycoprotein (P-gp)-mediated multidrug resistance. Although paclitaxel and docetaxel have very similar mechanisms of action, cross-resistance between the two chemotherapy agents is incomplete. Myelosuppression and peripheral neuropathy frequently occur with both docetaxel and paclitaxel. Fluid retention is more common with docetaxel, and hypersensitivity reactions may be more frequent with conventional paclitaxel. Both require premedication to decrease the likelihood of hypersensitivity reactions; docetaxel's premedication also reduces fluid retention.

Two paclitaxel formulations are available. The original product (ie, conventional paclitaxel) contains Cremophor and ethanol. The subsequent product (nab-paclitaxel) contains paclitaxel bound to albumin and does not include the Cremophor excipient believed to contribute to hypersensitivity reactions. In clinical trials, nab-paclitaxel has shown comparable activity to conventional paclitaxel with a lower incidence of hypersensitivity reactions. Peripheral neuropathy remains a common adverse event with nab-paclitaxel. Nab-paclitaxel is approved for the treatment of metastatic breast cancer, NSCLC, and pancreatic cancer. The products are not interchangeable, and the doses are not comparable on a mg-to-mg basis.

Cabazitaxel is a semisynthetic derivative of docetaxel that has demonstrated anticancer activity in castrate-resistant prostate cancer that has progressed following treatment with docetaxel-based chemotherapy. Despite having the same mechanism of action, the lack of affinity for P-gp allows cabazitaxel to remain inside the cancer cells, partially accounting for its benefit in the refractory setting. Toxicities and premedications are similar to docetaxel.

Vinca Alkaloids

Vincristine, vinblastine, and vinorelbine are natural alkaloids derived from the periwinkle (vinca) plant. These agents act as mitotic inhibitors or spindle poisons. Although these alkaloids have a very similar structure, they have different activities and patterns of toxicity. These agents are used to treat different cancers. For example, vinblastine may be used to treat testicular cancer and Hodgkin lymphoma; vincristine may be used to treat NHL and Hodgkin lymphoma; and vinorelbine may be used to treat NSCLC and breast cancer. Vinorelbine and vinblastine are associated with dose-limiting myelosuppression, while vincristine is associated with dose-limiting neurotoxicity, including constipation and paralytic ileus. All vinca alkaloids are vesicants upon extravasation; local heat application allows dispersal or dilution of the alkaloid to minimize tissue damage. Vinca alkaloids should never be administered intrathecally, and accidental overdose is associated with a very high mortality rate.

Vinca alkaloids bind to tubulin and disrupt the normal balance between polymerization and depolymerization of microtubules, inhibiting the assembly of microtubules and disrupting microtubule dynamics. This interferes with the formation of the mitotic spindle and causes cells to accumulate in mitosis. These agents also disturb a variety of microtubule-related processes in cells and induce apoptosis. Resistance to the vinca alkaloids develops primarily from P-gp-mediated multidrug resistance, decreasing drug accumulation and retention within cancer cells.

Miscellaneous Antimicrotubule Agents

Eribulin is a fully synthetic antimicrotubule analogue of the macrolide halichondrin B. Eribulin inhibits tubulin polymerization by inhibiting microtubule growth, but it does not shorten or promote microtubule depolymerization. Additionally, eribulin only binds to the β-tubulin subunit and has demonstrated the ability to overcome taxane resistance conferred by β-tubulin mutations. The most common toxicities are similar to other microtubule inhibitors, but eribulin demonstrates a decreased incidence of neuropathy than vincristine and taxanes. Eribulin is approved for the treatment of metastatic breast cancer and unresectable or metastatic liposarcoma.

Ixabepilone is a synthetic epothilone approved for the treatment of metastatic breast cancer. Its binding to microtubules appears distinct from other microtubule inhibitors such as the taxanes. Thus, it has demonstrated activity in taxane-resistant cells. Dose-limiting toxicities are leukopenia and neuropathy, consistent with other microtubule inhibitors. Other toxicities include anemia, thrombocytopenia, diarrhea, myalgia, and alopecia. Premedication with antihistamines must be administered to reduce the risk of hypersensitivity reactions.

Topoisomerase Inhibitors

Topoisomerases (I and II) are essential enzymes involved in maintaining DNA topologic structure during replication. These enzymes cleave DNA

strands and form intermediates with the strands during replication, producing a gap through which DNA strands can pass and then reseal the strand breaks. Topoisomerase I produces single-strand breaks, and topoisomerase II produces double-strand breaks. Several important anticancer agents interact with topoisomerase enzymes: camptothecins, anthracyclines, and podophyllotoxins.

Camptothecins

Topotecan and irinotecan, through an active metabolite SN-38, inhibit topoisomerase I enzyme activity. Topoisomerase I enzymes stabilize DNA single-strand breaks and inhibit strand resealing. Topotecan is available for oral and intravenous administration, and it is used to treat ovarian cancer and small cell lung cancer (SCLC). Irinotecan is used for the treatment of colorectal cancer and other gastrointestinal malignancies. SN-38 undergoes metabolism in part by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1). Although variant tandem repeats in the promoter of this gene have been associated with a higher risk of diarrhea and neutropenia, genotyping has not been widely adopted in clinical practice. A starting dose reduction should be considered for patients known to be homozygous for the UGT1A1*28 allele, but specific dosing recommendations have yet to be determined. All patients receiving irinotecan are at risk of developing early and/or late diarrhea. Early diarrhea (ie, within 24 hours of irinotecan administration) is a cholinergic effect and may be prevented or treated with atropine, whereas late diarrhea is typically treated with loperamide.

In combination with fluorouracil and leucovorin, liposomal irinotecan is approved for the treatment of patients with metastatic adenocarcinoma of the pancreas whose disease has progressed following gemcitabine-based therapy. The common toxicities associated with irinotecan have been observed with liposomal irinotecan, including gastrointestinal toxicity and myelosuppression.

Anthracyclines

The anthracyclines include doxorubicin, daunorubicin (daunomycin), idarubicin, and epirubicin. These agents share a common, four-membered anthracene ring complex with an attached aglycone or sugar portion. The ring complex is a chromophore and accounts for the intense colors of these derivatives.[15] Anthracyclines are sometimes classified as antitumor antibiotics, but they have multiple mechanisms of action, including intercalation into DNA and inhibition of topoisomerase II. The production of free radicals following their metabolism may also contribute to their anticancer activity. These agents are used to treat many cancers, including leukemias, lymphomas, and multiple solid tumors.

Although the dose-limiting toxicity is myelosuppression, development of cardiomyopathy is a significant concern with these agents. All patients should have a baseline study to evaluate left ventricular ejection fraction (LVEF). Since the probability of congestive heart failure increases with the cumulative dose, a maximum cumulative dose has been suggested for each anthracycline. The relatively low level of defensive enzymes found in cardiac muscle that scavenge against oxygen-free radicals may account for the relative risk of cardiomyopathy compared to toxicity in other organs. Oxygen-free-radical formation likely contributes to extravasation injury associated with these agents, as well. When extravasated (ie, leaked from the intravascular space into the surrounding tissues), anthracyclines are vesicants known to cause significant tissue damage, including blistering and necrosis. Other common toxicities include nausea, vomiting, and alopecia. Doxorubicin also causes a red discoloration of the urine. Resistance to anthracyclines is usually secondary to P-gp-mediated multidrug resistance, but altered topoisomerase II activity may also contribute to the development of resistance.

Liposomal formulations of both doxorubicin and daunorubicin were developed to improve the safety profile of these agents while maintaining their efficacy. A liposomal combination product containing daunorubicin and cytarabine is also available in a fixed 1:5 molar ratio, which is approved for the treatment of AML.

Mitoxantrone has been identified as an anthracendione. It was synthesized to develop a chemotherapy agent with comparable antitumor activity to doxorubicin but with an improved safety profile. Similar to the anthracyclines, mitoxantrone is an intercalating topoisomerase II inhibitor, but its potential for free-radical formation is much less than that of the anthracyclines. This decreased tendency for free-radical formation may explain the reduced risks of cardiac toxicity and ulceration after extravasation. Mitoxantrone may be used with other anticancer agents to treat leukemias and lymphomas. Common toxicities include nausea, vomiting, alopecia, and blue discolored urine.

Etoposide

Etoposide is a semisynthetic podophyllotoxin derivative that binds to tubulin and interferes with microtubule formation. Etoposide also damages cancer cells by causing strand breakage through inhibition of topoisomerase II. Resistance may be caused by differences in topoisomerase II levels, increased cell ability to repair strand breaks, or increased levels of P-gp. Etoposide is cell-cycle phase-specific and arrests cells in the S or early G_2

phase. As a result, activity is much greater when administered in divided doses over several days rather than in large single doses. Etoposide may be used to treat testicular cancer and SCLC. Toxicities include dose-limiting myelosuppression, as well as nausea, vomiting, and alopecia.

Alkylating Agents

The alkylating agents are among the oldest and most widely used class of chemotherapy agents. Their clinical use evolved from the observation of myelosuppression and lymph node shrinkage in soldiers exposed to sulfur mustard gas warfare during World War I. In an effort to develop similar agents that might be useful in treating lymphomas, less reactive derivatives were synthesized. Clinical trials confirmed their anticancer activity in the mid-1940s.

All alkylating agents work by covalently bonding to highly reactive alkyl groups or substituted alkyl groups with nucleophilic groups of proteins and nucleic acids. Some agents react directly with biologic molecules, but others form an intermediate compound that reacts with these molecules. The most common binding site for alkylating agents is the seven-nitrogen group of the DNA base guanine. These covalent interactions result in cross-linking between two DNA strands or between two bases in the same DNA strand and prevent the separation of DNA strands that need to occur during replication. Reactions between DNA and RNA and between drugs and proteins may also occur. Alkylating agents are cell-cycle phase-nonspecific, but their greatest effect is seen in rapidly dividing cells.

As a class, alkylators are cytotoxic, mutagenic, teratogenic, carcinogenic, and myelosuppressive. Resistance to these chemotherapies can occur from increased DNA repair capabilities, decreased entry into or accelerated exit from cells, increased inactivation inside cells, or lack of cellular mechanisms to result in cell death after DNA damage. They are inactivated by hydrolysis, making spontaneous degradation an important component of their elimination.[16]

Nitrogen Mustards

Bendamustine

Bendamustine is an alkylating agent with a benzimidazole ring that demonstrates only partial cross-resistance in vitro with other alkylating agents.[17] It is used primarily to treat lymphoid malignancies, such as CLL and NHL. Bendamustine is incompatible with polycarbonate or acrylonitrile-butadiene-styrene found in syringes and adapters and has been shown to minimize the integrity of these supplies. Typical adverse drug reactions associated with alkylating agents have been observed with bendamustine, but it appears to cause less alopecia.

Cyclophosphamide and Ifosfamide

Cyclophosphamide and ifosfamide are nitrogen mustard derivatives and are widely used to treat solid tumors and hematologic malignancies. These mustards are closely related in structure, clinical use, and toxicity. Neither agent is active in its parent form and must be activated by cytochrome P450 enzymes. The cytochrome P450-mediated metabolites 4-hydroxycyclophosphamide and 4-hydroxyifosfamide are also cytotoxic compounds. Acrolein, a metabolite of cyclophosphamide and ifosfamide, has little anticancer activity but is responsible for hemorrhagic cystitis associated with ifosfamide and high-dose cyclophosphamide. Mesna is used to reduce the incidence of hemorrhagic cystitis by supplying a free thiol group that binds to and deactivates acrolein. Encephalopathy after ifosfamide can occur within 48 to 72 hours after the infusion and is generally reversible once the infusion is stopped. Methylene blue has been suggested to manage neuropathy, but data is lacking to support its routine use. The increased production of dechloroethylated metabolites after administering ifosfamide compared with cyclophosphamide may explain the increased risk of CNS toxicity associated with ifosfamide.

Melphalan

Originally approved in the 1960s, melphalan is one of the oldest chemotherapy agents still used in clinical practice. It is indicated for the palliative treatment of patients with multiple myeloma and as a high-dose conditioning regimen before HSCT. Nausea/vomiting, diarrhea, and mucositis are commonly reported. Serious adverse drug reactions include myelosuppression, infections, hypersensitivity reactions, and secondary malignancies.

Nitrosoureas

Carmustine and Lomustine

Carmustine and lomustine are characterized by their lipophilicity and ability to cross the blood-brain barrier; both agents are used to treat brain cancers. Carmustine is also used to treat multiple myeloma and lymphoma and in preparation for an HSCT. It is available as an intravenous preparation and a drug-impregnated biodegradable wafer for direct application to the tumor cavity after surgical resection of brain tumors. Both agents cause dose-limiting myelosuppression, but the nadir is typically delayed to 4 to 6 weeks after administration. The nitrosoureas decompose to reactive alkylating metabolites and isocyanate compounds that have several effects on reproducing cells.[18]

Nonclassic Alkylating Agents

Several other chemotherapy agents appear to act as alkylators, although their structures do not include the classic alkylating groups. These agents are capable of binding covalently to cellular components and include procarbazine, dacarbazine, temozolomide, and platinum analogues.[18]

Dacarbazine and Temozolomide

Dacarbazine and temozolomide are commonly classified as triazenes and undergo demethylation to the same active intermediate (monomethyl triazeno-imidazole-carboxamide, or MTIC) that interrupts DNA replication by causing methylation of guanine. Unlike dacarbazine, temozolomide does not require the liver for activation and is chemically degraded to monomethyl triazeno-imidazole-carboxamide at physiologic pH. Both agents inhibit DNA, RNA, and protein synthesis.[18]

Important pharmacokinetic differences exist between these two agents. Dacarbazine is poorly absorbed and must be administered by intravenous infusion. Temozolomide is rapidly absorbed after oral administration; it demonstrates nearly 100% bioavailability under fasted conditions. Dacarbazine penetrates the CNS poorly, but temozolomide readily crosses the blood-brain barrier, achieving therapeutically active concentrations in cerebrospinal fluid and brain tumor tissues. Temozolomide is approved for the treatment of glioblastoma, and dacarbazine used to treat Hodgkin lymphoma. Common adverse drug reactions include nausea and vomiting, alopecia, and myelosuppression.

Platinum Analogues

The platinum derivatives—cisplatin, carboplatin, and oxaliplatin—are chemotherapy agents with remarkable usefulness in cancer treatment. Recognition of cisplatin's cytotoxic activity resulted from a serendipitous observation that bacterial growth in culture was altered when an electric current was delivered to the media through platinum electrodes. The growth change was noted to be similar to that produced by alkylating agents and radiation. It was found that a platinum–chloride complex, now known as cisplatin, generated by the current was responsible for the changes. Carboplatin is a structural analogue of cisplatin in which a carboxycyclobutane moiety replaces the chloride groups of the parent compound. It shares a similar spectrum of clinical activity with cisplatin, and cross-resistance is common. Oxaliplatin is an organoplatinum compound in which the platinum is complexed with an oxalate ligand as the leaving group and to diaminocyclohexane. Its spectrum of activity differs substantially from the other platinum compounds and includes notable activity against colorectal cancers.

The cytotoxicity of the platinum derivatives depends on platinum binding to DNA and the formation of intrastrand cross-links or adducts between neighboring guanines. These intrastrand links cause a major bending of the DNA. These agents may cause cellular damage by distorting the normal DNA conformation and preventing bases normally paired from lining up with each other. Interstrand cross-links also occur.

The aquated species differ among these platinum compounds, but all of these species contribute to anticancer activity. The cytotoxic form of cisplatin is the aquated species in which hydroxyl groups or water molecules replace the two chloride groups. This reaction occurs readily in low chloride concentrations, such as the concentrations present within cells, and produces a positively charged compound that can react with DNA. The aquated species is responsible for both the efficacy and toxicity of cisplatin. Carboplatin also undergoes aquation but at a slower rate. Oxaliplatin becomes active when the oxalate ligand is displaced in physiologic solutions.[18]

Resistance to the therapeutic effects of platinum compounds may occur through several mechanisms. The ability to repair platinum-induced DNA damage may be increased, or the compounds may be inactivated by increased intracellular glutathione levels, metallothioneins, or other thiol-containing proteins. Altered uptake into cells may also affect sensitivity to platinum compounds.

The dose-limiting toxicities differ substantially among these compounds. Cisplatin can cause serious nephrotoxicity, ototoxicity, peripheral neuropathy, emesis, and anemia, but its significant anticancer activity in many tumors makes it a valuable agent despite these toxicities. Most of these

toxicities can be prevented or managed with aggressive supportive care measures. Intravenous hydration, mannitol, and diuretics have been used to minimize the risk of nephrotoxicity, but it appears intravenous hydration alone is adequate. In contrast, carboplatin administration is limited by hematologic toxicity. Patients with compromised renal function require dose reductions to limit myelosuppressive toxicity. The most widely used dosage schema, the Calvert formula, uses a target area-under-the-curve and renal and nonrenal parameters to estimate the carboplatin dose. Carboplatin's potential to cause renal damage, peripheral neuropathy, and ototoxicity is much less than comparable cisplatin doses. Oxaliplatin is not nephrotoxic or ototoxic, but it can cause peripheral neuropathies and unique cold-induced neuropathies. Intravenous calcium and magnesium were commonly used to minimize the risk of neuropathy. Still these measures do not appear to decrease the risk of acute neurotoxicity or cumulative sensory neurotoxicity based on the results of a controlled trial.[19] All of the platinum derivatives have the potential to cause hypersensitivity reactions, including anaphylaxis after a threshold exposure is reached. Desensitization protocols may be successful in reestablishing tolerance to these agents.

Trabectedin and Lurbinectedin

Both trabectedin and lurbinectedin (an analogue of trabectedin) are alkylating agents that bind guanine residues in the minor groove of DNA. Subsequently, adducts form and cause a bending of the DNA helix toward the major groove. Trabectedin is approved for the treatment of patients with unresectable or metastatic soft tissue sarcoma who have received a prior anthracycline-containing regimen, whereas lurbinectedin is indicated for metastatic SCLC following progression with platinum-based therapy. Warnings associated with both agents include myelosuppression, hepatotoxicity, and embryo-fetal toxicity. Additionally, trabectedin has been associated with rhabdomyolysis, cardiomyopathy, and capillary leak syndrome.

Endocrine Therapies

Endocrine therapies are perhaps the earliest successful approach to target the growth processes of cancer cells. Endocrine manipulation is an option for managing cancers in which growth is under gonadal hormonal control, such as breast, prostate, and endometrial cancers. These cancers may regress if the feeding hormone is eliminated or antagonized. Major organ system toxicity is uncommon from endocrine therapies. These therapies are discussed in detail in Chapters 151, "Breast Cancer," and 154, "Prostate Cancer."

Corticosteroids

Corticosteroids are also useful anticancer therapies because of their lymphotoxic effects. These agents are primarily used to treat hematologic malignancies and are also given in combination with chemotherapy for prostate cancer. In addition to their cytotoxic effects, corticosteroids have many other applications as part of supportive care measures and management of oncologic emergencies. Short-term corticosteroid regimens are generally well tolerated.

Therapeutic Radiopharmaceuticals

An oncology therapeutic radiopharmaceutical is an agent that contains a radionuclide and is used to treat cancer or palliate tumor-associated symptoms. Radioisotopes can emit either alpha or beta particles as their payload.[20] Alpha emitters have high energy and travel only the length of a few cell diameters resulting in double-strand DNA breaks of adjacent cells. In contrast, beta emitters have lower energy and travel the length of hundreds of cell diameters. As a result, these agents affect the cancer cells they bind and other cells within the path length of the radioisotope's emissions (ie, bystander effect). Additionally, some radioisotopes emit gamma radiation with no mass or charge and can travel further than alpha or beta particles.

Ibritumomab Tiuxetan

Ibritumomab tiuxetan is a radioimmunoconjugate that consists of the murine anticluster of differentiation (CD)20 antibody ibritumomab and a linker chelator tiuxetan that allows the attachment of yttrium-90 (active radiotherapy). This therapeutic radiation isotope selectively delivers beta particles to B-cells that express the CD20 antigen. Consequently, ibritumomab tiuxetan can induce cell death in CD20-positive and -negative cancer cells while also inducing antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. These processes are described later in the chapter. Ibritumomab tiuxetan is indicated for the treatment of low-grade or follicular B-cell NHL. The therapeutic regimen consists of two steps: rituximab is administered on day 1, and about 1 week later (day 7, 8, or 9), an additional dose of rituximab is administered, followed by yttrium-90-ibritumomab within 4 hours after completion of the rituximab infusion.

Adverse drug reactions include severe infusion-related reactions and myelosuppression. Ibritumomab tiuxetan results in prolonged

thrombocytopenia and neutropenia, and dose modifications are necessary based on baseline neutrophil and platelet blood counts. The median duration of thrombocytopenia and neutropenia were 24 and 22 days, respectively. Monitoring and managing cytopenias and their complications is necessary for up to 3 months after completing treatment.

Iobenguane I 131

Iobenguane is a molecule structurally similar to norepinephrine and is therefore involved in the same uptake pathways. Labeled with I 131, this agent targets the norepinephrine transporter and is a beta emitter. Two rare tumors, pheochromocytoma and paraganglioma, express high levels of norepinephrine on their cell surfaces. When iobenguane I 131 is administered, it accumulates in these tumor cells allowing the radioisotope to cause cell death and tumor necrosis. Of note, this agent is only approved for patients with an iobenguane positive scan.

Before administration of iobenguane I 131, patients should receive thyroid-blocking medication. Additionally, medications that reduce catecholamine uptake or deplete stores should not be administered concurrently with iobenguane I 131 as they may interfere with the efficacy. The most common toxicities include myelosuppression, fatigue, hypertension, nausea, and vomiting.

Lutetium Lu 177

Lutetium Lu 177 dotatate is a radiolabeled somatostatin analogue that emits beta and gamma radiation and is approved for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NET). After binding to somatostatin receptor-expressing cells, such as GEP-NET cells, lutetium Lu 177 is taken up into the cell where the beta emission induces cellular damage.

Special precautions should be taken with the administration of somatostatin analogues before lutetium Lu 177. An amino acid solution must be administered before, during, and after lutetium Lu 177 to decrease reabsorption of the radiopharmaceutical through the proximal tubules, thereby reducing the radiation exposure to the kidneys. In addition, patients must be advised on minimizing exposure to contacts. Reported adverse drug reactions include increased hepatic enzymes, hyperglycemia, hypokalemia, nausea, and vomiting. Patients should also be monitored for neuroendocrine hormonal crisis.

Similarly, lutetium Lu 177 vipivotide tetraxetan is a therapeutic agent utilizing the radionuclide lutetium 177. However, lutetium Lu 177 vipivotide tetraxetan binds to prostate-specific membrane antigen which is highly expressed on prostate cancer cells. After binding to prostate-specific membrane antigen-expressing cells, the beta emission delivers radiation resulting in DNA damage. Lutetium Lu 177 vipivotide tetraxetan is indicated for metastatic castration-resistant prostate cancer. Notable adverse drug reactions include salivary gland hypofunction and xerostomia. Bone marrow suppression and kidney toxicity have also been reported.

Radium Ra 223 dichloride

Radium Ra 223 dichloride (ie, radium-223) is an alpha emitter, which is indicated for the treatment of patients with castration-resistant prostate cancer who have symptomatic bone metastases and no known visceral metastatic disease. Radium-223 mimics calcium and forms complexes with hydroxyapatite at areas of increased bone turnover, such as bone metastases. Alpha particles are then emitted, resulting in DNA breaks and an antitumor effect. Toxicities of radium-223 include bone marrow suppression, gastrointestinal adverse drug reactions, dehydration, and potentially increased risk of fractures in select patients.

Miscellaneous Agents

Arsenic Trioxide

Arsenic is an organic element and a well-known poison that is an effective treatment for acute promyelocytic leukemia, or APL. As an anticancer agent, arsenic trioxide acts as a differentiating agent, inducing the growth progression of cancer cells into mature, more normal cells. It also induces apoptosis. Notable adverse drug reactions associated with arsenic trioxide include QTc prolongation, hepatotoxicity, and differentiation syndrome. Previously known as “retinoic acid syndrome,” differentiation syndrome is a potentially fatal complication of arsenic trioxide. It has been reported with other agents, including tretinoin, enasidenib, ivosidenib, and gilteritinib, which are discussed later in the chapter. This syndrome, which is thought to be caused by a rapid release of cytokines, may present with fever, difficulty breathing, edema, weight gain, and hypotension and must be rapidly treated with corticosteroids.

Asparaginase

L-Asparaginase is unique among anticancer agents in its unusual mechanism of action, source, and patterns of toxicity. It is an enzyme produced by *Escherichia coli* or *Erwinia chrysanthemi*. L-Asparagine is a nonessential amino acid that can be synthesized by most mammalian cells except cells with certain lymphoid malignancies, which have no or limited synthetase levels required for L-asparagine formation. L-Asparagine is degraded by the enzyme L-asparaginase, which depletes existing supplies and inhibits protein synthesis.

Multiple asparaginase products are commercially available. Recombinant asparaginase (*Erwinia*) is produced by fermentation of a genetically engineered *Pseudomonas* bacterium. Pegaspargase and calaspargase pegol are modified versions of L-asparagine conjugated to monomethoxypolyethylene glycol which permits a longer half-life and therefore less frequent administration. All of these products are approved to treat patients with ALL when used as part of a combination chemotherapy regimen. Additionally, recombinant asparaginase (*Erwinia*) is approved to treat patients with lymphoblastic lymphoma. Increased L-asparagine synthetase activity within cancer cells causes treatment resistance. Severe toxicities include anaphylaxis, thrombosis, pancreatitis, glucose intolerance, hemorrhage, and hepatotoxicity.

Bleomycin

Bleomycin is an antitumor antibiotic used with other anticancer agents to treat Hodgkin lymphoma and testicular cancer. It is also used for pleurodesis to prevent a pleural effusion recurrence. Bleomycin is a mixture of peptides from fungal *Streptomyces* species. Its strength is expressed in units of drug activity, and one unit is roughly equal to 1 mg of polypeptide protein. The predominant peptide is bleomycin A2, which makes up about 70% of the commercial drug product. Its cytotoxicity is secondary to DNA strand breakage, which it produces via free-radical formation. Cytotoxicity depends on the binding of the bleomycin–iron complex to DNA. The bleomycin–iron complex then reduces molecular oxygen to free oxygen radicals that cause primarily single-strand breaks in DNA. Bleomycin has greatest effect on cells in the G2 and M phases of the cell cycle.

Bleomycin is inactivated within cells by the enzyme aminohydrolase. This enzyme is widely distributed but is present in only low concentrations in the skin and the lungs, explaining the predominant toxicities of bleomycin to those sites. Therefore, baseline pulmonary function tests and monitoring for pulmonary toxicity are necessary. The risk of pulmonary toxicity increases with age over 70 years and cumulative lifetime bleomycin doses 400 units or higher. The presence of hydrolase enzymes in cancer cells is the primary mechanism of resistance to bleomycin. As a result, cells can also become resistant by repairing the DNA breaks produced by bleomycin.

Hydroxyurea

Hydroxyurea is a unique drug that inhibits ribonucleotide reductase. Cells accumulate in the S phase because DNA synthesis is inhibited, and only abnormally short DNA strands are produced. This anticancer agent was used to treat chronic myeloid leukemia (CML) because of its ability to cause a rapid decline in white blood cells.

Lanreotide

As an octapeptide analogue of somatostatin, the mechanism of lanreotide is believed to be similar to that of natural somatostatin through the inhibition of neuroendocrine functions. Somatostatin analogues are commonly used to treat hypersecretion syndromes associated with neuroendocrine tumors, but only recently have been proven to have an antitumor effect associated with prolonged progression-free survival. Lanreotide is approved for the treatment of unresectable, well or moderately differentiated, locally advanced, or metastatic GEP-NET. Common toxicities include abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, and hypertension. In addition, patients should be monitored for hypoglycemia, hyperglycemia, and gallstones.

Mitomycin

Mitomycin, also known as mitomycin C, is a natural product classified as an antitumor antibiotic. It has similarities to nitrogen mustards and may function as an alkylating agent, although its toxicity pattern differs from conventional alkylating agents. Mitomycin may be given intravenously in combination with other chemotherapy agents to treat gastric or pancreatic cancer. When given by this route of administration, delayed myelosuppression may occur, so treatment is typically given every 6 weeks. Mitomycin may also be given as an instillation directly into the bladder (ie, intravesical instillation) for the treatment of localized bladder cancer. Additionally, a ureteral gel formulation is available, which is administered via a

ureteral catheter or nephrostomy tube to treat upper tract urothelial cancer.

Omacetaxine Mepesuccinate

Omacetaxine mepesuccinate is a natural ester of the alkaloid cephalotaxine. It inhibits protein translation and thus prevents the initial elongation step of protein synthesis. It is given subcutaneously for treatment of patients with CML who have failed two or more approved therapies for this disease. Additionally, synergy with these approved therapies has been demonstrated in a few clinical studies, and additional combination trials are ongoing. Adverse drug reactions include myelosuppression, hemorrhage, and hyperglycemia.

Retinoids

Three retinoids are available to treat patients with cancer. Tretinoin (all-trans-retinoic acid), a naturally occurring derivative of vitamin A (retinol), is used to treat acute promyelocytic leukemia. Other retinoids indicated for the treatment of cancers include alitretinoin (9-cis-retinoic acid) gel for topical management of Kaposi's sarcoma lesions and bexarotene gel or capsules for treatment of cutaneous T-cell lymphoma.

Retinoids are classified as morphogens, small molecules released from one type of cell that can affect the growth and differentiation of neighboring cells. Their normal roles in the human body are to induce differentiation of some cells, stop the differentiation of others, and both suppress and induce apoptosis in different cell types. Their diverse actions come from the diversity of their receptors. The two classes of retinoid receptors are retinoid X receptors and retinoic acid receptors. Retinoid X receptors are versatile; they bind to retinoic acid receptors and to other nuclear receptors, such as thyroid hormone receptors. After being activated, the receptors act as transcription factors that regulate the expression of genes that control cellular growth and differentiation.

Tretinoin binds primarily to the retinoic acid-α receptors. Alitretinoin is considered a pan-agonist, which means that it binds to all known retinoid receptors, producing diverse regulatory effects. Bexarotene is synthetic and is classed as a rexinoid. It is the first retinoid X receptor–selective retinoid agonist.

The common adverse drug reactions differ for these three agents. Tretinoin may be associated with differentiation syndrome. Alitretinoin is associated with pain, itching, and rash, and bexarotene is associated with skin reactions, thyroid disorders, hypercholesterolemia, and hyperlipidemia.

Thalidomide, Lenalidomide, and Pomalidomide

Thalidomide, the infamous drug that caused severe limb deformities when used by pregnant individuals as a nonprescription sedative in the 1960s, is approved to treat leprosy and multiple myeloma. Thalidomide is a glutamic acid derivative and is broadly classified as an immunomodulatory drug. Lenalidomide and pomalidomide are analogues of thalidomide with similar therapeutic activity but different adverse drug reaction profiles. Lenalidomide is approved for the treatment of multiple myeloma, transfusion-dependent anemia caused by MDS with a specific mutation, follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma. Pomalidomide is approved for the treatment of multiple myeloma and Kaposi sarcoma.

These drugs have many potential mechanisms of action, but the most important is angiogenesis inhibition, which is also linked to their teratogenic effects. Other possible mechanisms include direct inhibition of cancer cells, free radical oxidative damage to DNA, interference with adhesion of cancer cells, inhibition of TNF-α production, or alteration of cytokine secretion that affects the growth of cancer cells.

The most common toxicities for thalidomide include somnolence, constipation, dizziness, orthostatic hypotension, rash, and peripheral neuropathies. In contrast, lenalidomide is associated with much less somnolence and neuropathies compared with thalidomide. Neutropenia, thrombocytopenia, and thrombotic events are common with thalidomide, lenalidomide, and pomalidomide. To avoid embryo-fetal exposure and inform healthcare professionals and patients of the teratogenic potential, these agents are only available through a risk evaluation and mitigation strategy (REMS) program.

TARGETED AGENTS: SMALL MOLECULES

6 Small-molecule targeted agents (molecular weight less than 1,000 Da) are typically identified as kinase inhibitors. Kinases are enzymatic proteins that constitute the intracellular signaling pathways, such as the JAK-STAT and MAPK/ERK pathways described earlier. Following ligand binding to an

extracellular receptor, kinases transmit signals to the cell interior that stimulates activation of the pathway. The small-molecule targeted agents turn off or inhibit these pathways by inhibiting the adenosine triphosphate (ATP) binding domain of the kinases. Most of the approved kinase inhibitors inhibit more than one kinase. The binding to multiple kinases typically leads to off-target effects or toxicities; some toxicities are attributed to specific kinase families. Although most inhibitors are given orally continuously for months to years, their anticancer activity is typically limited by the development of resistance. Before initiating therapy, some targeted drugs require identification of the target within the tumor using a companion or complementary diagnostic test. Of note, most kinase inhibitors and mAbs are associated with a warning for embryo-fetal toxicity. The individual product labeling should be referenced for contraception guidelines in females of reproductive potential and males with female partners of reproductive potential.

Anaplastic Lymphoma Kinase (ALK) Inhibitors

Crizotinib

Crizotinib binds to the ATP intracellular domain of activated ALK, thereby inhibiting phosphorylation and subsequent downstream signaling. ALK rearrangements were first identified in large cell lymphomas and later in NSCLC. In NSCLC, the most common rearrangement involves inversion of chromosome 2p that is primarily fused to the echinoderm microtubule-like protein 4 (EML4), which forms the ALK-EML4 oncogene fusion protein. This rearrangement leads to the activation of downstream signaling pathways and inhibition of apoptosis. ALK-EML4 has a higher prevalence in younger patients, never or light smokers, and adenocarcinoma histology. Crizotinib also inhibits other kinases, such as ROS1, RON, and mesenchymal-epithelial transition (MET). Crizotinib is approved for the treatment of patients with metastatic NSCLC that is ALK or ROS1-positive and for ALK-positive anaplastic large cell lymphoma.

The most common toxicities reported in patients taking crizotinib include nausea, vomiting, diarrhea, constipation, fatigue, and elevated transaminases. Visual disorders occur in about half of patients and usually occur within the first weeks of therapy. Edema is also commonly seen and is most likely attributed to the inhibition of MET. Crizotinib has been associated with interstitial lung disease/pneumonitis, hepatotoxicity, QTc interval prolongation, and bradycardia.

Many patients with ALK-positive NSCLC initially respond to crizotinib. Still most patients will develop resistance possibly related to the development of brain metastases or genetic alterations in ALK. The L1196M mutation has been recently identified as a mechanism of crizotinib resistance.

Alectinib, Brigatinib, and Ceritinib

Alectinib, brigatinib, and ceritinib are second-generation ALK inhibitors approved for the treatment of patients with metastatic ALK-positive NSCLC. Similar to crizotinib, these agents inhibit autophosphorylation of ALK and subsequent downstream signaling. In addition to ALK, ceritinib also inhibits insulin-like growth factor 1 receptor, although to a lesser extent.[21]

Toxicities that are seen with both alectinib and ceritinib include fatigue, bradycardia, and hepatotoxicity. Additional adverse drug reactions seen in patients taking alectinib include anemia, constipation, edema, and myalgia. Brigatinib has been associated with pulmonary toxicities and bradycardia. Patients taking ceritinib should be monitored for QTc interval prolongation, gastrointestinal toxicity, pancreatitis, and hyperglycemia. Visual disturbances have been reported with second-generation ALK inhibitors, although to a much lesser extent. While crizotinib and brigatinib may be taken without regard to food, alectinib should be taken with food. Of note, ceritinib was previously recommended at a higher dose administered on an empty stomach, but the currently approved dose is lower and is to be taken with food to improve gastrointestinal tolerability. To decrease the risk of early onset pulmonary toxicities, a dose-escalation approach must be used with brigatinib.

Lorlatinib

A third-generation ALK and ROS1-inhibitor, lorlatinib, is approved for the treatment of ALK-positive NSCLC. It has demonstrated activity in the first-line setting and following progression on one or more ALK inhibitors.[22] Similar to other agents in this category, lorlatinib is associated with hepatotoxicity and interstitial lung disease/pneumonitis. CNS toxicities, hyperlipidemia, and atrioventricular block have also been reported.

BCL-2 Inhibitor

Venetoclax is a selective inhibitor of BCL-2, an antiapoptotic protein overexpressed in CLL. Permeabilization of the mitochondrial membrane, with the

help of mediators BAX and BAK, is the last step in the apoptosis pathway. BCL-2 constrains BAX and BAK, resulting in CLL cells resistant to apoptosis.[23] Venetoclax binds directly to the BCL-2 protein restoring the apoptotic process. It is approved for the treatment of patients with CLL, small lymphocytic lymphoma, and newly diagnosed AML in adults who are unable to receive intensive induction chemotherapy (eg, age 75 years or older). Reported toxicities associated with venetoclax include myelosuppression, fatigue, diarrhea, cough, and upper respiratory tract infection. To reduce the risk of TLS, a weekly dose escalation over the first 5 weeks is required, and patients should receive antihyperuricemic agents and hydration. Oral administration of venetoclax should be with food.

Abelson (ABL) Inhibitors

Breakpoint Cluster Region-Abelson (BCR-ABL) Inhibitors

Imatinib is a selective inhibitor of the *bcr-abl* fusion gene, the product of the Philadelphia chromosome (Ph). The Ph chromosome is the hallmark finding of CML, and it is a translocation of genetic material between chromosomes 9 and 22. Imatinib binds to the kinase-binding site of the *bcr-abl* gene, competitively blocking access to ATP. This prevents tyrosine-kinase phosphorylation of the gene and downstream activation of cellular proliferation. An additional effect of imatinib is its ability to inhibit stem-cell factor receptor (KIT) and PDGF receptor (PDGFR).

Imatinib is a standard treatment option for newly diagnosed Ph positive (Ph^+) CML and gastrointestinal stromal tumors (GIST). A major advantage of imatinib is that it can eliminate the Ph, resulting in cytogenetic responses (ie, elimination of the genetic defect). Imatinib and other BCR-ABL inhibitors are further discussed in Chapter 158, “Chronic Leukemias.” Imatinib is also approved for the treatment of Ph^+ALL and other rare diseases.

Potential serious adverse drug reactions observed with imatinib include fluid retention and rash. Severe fluid retention (ie, pleural effusion, pericardial effusion, and ascites) occurs in fewer than 10% of patients taking imatinib, but patients should be monitored regularly for early signs and symptoms of fluid retention and instructed to call their health professionals when symptoms first develop. Additionally, a rash may require early intervention because Stevens-Johnson syndrome has been reported.

The second-generation kinase inhibitors dasatinib, nilotinib, and bosutinib share the same binding site on the BCR-ABL kinase ATP-binding domain with imatinib. These inhibitors maintain clinical activity in patients with CML with some mutations in the BCR-ABL binding site that confer imatinib resistance. Still, none of these inhibitors are active against the genetic alteration identified as T315I. Dasatinib is approved for the treatment of Ph^+CML and Ph^+ALL. Nilotinib and bosutinib are approved for the treatment of Ph^+CML. Both bosutinib and dasatinib also inhibit a family of kinases called sarcoma kinases that are believed to mediate cellular differentiation, proliferation, and survival; sarcoma kinases have been implicated in modulating multiple oncogenic signal transduction pathways.

These second-generation agents have a toxicity profile similar to that of imatinib, with myelosuppression, nausea, vomiting, headache, and fluid retention being commonly reported. Bosutinib does not inhibit KIT or PDGFR, which may account for its reported decrease in the incidence of myelosuppression.

As mentioned earlier, the T315I mutation, often referred to as the gatekeeper mutation, confers resistance to the above BCR-ABL inhibitors. Ponatinib, a third-generation agent, was developed to inhibit this mutated conformation of BCR-ABL and provide an effective treatment for this traditionally resistant tumor. Ponatinib is approved for the treatment of Ph^+ALL and Ph^+CML in patients for whom no other kinase inhibitors are indicated, such as those with a T315I mutation. Common toxicities are similar to other BCL-ABL inhibitors, such as hypertension, rash, headache, constipation, fever, and nausea. Arterial thrombosis and hepatotoxicity have also been observed.

Specifically Targeting the ABL Myristoyl Pocket (STAMP) Inhibitor

While the BCR-ABL inhibitors (eg, imatinib) bind to the ATP binding site of the kinase and inhibit downstream phosphorylation, asciminib instead binds to the ABL pocket of the allosteric site and is therefore classified as a STAMP inhibitor.[24] Asciminib is indicated for the treatment of patients with Ph^+CML in chronic phase who have been previously treated with at least two kinase inhibitors. Additionally, asciminib is approved in patients with Ph^+CML in chronic phase and a T315I mutation. Notable toxicities include myelosuppression, hypertension, cardiovascular events, musculoskeletal pain, and elevated creatine phosphokinase. Hypersensitivity reactions have been reported in approximately one third of patients and may present as rash, edema, and bronchospasm. Elevated pancreatic enzymes are common and may require a dose modification. Multiple drug-drug interactions

must also be considered.

BRAF Inhibitors

BRAF is mutated in a variety of solid tumors, with most mutations occurring at codon 600. This codon is in the activation loop of BRAF and increases downstream activity at MEK then ERK, which results in proliferation and survival of cancer cells. BRAF is altered in approximately 65% of papillary thyroid carcinomas, 35% of melanomas and anaplastic thyroid carcinomas, 11% of colorectal cancers, and 5% of NSCLC.[25] The most common BRAF mutations in melanomas are the V600E mutation, which replaces valine with glutamic acid at codon 600 (~80% of cases), and the V600K mutation, which replaces valine with lysine (~8% of cases). Dabrafenib, encorafenib, and vemurafenib inhibit BRAF V600, thereby blocking the MAPK pathway in BRAF-mutated cells.

For patients with BRAF-mutated melanoma, combination therapy with a BRAF and MEK inhibitor has been associated with improved outcomes, so doublet therapy is given in clinical practice: dabrafenib with trametinib, encorafenib with binimetinib, and vemurafenib with cobimetinib. Dabrafenib is approved for V600E and V600K mutated melanoma, V600E NSCLC, and V600E anaplastic thyroid cancer. Additionally, dabrafenib holds a site agnostic approval for patients with solid tumors harboring a V600E mutation. Vemurafenib is approved for melanoma with a V600E mutation and for the treatment of Erdheim-Chester disease with a V600 mutation. Encorafenib is approved for melanoma with a V600E or V600K mutation (in combination with binimetinib) and for patients with colorectal cancer with a BRAF V600E mutation (in combination with cetuximab).

Toxicities associated with all BRAF inhibitors either as monotherapy or in combination with a MEK inhibitor include uveitis, arthralgia, fatigue, and nausea. Patients should be monitored for the development of new cutaneous malignancies and noncutaneous squamous cell carcinoma associated with the dabrafenib-, encorafenib-, and vemurafenib-induced paradoxical activation of the MAPK pathway.[26] PPE and pyrexia are commonly seen with dabrafenib, whereas QTc prolongation is more commonly reported with encorafenib and vemurafenib. Vemurafenib is also associated with severe dermatologic reactions and photosensitivity.

Bruton's Tyrosine Kinase (BTK) Inhibitors

BTK is involved in the B-cell receptor signaling pathway that leads to B-cell proliferation and differentiation upon its activation. In B-cell malignancies, the B-cell receptor signaling pathway promotes disease progression, although the exact mechanism of B-cell receptor stimulation has not been determined. The first-generation BTK inhibitor, ibrutinib, forms an irreversible covalent bond with a cysteine residue of BTK, resulting in the inhibition of malignant B-cell proliferation and survival. Ibrutinib is approved for the treatment of chronic graft-versus-host disease and the following B-cell malignancies: Waldenstrom's macroglobulinemia; mantle cell lymphoma; marginal zone lymphoma; and CLL. Second-generation inhibitors include acalabrutinib and zanubrutinib which are more selective and likely associated with fewer off-target effects. Acalabrutinib is approved for both CLL and mantle cell lymphoma while zanubrutinib is only approved for mantle cell lymphoma. Pirtobrutinib, a third-generation BTK inhibitor, binds to both wild-type BTK (ie, BTK without mutation) and BTK with a C481 mutation, which has been associated with ibrutinib-resistance. Although the frequency of adverse drug reactions varies between BTK inhibitors, patients should generally be monitored for hemorrhage, infections, cytopenias, cardiovascular effects (eg, atrial fibrillation), and TLS. Additional common toxicities include diarrhea, fatigue, musculoskeletal pain, nausea, and rash.

CDK Inhibitors

As discussed earlier in this chapter, CDKs play an important role in cell-cycle progression. Specifically, CDK 4/6 and cyclin D1 regulate transition from the G_1 phase to the S phase by phosphorylating the retinoblastoma protein. Palbociclib, ribociclib, and abemaciclib inhibit CDK 4/6, resulting in the blockade of retinoblastoma protein hyperphosphorylation and ultimately G_1 arrest.[27] In breast cancer, it has been demonstrated that cyclin D1 expression and subsequent retinoblastoma protein phosphorylation can be maintained despite estrogen receptor (ER) antagonism. Therefore, inhibiting CDK 4/6 may overcome acquired resistance to hormonal therapy observed in ER-positive breast cancer.[27]

Palbociclib, ribociclib, and abemaciclib are approved for use in ER-positive, HER2-negative breast cancer in combination with endocrine therapy. Patients receiving these agents should be monitored for hematologic toxicities, infections, and pulmonary embolisms. Ribociclib has been associated with concentration-dependent QTc prolongation, so electrocardiograms (ECGs) and electrolytes should be regularly monitored.

Colony-Stimulating Factor-1 Receptor Inhibitors

Tenosynovial giant cell tumors are rare malignancies that often arise from the joints, bursae, or tendon sheaths and may be associated with significant morbidity and functional limitations.[28] These tumors are characterized by the overexpression of colony-stimulating factor–1 receptor ligand that promotes cell proliferation and accumulation in the synovium. Pexidartinib inhibits colony-stimulating factor–1 receptor and is approved for the treatment of select patients with tenosynovial giant cell tumors. However, due to the severe risk of hepatotoxicity, pexidartinib is only available through a REMS program. Pexidartinib should be administered with a low-fat meal as high-fat foods may increase serum concentrations and the risk of adverse drug reactions, including hepatotoxicity. It is also associated with many known drug-drug interactions.

EGFR Inhibitors

Approximately 30% of NSCLC tumors harbor a mutation in the EGFR gene which may predict sensitivity to EGFR-targeted kinase inhibitors. Approximately 85% of these mutations are exon 21 L858R or exon 19 deletions/insertions.[29] Exon 20 insertions are less common but notoriously unresponsive to early generation EGFR kinase inhibitors, such as erlotinib. A common mechanism of resistance to EGFR inhibitors is the T790M secondary mutation, also known as the EGFR gatekeeper mutation, which occurs in about 50% of patients who develop acquired resistance to first-line therapy with erlotinib or gefitinib.[30]

Erlotinib and gefitinib are an oral first-generation selective EGFR kinase inhibitors approved for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations detected by an US Food and drug Adminsitration (FDA)-approved test. Erlotinib is also approved for use in pancreatic cancer in combination with gemcitabine. The most common adverse drug reactions that occur with erlotinib and gefitinib result from the abundance of EGFR in skin and mucosa and include acneiform rash and diarrhea. Some studies suggest that the development of a rash may be predictive of a response to therapy and correlates with clinical benefit.[31] Interstitial lung disease is a rare adverse drug reaction reported in patients taking EGFR inhibitors.

Unlike first-generation inhibitors which reversibly binds to EGFR, afatinib and dacomitinib irreversibly block all kinases of the ErbB family by covalently binding to the intracellular kinase domain which subsequently inhibits tumor growth. Afatinib is approved for the treatment of patients with EGFR mutation-positive NSCLC and previously treated squamous NSCLC. Dacomitinib is approved for the first-line treatment of patients with metastatic NSCLC harboring an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation. Adverse drug reactions observed with afatinib and dacomitinib are similar to those reported with erlotinib and gefitinib.

Osimertinib is a third-generation EGFR inhibitor that was developed to overcome T790M-mediated resistance reported with other kinase inhibitors targeting EGFR. It is indicated for EGFR T790M mutation-positive NSCLC after disease progression on or after an EGFR inhibitor. Osimertinib is also approved for the treatment of patients with metastatic NSCLC whose tumors harbor EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test. It is also indicated for EGFR T790M mutation-positive NSCLC after disease progression on or after an EGFR inhibitor. The T790M mutation, also referred to as the EGFR gatekeeper mutation, occurs in about 50% of patients who develop acquired resistance to first-line therapy with erlotinib or gefitinib.[32] Gastrointestinal and dermatologic toxicities are commonly reported with osimertinib. Serious adverse drug reactions include interstitial lung disease/pneumonitis, pneumonia, and pulmonary embolism. Although rare, cardiac toxicity may be more commonly reported in patients receiving osimertinib compared to those receiving first- or second-generation EGFR inhibitors.

Mobocertinib is a novel EGFR kinase inhibitor designed to overcome EGFR inactivity by selectively targeting exon 20 mutations over wild-type EGFR.[33] It is approved for the treatment of metastatic NSCLC with EGFR exon 20 insertion mutations (as detected by an FDA-approved test) following progression on or after platinum-based chemotherapy. Serious adverse drug reactions associated with mobocertinib include cardiac toxicity; monitor LVEF and QTc at baseline and periodically during treatment. Other adverse drug reactions reported with mobocertinib include dermatologic and gastrointestinal effects, which are anticipated with all EGFR inhibitors. Interstitial lung disease/pneumonitis has also been rarely reported.

Enhancer of Zest Homolog 2 (EZH2) Inhibitors

EZH2 is overexpressed or mutated in many malignancies, including follicular lymphoma and various solid tumors. Tazemetostat, a selective inhibitor of histone methyltransferase EZH2, is approved for the treatment of patients with epithelioid sarcoma. It is also indicated for patients with follicular lymphoma that is EZH2 mutation-positive or for those with no satisfactory alternative treatment options. It is commonly associated with fatigue and gastrointestinal adverse drug reactions. Secondary malignancies, including T-cell lymphoblastic lymphoma, MDS, and AML, have also been associated with the use of tazemetostat.

Fibroblast Growth Factor Receptor (FGFR) Inhibitors

The FGFR pathway regulates numerous physiological processes, including embryogenesis, wound healing, inflammation, and angiogenesis.[34] Alterations occur in approximately 7% of solid tumors, and multiple oral FGFR inhibitors are currently approved for use. Erdafitinib is a pan-FGFR inhibitor (FGFR1-4) approved for the treatment of patients with urothelial carcinoma with a susceptible FGFR3 or FGFR2 alteration. Pemigatinib inhibits FGFR1, 2, and 3, and is approved for the treatment of patients with cholangiocarcinoma with an FGFR2 fusion. Futibatinib is the most recently approved FGFR inhibitor with selectivity for FGFR1-4. However, unlike erdafitinib and pemigatinib which compete with ATP to bind FGFR, futibatinib binds covalently and irreversibly to a cysteine in the FGFR domain.[35] Adverse drug reactions are similar for all FGFR inhibitors. Patients should be monitored for the development of ocular disorders which can be serious. Interestingly, elevated phosphate levels are common with FGFR inhibitors as the FGFR pathway is involved in a sodium-dependent phosphate cotransporter in the proximal renal tubule. Monitor phosphate levels closely and adjust or hold treatment according to the guidance provided in the prescribing information.

FMS-Like Tyrosine Kinase-3 (FLT3) Inhibitors

FLT3 is one of the most common mutations in AML and is known to play a role in the normal growth and differentiation of hematopoietic precursor cells. FLT3 mutations can be divided into internal tandem duplications or point mutations of the activation loop of the tyrosine kinase domain.

Midostaurin inhibits multiple receptors, including FLT3 mutant kinases, resulting in apoptosis of leukemic cells. It is indicated in combination with cytotoxic chemotherapy for the treatment of FLT3-positive AML. Other indications include mast cell leukemia and systemic mastocytosis. Adverse drug reactions reported with midostaurin include pulmonary toxicity, febrile neutropenia, gastrointestinal toxicities, fatigue, and hyperglycemia.

Similarly, gilteritinib inhibits multiple receptors including FLT3. It is a second-generation agent indicated for the treatment of adult patients who have relapsed or refractory AML with an FLT3 mutation. Patients taking gilteritinib must be monitored for differentiation syndrome, QTc prolongation, pancreatitis, posterior reversible encephalopathy syndrome, and creatine phosphokinase elevation. Other common adverse drug reactions include edema, stomatitis, rash, and elevated serum transaminases. Both midostaurin and gilteritinib are oral agents; midostaurin should be administered with food, whereas gilteritinib may be administered without regard to food. Fedratinib is another FLT3 inhibitor but will be discussed later in the chapter with the JAK inhibitors.

HDAC Inhibitors

The mechanism of HDAC inhibitors was discussed earlier in the chapter. Belinostat is an HDAC inhibitor that is approved for the treatment of relapsed or refractory peripheral T-cell lymphoma. The most common toxicities reported with belinostat include pyrexia, nausea, fatigue, and anemia.

Similar to belinostat, romidepsin and vorinostat inhibit HDAC. Romidepsin is approved for the treatment of cutaneous or peripheral T-cell lymphoma who have received at least one prior therapy, and vorinostat is approved for patients with cutaneous T-cell lymphoma who have received at least two prior therapies. Patients receiving romidepsin should be monitored for myelosuppression, ECG changes, and infections. Reactivation of DNA viruses, including Epstein Barr virus and hepatitis B virus (HBV), have been reported with romidepsin. Additional serious adverse drug reactions reported with vorinostat include venous thromboembolism (VTE), dose-related thrombocytopenia, and anemia.

Hedgehog Inhibitors

Sonidegib, vismodegib, and glasdegib are oral inhibitors of the Hedgehog signaling pathway that is abnormally activated in basal cell carcinoma, medulloblastoma, and leukemias. Through binding to smoothened, or SMO receptor, these agents prevent downstream signaling and activation of the Hedgehog pathway leading to the inhibition of tumor growth.

The Hedgehog pathway is essential for early embryogenesis. Therefore, sonidegib, vismodegib, and glasdegib can cause embryotoxicity, fetotoxicity, and teratogenicity. The approved labeling for these drugs contains specific recommendations regarding contraception for patients of child-bearing potential and for patients with a pregnant partner or a partner of child-bearing potential, as well as limitations regarding blood and sperm donation during treatment and for several months following the last dose.

Vismodegib is approved for metastatic or locally advanced basal cell carcinoma, while sonidegib is approved only for locally advanced disease. Vismodegib is generally well tolerated, and toxicities include muscle spasm, alopecia, dysgeusia, fatigue, and nausea. Sonidegib is associated with an

increased risk of serious musculoskeletal toxicities, and the probability of developing this adverse drug reaction appears to rise with increasing sonidegib exposure. Grades 3 and 4 serum lipase and creatine phosphokinase elevations have also been reported. Sonidegib uniquely has a very long elimination half-life of 28 days compared to vismodegib and other small-molecular targeted agents.

Glasdegib is given in combination with low-dose cytarabine and is indicated for the treatment of newly diagnosed AML in patients 75 years of age or older or for those with comorbidities that preclude intensive induction chemotherapy. Similar to vismodegib and sonidegib, muscle spasms and fatigue have been reported with glasdegib. QTc prolongation may occur so ECGs and electrolytes should be monitored while on treatment.

HER2 Inhibitors

Lapatinib is a 4-anilinoquinazoline kinase inhibitor that inhibits the intracellular kinase domains of both EGFR (ErbB1) and HER2 (ErbB2). It has demonstrated clinical activity with capecitabine in patients with previously treated breast cancer whose tumors overexpress HER2. Lapatinib is also approved for use with letrozole in postmenopausal patients for the treatment of hormone receptor–positive metastatic breast cancer that overexpresses HER2. Warnings associated with lapatinib include reduced LVEF, interstitial lung disease, diarrhea, rash, and QTc prolongation in addition to a boxed warning for hepatotoxicity. Two specific mutations observed in the HLA-DQA and HLA-DRB genes have been associated with an increased risk of hepatotoxicity.[36]

In addition to EGFR and HER2, neratinib irreversibly inhibits HER4 and is approved for HER2-positive breast cancer. Diarrhea is the most common toxicity associated with neratinib. Antidiarrheal prophylaxis during the first two treatment cycles or a neratinib dose-escalation strategy is recommended to improve tolerability and reduce the rate and severity of neratinib-associated diarrhea. Patients should be monitored for gastrointestinal toxicities, fatigue, dehydration, and hepatotoxicity.

Unlike lapatinib and neratinib, tucatinib is selective for HER2 inhibition but has minimal effects on EGFR. It is approved for HER2-positive breast cancer in combination with trastuzumab and capecitabine. Serious adverse drug reactions associated with tucatinib are similar to lapatinib and neratinib and include diarrhea and hepatotoxicity. Additionally, tucatinib may cause a “false” elevation in serum creatinine resulting from the inhibition of proximal tubule transporters which reduces creatinine secretion. This increase in serum creatinine does not affect glomerular filtration and is reversible upon treatment discontinuation.

Hypoxia-inducible Factor 2 Alpha (HIF-2α)

In a normal cell, HIF-2α regulates adaptation to hypoxia. The von Hippel-Lindau (VHL) protein maintains balance by targeting HIF-2α for degradation. However, in conditions where the VHL protein is impaired, such as in patients with VHL-associated renal cell carcinoma, HIF-2α is not degraded and becomes more abundant, ultimately translocating to the nucleus. There, HIF-2α interacts with HIF-1β which induces VEGFR and other factors ultimately resulting in angiogenesis and cell proliferation.[37]

Belzutifan, a HIF-2α inhibitor, blocks the HIF-2α and HIF-1β interaction, thus halting cell proliferation in conditions where the VHL protein is impaired.[37] It is approved for adult patients with VHL disease who require therapy for associated renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors, not requiring immediate surgery. Adverse drug reactions reported with belzutifan are associated with its mechanism of action and include hypoxia and anemia.

IDH Inhibitors

As discussed earlier in the chapter, IDH mutations are associated with impaired cellular differentiation in about 15% to 20% of patients with AML. Ivosidenib and olutasidenib are approved for the treatment of AML with a susceptible IDH1 mutation whereas enasidenib is approved for patients with AML and a susceptible IDH2 mutation. Nausea, vomiting, diarrhea, and hepatotoxicity have been reported with enasidenib and olutasidenib. Common toxicities associated with ivosidenib include nausea, mucositis, rash, and leukocytosis. Warnings for ivosidenib include QTc prolongation and Guillain-Barré syndrome. Differentiation syndrome, as discussed above with arsenic trioxide, is a potentially fatal complication associated with all IDH inhibitors.

JAK Inhibitors

Ruxolitinib is an oral inhibitor of JAK1 and JAK2 of the JAK-STAT signaling pathway; these kinases are involved in the regulation of blood and

immunologic functioning. In myelofibrosis and polycythemia vera, JAK1 and JAK2 activity is dysregulated. Ruxolitinib has been shown to modulate the affected JAK1 and JAK2 activity resulting in clinical responses and symptomatic improvement. Approved indications for ruxolitinib include the treatment of intermediate- or high-risk myelofibrosis and the treatment of polycythemia vera in patients who have had an inadequate response to or are intolerant of hydroxyurea. It is also approved for acute, corticosteroid-refractory graft-versus-host disease. The most common toxicities include thrombocytopenia, anemia, bruising, dizziness, and headache. Caution must be used when stopping ruxolitinib as severe cases of withdrawal syndrome have been reported.

While ruxolitinib inhibits both JAK1 and JAK2, fedratinib has a higher affinity for JAK2. Fedratinib is approved for myelofibrosis. The product labeling includes a boxed warning for encephalopathy so thiamine should be assessed and repleted at baseline and periodically throughout treatment. Additional adverse drug reactions associated with fedratinib include hematologic toxicities, gastrointestinal toxicities, and hepatotoxicity.

MEK Inhibitors

Reported resistance mechanisms of the BRAF inhibitors dabrafenib, encorafenib, and vemurafenib include reactivation of the MAPK pathway. The combination of BRAF and MEK inhibition has demonstrated delayed resistance in melanoma and decreased incidence of secondary cancers. MEK inhibitors, including binimetinib, cobimetinib, and trametinib, are given in combination with a BRAF inhibitor, and their indications in BRAF V600 mutated tumors are discussed above. Severe toxicities associated with MEK inhibitors include cardiomyopathy and hemorrhage. Rhabdomyolysis and hepatotoxicity have been reported with binimetinib and cobimetinib. Additionally, VTE and interstitial lung disease have been associated with binimetinib and trametinib.

Unlike the other agents in this class, selumetinib has not demonstrated success in early trials with BRAF-mutated tumors. However, selumetinib has shown tumor shrinkage and clinical benefit in children with neurofibromatosis type 1, a rare genetic disorder associated with peripheral-nerve sheath tumors known as plexiform neurofibromas.[38] Inhibition of MEK has proven successful since overactivation of the RAS pathway has been associated with neurofibromatosis type 1. Common toxicities are similar to other MEK inhibitors and include nausea, vomiting, diarrhea, increased creatine phosphokinase, rash, and paronychia. Interestingly, selumetinib capsules contain vitamin E, and, therefore, its use comes with a warning regarding increased vitamin E levels and risk of bleeding.

MET Inhibitors

The MET gene is a proto-oncogene associated with tumor cell growth and survival. MET Exon 14 skipping results in aberrant downstream signaling from the MET receptor resulting in tumor invasion, migration, and metastasis. Alterations in MET are reported in approximately 3% of solid tumors, including NSCLC. Both capmatinib and tepotinib inhibit the MET signaling pathway and are approved for patients with NSCLC harboring a MET Exon 14 skipping alteration. Hepatotoxicity and interstitial lung disease have been reported in clinical trials with capmatinib and tepotinib. Additionally, capmatinib has been associated with photosensitivity so patients should be instructed to limit ultraviolet exposure during treatment.

mTOR Inhibitors

Temsirolimus and its primary active metabolite, sirolimus, bind to the intracellular protein 12-kilodalton FK506 binding protein 12 and this protein-drug complex inhibits mTOR by blocking its kinase activity. mTOR inhibition suppresses the production of proteins that regulate progression through the cell cycle resulting in G_1-phase arrest. Temsirolimus is administered via IV infusion and is approved for the treatment of advanced renal cell carcinoma.

The most common adverse drug reactions with temsirolimus are rash, asthenia, mucositis, nausea, edema, and anorexia. Infusion reactions may occur and pretreatment with an antihistamine is recommended. Metabolic abnormalities are common with temsirolimus, including hyperglycemia and hyperlipidemia. Rare but potentially serious toxicities include interstitial lung disease, immunosuppression, and renal failure.

Similar to temsirolimus, everolimus is an mTOR inhibitor that reduces protein synthesis and cell proliferation by binding to FK506 binding protein 12. Everolimus is administered orally and has the following indications: advanced renal cell carcinoma; hormone receptor–positive, HER2-negative breast cancer with exemestane in postmenopausal patients; subependymal giant cell astrocytoma with tubular sclerosis complex; renal angiomyolipoma with tubular sclerosis complex; and pancreatic, gastrointestinal, and lung neuroendocrine tumors. Dosage forms for everolimus include traditional oral tablets and tablets for oral suspension, but it is important to note that the indications differ depending on formulation. Stomatitis is one of the most

common toxicities with everolimus, and other adverse drug reactions are similar to those of temsirolimus.

Nuclear Export Inhibitor

Selinexor is a first-in-class nuclear export inhibitor approved for patients with treatment-refractory diffuse large B-cell lymphoma and multiple myeloma. Through binding to exportin-1, selinexor inhibits nuclear export resulting in the retention of tumor suppressor proteins in the nucleus and the prevention of oncoprotein messenger RNA translation.[39] Exportin-1 is overexpressed in many cancer cells and has been associated with the development of resistance to anticancer agents.

Patients receiving selinexor should be monitored for thrombocytopenia, neutropenia, gastrointestinal toxicities, and hyponatremia. Additionally, infections are commonly reported and may include upper respiratory infection, pneumonia, and sepsis. Patients should be counseled on the potential neurotoxicity associated with selinexor, which may include syncope, hallucinations, amnesia, and mental status changes, among others.

PARP Inhibitors

PARP is essential for the repair of single-stranded DNA breaks through the base-excision-repair pathway. Tumors with breast cancer gene 1 (*BRCA1*) or *BRCA2* mutations are highly sensitive to the accumulation of single-strand DNA breaks because they exhibit a compromised ability to repair double-strand DNA breaks. Typically, double-strand DNA breaks are repaired through the homologous recombination repair pathway which involves proteins such as *BRCA1* and *BRCA2*. When tumors have deficiencies in homologous recombination repair (through a *BRCA* or other mutation), they lack the ability to repair DNA damage and are therefore more susceptible to the effects of PARP inhibition. This concept is known as *synthetic lethality* and occurs when there is a lethal synergy between two nonlethal events.[2] Four PARP inhibitors are currently available and their corresponding FDA-approved indications are as follows: niraparib is approved for ovarian, fallopian tube, or primary peritoneal cancers; olaparib is approved for *BRCA*-mutated, HER2-negative breast cancer, *BRCA*-mutated ovarian cancer, homologous recombination deficient-positive ovarian cancer, *BRCA*-mutated pancreatic cancer, and homologous recombination repair gene-mutated prostate cancer; rucaparib is approved for *BRCA*-mutated ovarian cancer and *BRCA*-mutated prostate cancer; and talazoparib is approved for *BRCA*-mutated, HER2-negative locally advanced or metastatic breast cancer.

As a class, these agents are commonly associated with anemia, fatigue, and nausea. Secondary malignancies of MDS/AML have been reported. Similar to tucatinib described earlier in the chapter, olaparib and rucaparib are commonly associated with a “false” elevation in serum creatinine. Niraparib is more often associated with thrombocytopenia and hypertension, whereas transaminase elevation is most commonly seen with rucaparib and talazoparib. Talazoparib is also associated with myelosuppression.

PDGFR-α Inhibitors

PDGFR-α belongs to a family of growth factors that act as mitogens (peptides that induce cell division) for cells of mesenchymal origin and is a hallmark of GIST. Signaling of this pathway results in differentiation, growth, and angiogenesis. Ripretinib and avapritinib are oral PDGFR-α inhibitors. Ripretinib is approved for the treatment of refractory GIST and avapritinib is approved for the treatment of GIST harboring a PDGFR-α Exon 18 mutation and advanced systemic mastocytosis. In addition to inhibiting PDGFR, ripretinib also inhibits BRAF and VEGFR, which are reflected in its toxicity profile. Ripretinib has been associated with cutaneous malignancies (including squamous cell carcinoma and melanoma), hypertension, cardiac dysfunction, PPE, and impaired wound healing. Warnings for avapritinib include intracranial hemorrhage and CNS effects.

PI3K Inhibitors

Malignant B-cell proliferation and survival depend on PI3K signaling. The p110δ isoform is highly expressed in malignant lymphoid B-cells and plays a direct role in activation of the PI3K pathway. The three PI3K inhibitors that are approved for hematologic indications have different affinities for the PI3K isoforms: idelalisib primarily inhibits p110δ; duvelisib inhibits p110δ and p110γ; and copanlisib preferentially targets p110α and p110δ.[40] Idelalisib is an oral agent approved for the treatment of relapsed CLL (in combination with rituximab). Duvelisib is an oral agent indicated for relapsed or refractory CLL and small lymphocytic lymphoma. Copanlisib, the only intravenously administered PI3K inhibitor, is indicated for relapsed follicular lymphoma. In solid tumors, mutations in the p110α subunit of PI3K result in dysregulation of the PI3K/mTOR pathway.[41] Alpelisib, an oral PI3Kα-selective inhibitor, is the only PI3K inhibitor approved for the treatment of a solid tumor: PI3KCA-mutated, hormone receptor–positive, HER2-negative breast cancer (in combination with fulvestrant).

Serious adverse drug reactions are associated with these agents. Duvelisib has a REMS program to increase awareness and mitigate the risks of infections, diarrhea/colitis, cutaneous reactions, and pneumonitis. Similarly, idelalisib has a REMS program for hepatotoxicity, diarrhea/colitis, pneumonitis, and intestinal perforation. *P. jirovecii* pneumonia prophylaxis should be administered during treatment with both duvelisib and idelalisib, and should be considered for patients receiving copanlisib. Antiviral prophylaxis to prevent cytomegalovirus infection should also be considered in select patients. Both alpelisib and copanlisib have been associated with hyperglycemia. Serious hypertension, including infusion-related hypertension, has been commonly reported with copanlisib.

Proteasome Inhibitors

The proteasome is an enzyme complex that is responsible for degrading proteins that control the cell cycle. Some of the proteins degraded by proteasomes regulate critical functions for cancer growth, such as regulation of the cell cycle, transcription factors, apoptosis, angiogenesis, and cell adhesion.

Bortezomib reversibly inhibits the 26S proteasome resulting in accumulation of IκB, an inhibitor of the major transcription factor nuclear factor κB (NF-κB). NF-κB induces transcription of genes that block cell death pathways and promote cell proliferation. Its activity depends on its release from its inhibitory partner protein, IκB, in the cytoplasm and its move to the nucleus. When IκB fails to degrade, through the actions of bortezomib, NF-κB remains in the cytoplasm, preventing it from transcribing the genes that promote cancer growth. Bortezomib is approved for the treatment of multiple myeloma and mantle cell lymphoma.

The most commonly reported toxicities with bortezomib include fatigue, nausea, diarrhea, thrombocytopenia, and fever. Peripheral neuropathy may develop or worsen with the use of bortezomib. Subcutaneous administration of bortezomib has been associated with a lower incidence of severe peripheral neuropathy when compared with intravenous administration. Caution should be used when treating patients with existing heart disease as cardiac failure has been reported. Patients should also be monitored for hypotension and acute respiratory syndrome. At least 72 hours should elapse between consecutive doses of bortezomib to minimize cumulative toxicity by permitting the restoration of proteasome function between doses. Proteasome inhibitors are associated with herpes reactivation so antiviral prophylaxis should be considered.

Carfilzomib is a second-generation, irreversible inhibitor of the 20S proteasome and is approved for relapsed or refractory multiple myeloma. As a result of its irreversible inhibition, carfilzomib produces more sustained inhibition of the proteasome. Carfilzomib is a more potent and selective inhibitor of the chymotrypsin-like activity of the proteasome and immunoproteasome and has demonstrated the ability to overcome bortezomib resistance in cell lines. Compared to bortezomib, carfilzomib is associated with a lower incidence of peripheral neuropathy, but serious cardiovascular and renal adverse drug reactions have been reported.

Ixazomib is an oral 20S proteasome inhibitor approved with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma. Common adverse drug reactions are gastrointestinal toxicity, thrombocytopenia, peripheral neuropathy, peripheral edema, and back pain. Ixazomib has a unique administration schedule for an oral agent (given on days 1, 8, and 15 of a 28-day cycle) and should be taken on an empty stomach.

Ras Inhibitors

The Kirsten ras (KRAS) oncogene is the most prevalent genomic driver in NSCLC and activating mutations occur in 25% to 30% of nonsquamous NSCLC tumors.[42] In response to extracellular stimuli, KRAS cycles between active guanosine triphosphate-bound and inactive guanosine diphosphate-bound states. The KRAS G12C mutation is the most frequent KRAS variant and, when present, favors active guanosine triphosphate resulting in increased cell signaling. Sotorasib binds to the switch II region only found on the inactive configuration, locking it in the inactive state and preventing downstream activation.[42] Patients taking sotorasib should be monitored for hepatotoxicity and interstitial lung disease. Common adverse drug reactions include diarrhea, musculoskeletal pain, fatigue, and cough.

Similar to the mechanism of sotorasib, adagrasib also binds to and inhibits KRAS G12C. However, differences in pharmacologic properties between the two drugs exist which include a longer half-life and potential CNS penetration with adagrasib.[43] Patients taking adagrasib must be monitored for QTc prolongation. Other adverse drug reactions are similar to those reported with sotorasib.

Rearranged During Transfection (RET) Inhibitors

RET is a proto-oncogene with downstream signaling pathways of MAPK and PI3K-AKT. Activating mutations are associated with medullary thyroid

cancer, and oncogenic kinase fusions have been discovered in NSCLC. Pralsetinib and selpercatinib are both oral RET inhibitors approved for the treatment of the following RET fusion-positive solid tumors: metastatic NSCLC; advanced or metastatic medullary thyroid cancer; and advanced or metastatic thyroid cancer refractory to radioactive iodine.

Although approved for the same indications, pralsetinib and selpercatinib have different off-target effects: pralsetinib inhibits FLT3, JAK1-2, VEGFR, PDGFR, and FGFR, whereas selpercatinib inhibits VEGFR and FGFR. Their toxicity profile is reflective of their inhibition of VEGFR. Notably, more hematologic adverse drug reactions have been reported with pralsetinib. Selpercatinib has been associated with concentration-dependent QTc prolongation, which is not common with pralsetinib.

Tropomyosin Receptor Kinase (TRK) Inhibitors

Chromosomal rearrangements involving in-frame fusions of neurotrophic tyrosine receptor kinase (*NTRK*) genes with various partners can result in constitutively activated chimeric TRK fusion proteins that can act as oncogenic drivers. Larotrectinib is an inhibitor of TRK proteins and has received a tissue/site agnostic approval. It is indicated for the treatment of adult and pediatric patients with solid tumors that have an *NTRK*-gene fusion. Adverse drug reactions include fatigue, nausea, dizziness, vomiting, transaminitis, cough, constipation, and diarrhea. Warnings with larotrectinib include neurotoxicity and hepatotoxicity.

Similar to larotrectinib, entrectinib is a TRK inhibitor approved for the treatment of solid tumors with an *NTRK*-gene fusion. Entrectinib also inhibits ROS1 and ALK and is indicated for the treatment of ROS1-positive NSCLC. Patients receiving entrectinib should be monitored for cardiac toxicities (including QTc prolongation), CNS effects, fractures, hepatotoxicity, hyperuricemia, and vision disorders.

VEGFR Multikinase Inhibitors

Most small-molecule kinase inhibitors are promiscuous; significant off-target activity is associated with these agents due to the inhibition of multiple kinases. The oral multikinase inhibitors described in this section all inhibit VEGFR and, thus, angiogenesis. However, their activity and adverse drug reaction profile may differ because of off-target effects. Inhibiting downstream signaling from the VEGFR results in class toxicities, including hypertension, proteinuria, wound healing complications, bleeding, VTE, and gastrointestinal perforations/fistulas. Hypertension must be well-controlled prior to therapy initiation. Additionally, patients with recent serious cardiovascular events (eg, myocardial infarction), hemorrhage, or gastrointestinal perforation/fistula should avoid VEGFR inhibitors. Due to altered wound healing, VEGFR inhibitors should be held before elective surgery and after major surgery until adequate wound healing.

Sorafenib and Sunitinib

First-generation inhibitors, sunitinib and sorafenib, inhibit multiple growth factor receptors (eg, VEGFR-2 and PDGFR), cell surface proteins (eg, KIT), and cytokine receptors (eg, FLT3), and, thus, disrupt multiple aberrant intracellular signaling pathways. In addition, sorafenib inhibits Raf, which is part of the MAPK signaling pathway. Sunitinib is approved for GIST, pancreatic neuroendocrine tumors, and renal cell carcinoma; and sorafenib is approved for unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and differentiated thyroid carcinoma refractory to radioactive iodine treatment.

In addition to the traditional VEGFR inhibitor toxicities listed above, sunitinib is uniquely associated with a yellow discoloration of the skin or hair which is related to the yellow color of the active drug. Although this adverse drug reaction is benign, patients who develop a yellowing of the skin must be evaluated for hepatotoxicity which has also been reported with sunitinib.

Axitinib, Pazopanib, and Tivozanib

The next-generation inhibitors axitinib, pazopanib, and tivozanib inhibit VEGFR-1, -2, -3, KIT, and PDGFR. However, axitinib and tivozanib have enhanced potency and selectivity to all VEGFR kinases with minor activity against PDGFR and KIT. All three agents are indicated for the treatment of advanced renal cell carcinoma. Pazopanib has an additional indication for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy.

Cabozantinib

Cabozantinib is a small-molecule inhibitor of numerous receptor kinases, most importantly RET, VEGFR-2, and MET. As described earlier, MET is required for several important processes during embryogenesis (eg, angiogenesis) and leads to abnormal growth and proliferation of several tumors. Medullary thyroid cancers express mutated RET as well as VEGFR-2 and MET. Cabozantinib is approved for the treatment of metastatic medullary thyroid cancer, renal cell carcinoma, and hepatocellular carcinoma. Toxicities reported in clinical trials include diarrhea, PPE, electrolyte abnormalities, transaminitis, and stomatitis. Of note, cabozantinib is available as both an oral capsule and tablet, which are not bioequivalent and therefore not interchangeable.

Lenvatinib

Lenvatinib primarily inhibits VEGFR-1, -2, and -3, but it can also inhibit other kinases including FGFR, PDGFR, KIT, and RET. Lenvatinib is approved for the following indications: as a single agent for the treatment of radioactive iodine-refractory differentiated thyroid cancer; as a single agent for the treatment of unresectable hepatocellular carcinoma; in combination with everolimus for the treatment of renal cell carcinoma; and in combination with pembrolizumab for patients with advanced endometrial carcinoma. Common toxicities seen with lenvatinib include fatigue, diarrhea, stomatitis, and PPE.

Regorafenib

Regorafenib is a multikinase inhibitor that blocks the activity of several protein kinases, including those involved in the regulation of tumor angiogenesis (VEGFR-1, -2, and -3), oncogenes and downstream targets (KIT, RET, RAF1, and BRAF), as well as PDGFR and FGFR. Many of these targets are important in gastrointestinal carcinomas, and regorafenib has demonstrated activity in these tumors. FDA-approved indications include colorectal cancer, GIST, and hepatocellular carcinoma. Serious adverse drug reactions reported with regorafenib include hepatotoxicity and reversible posterior leukoencephalopathy syndrome. Common adverse drug reactions with regorafenib include asthenia, mucositis, gastrointestinal toxicities, and PPE. To improve tolerability, a weekly dose-escalation strategy has been proposed.[44] Regorafenib should be given orally with a low-fat evening meal, as the toxicities appear minimized when given at night.

Vandetanib

Vandetanib is a small-molecule inhibitor of RET, VEGFR-2 and -3, and EGFR. It is approved for the treatment of metastatic medullary thyroid cancer. Toxicities observed with vandetanib include diarrhea and rash. Vandetanib can prolong the QTc interval, and cases of Torsades de pointes and sudden death have been reported. Because of this risk, vandetanib is only available through a REMS program where prescribers and pharmacies must be certified through the program before prescribing or dispensing vandetanib.

TARGETED AGENTS: ANTIBODIES

7 Biologic therapies are a diverse group of agents that include cytokines, mAbs, and growth factors. Biologics are generally large and complex molecules that are manufactured in a microorganism or other living system. The mAb is the most common biologic therapy available to treat patients with solid tumors and hematologic malignancies.

Biosimilars

Due to the complex process associated with manufacturing biologics, “generic” biologic products are not approved in the same manner as small-molecule pharmaceuticals. Unlike generic small-molecule agents that must demonstrate bioequivalence to a branded product, biosimilars must be “highly similar” to the reference product. Biosimilars must demonstrate that no clinically meaningful differences in safety, purity, and potency exist between it and the reference product. Some biosimilar agents undergo additional evaluation and testing to meet the requirements of an “interchangeable product.” An interchangeable product is expected to produce the same clinical result as the reference product and can generally be substituted without consulting the prescriber.[45] Of note, some institutions have a therapeutic interchange list that permits substitutions of biosimilars based on policies developed by the local Pharmacy and Therapeutics Committee.

Monoclonal Antibodies

A mAb is designed to target a pathway critical for the survival and proliferation of cancer cells resulting in selective destruction of the malignant cells

while minimizing toxicities to healthy tissues. The mAb can bind to either the extracellular receptor or its natural ligand and prevent the activation of downstream intracellular signaling. Additionally, some immunotherapies (eg, immune checkpoint inhibitors) are mAbs that target a specific pathway to allow for immune activation.

Each mAb consists of immunoglobulin sequences that are known to recognize a specific antigen or protein on the surface of cells. There are five classes of immunoglobulins, but IgG is the most commonly used therapeutically. Similar to endogenous antibodies, the Fab portion is composed of heavy and light chains that are responsible for binding to antigens, and the constant region determines the effector function of the antibody. The mAb may be naked (unconjugated) or conjugated to a toxin (immunotoxin), chemotherapy agent (antibody-drug conjugate [ADC]), or radioactive particle (radioimmunoconjugate).

In 2017, the standard nomenclature for mAbs was revised. As before, mAbs receive a random prefix, an infix indicating the target, and the suffix "-mab." However, the prior requirement to include the source (ie, -o-, -u-, -xi-, and -zu- to indicate murine, human, chimeric, and humanized, respectively) has been removed. The nonproprietary name of a mAb consists of a core name (eg, trastuzumab) and a distinguishing suffix composed of four lowercase letters (eg, trastuzumab-dkst). If the product is conjugated, a separate word is added to identify the toxin, chemotherapy, or radioactive particle. For example, the ADC ado-trastuzumab emtansine consists of the mAb trastuzumab plus emtansine which identifies the name of the cytotoxic payload and linker. The prefix "ado" was added to reduce the potential for confusion between the ADC and the unconjugated mAb.

The first mAbs used in humans were murine, but most of the antibodies used today are humanized or human. These agents differ in the amount of foreign component. Hypersensitivity and infusion-related reactions, with or without the development of antiproduct antibodies, are generally greatest with murine antibodies and least with humanized antibodies. The severity of these reactions can range from mild (eg, fever, chills, nausea, and rash) to severe, life-threatening anaphylaxis with cardiopulmonary collapse. Patients with a hypersensitivity or infusion-related reaction may also experience chest or back pain during the infusion. Patients with circulating cancer cells in the bloodstream are at highest risk for more severe reactions. Patients must be monitored closely during infusion. The reactions tend to be more severe with the initial few treatments and subside with subsequent infusions. Some mAbs require premedication, including antihistamines, acetaminophen, or corticosteroids, to minimize hypersensitivity reactions. Recommended infusion rates may be longer for the initial dose, with incremental increases as tolerated. For patients experiencing signs or symptoms of infusion-related reactions, the infusion should be interrupted, and prompt treatment with antihistamines, corticosteroids, and other supportive measures should be initiated. Other adverse drug reactions are typically determined by the selectivity of the target antigen. mAbs against antigens found on normal and cancer cells are expected to have increased toxicity compared with tumor-specific antigens found only on malignant tissues.

Unconjugated mAbs that target antigens on the cell surface of cancer cells may induce death of cancer cells by several mechanisms. These mAbs could directly mediate cell killing through CDC, ADCC, or inhibiting intracellular signaling. CDC occurs when the Fc portion of the antibody activates the complement system, leading to tumor cell lysis. ADCC occurs when effector cells that contain Fc receptors bind to the Fc portion of the antibody and either lyses or phagocytizes the antibody-containing cell. Natural killer cells, monocytes, and macrophages are all capable of mediating ADCC. Finally, antibody binding may result in the transmission of signals that induce apoptosis or programmed cell death in the targeted cell.

Immunoconjugates deliver a payload, typically a chemotherapy agent, toxin, or radioactive particle to a cell targeted by the antibody. After the antibody binds the target antigen, the payload is internalized by the target cell and kills cancer cells through traditional mechanisms of action. In addition to killing the target cell, radioimmunoconjugates are capable of killing antigen-negative cancer cells, sometimes termed the "bystander effect." Theoretically, immunoconjugates deliver therapy to specific sites of disease while limiting systemic exposure to the chemotherapy, radiation, or toxin. The mAb might also contribute to the observed anticancer effects.

Antibody-Drug Conjugates

ADCs were developed to exploit the selectivity and binding properties of mAbs to deliver cytotoxic chemotherapy directly to the targeted cell. These agents consist of three components: the antibody, the linker, and the cytotoxic payload. To cause cancer cell death, the antibody must first bind to the target antigen, and then the complex must be internalized into the cell through receptor-mediated endocytosis. The antibody-drug complex is then degraded, the cytotoxic payload is released, and cancer cell death occurs. Theoretical benefits of conjugates are a result of the delivery of cytotoxic chemotherapy directly to the target site resulting in decreased toxicity.

Antibodies That Target CD19

The CD19 antigen is a cell surface protein expressed on B-cell lymphocytes and B-cell malignancies. Overexpression leads to tumor cell proliferation.

Destruction of CD19-expressing malignant cells may be accomplished through a bispecific T-cell engager (eg, blinatumomab) or through CAR T-cell therapy (eg, axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, tisagenlecleucel) which are discussed later in the chapter.

Tafasitamab is a humanized mAb that targets CD19 and mediates ADCC, antibody-dependent cellular phagocytosis, and direct cytotoxicity.[46] It has demonstrated synergistic activity in combination with lenalidomide and is approved for the treatment of relapsed or refractory diffuse large B-cell lymphoma in patients who are not eligible for autologous HSCT. Patients receiving tafasitamab should be monitored for infusion-related reactions, myelosuppression, and infections.

Loncastuximab tesirine is an ADC-targeting CD19, and the cytotoxic payload is an alkylating agent (SG3199). It is approved for the treatment of patients with large B-cell lymphoma. Patients receiving loncastuximab tesirine must be monitored for effusions and edema, myelosuppression, infections, and cutaneous reactions. Photosensitivity reactions have also been reported so patients should be counseled to minimize or avoid exposure to sunlight.

Antibodies That Target CD20

Rituximab

Rituximab is a chimeric antibody directed against the CD20 antigen found on the surface of normal and cancerous B-cells. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis. The mechanisms of its anticancer effect include CDC and ADCC of malignant B-cells and possibly a direct apoptotic effect.

Rituximab is approved for the treatment of low-grade or follicular, CD20-positive, B-cell NHL in multiple settings and for the treatment of CD20-positive CLL with standard chemotherapy. Rituximab is also indicated for the treatment of a variety of immune-mediated diseases, including rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis. It is administered as an intravenous infusion.

Infusion-related reactions associated with rituximab primarily occur during the first infusion and are components of an infusion-related complex secondary to the amount of circulating B-cells. After the first infusion, the incidence and the severity of these reactions decrease dramatically. Premedication and additional supportive care medications may be required depending on indication. The most common reactions with the infusion-related complex are transient fever, chills, nausea, asthenia, and headache. Additionally, rituximab and other mAbs targeting CD20 may cause HBV reactivation and should not be administered in patients with severe, active infections.

Rituximab is also available in combination with hyaluronidase, which is administered via subcutaneous injection. When mAbs are administered subcutaneously, hyaluronidase is a necessary component because it degrades hyaluronan and allows for a more permeable extracellular matrix providing greater diffusion capacity and bioavailability of the mAb. All patients must receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse drug reactions before starting treatment with rituximab/hyaluronidase. The combination product is approved for follicular lymphoma, diffuse large B-cell lymphoma, and CLL.

Obinutuzumab

Obinutuzumab is a type II humanized anti-CD20 mAb approved for CLL and follicular lymphoma. When compared with the type I anti-CD20 antibodies such as rituximab, type II agents exhibit a different elbow hinge angle and therefore bind CD20 in a different orientation. Furthermore, the Fc portion of obinutuzumab has been glycoengineered to reduce fucosylation resulting in improved receptor affinity and enhanced ADCC potency.[47]

Adverse drug reactions associated with obinutuzumab include infusion-related reactions, myelosuppression, nausea, and diarrhea. HBV reactivation and progressive multifocal leukoencephalopathy have also been reported with obinutuzumab.

Ofatumumab

Ofatumumab is a type I human mAb that also targets the CD20 antigen. Its mechanism of action is similar to that of rituximab, but ofatumumab targets a different epitope than rituximab, has greater affinity for the antigen, and dissociates from the epitope slower than rituximab. Specifically, ofatumumab binds to two regions of the CD20 antigen, the small extracellular loop and the N-terminal region of the large extracellular loop. As a result, anticancer activity has been demonstrated in patients who have progressed on rituximab in a variety of B-cell cancers. Ofatumumab is approved for the treatment of CLL. Adverse drug reactions are similar to rituximab with fewer infusion-related reactions and a higher rate of infectious complications.

Ofatumumab is only available through a restricted distribution program for patients deemed appropriate for treatment.

Antibodies That Target CD22

CD22 is expressed on over 90% of leukemic blasts in patients with B-cell ALL. Inotuzumab ozogamicin is an ADC-targeting CD22 on B-cells. This agent consists of an IgG4 antibody linked to calicheamicin (an antitumor antibiotic) and is approved for the treatment of relapsed or refractory B-cell precursor ALL in adults. Prescribing information for inotuzumab ozogamicin warns of the risk for increased post-HSCT nonrelapse mortality rate. Potentially severe toxicities include hepatotoxicity, myelosuppression, infusion-related reactions, and QTc prolongation.

Antibodies That Target CD30

Brentuximab vedotin is an ADC that targets the CD30 antigen found on cancer cells. Upon binding to the CD30 antigen, brentuximab vedotin is internalized by endocytosis and the dipeptide bond that links the naked mAb to the chemotherapy monomethylauristatin E (also known as MMAE) is cleaved. Monomethylauristatin E then binds to microtubules and acts as an inhibitor of microtubule polymerization. It may also induce apoptosis by inhibiting NF-κB. Brentuximab vedotin is indicated for Hodgkin lymphoma, anaplastic large cell lymphoma, peripheral T-cell lymphoma, and mycosis fungoides. Infusion-related reactions, peripheral neuropathy, and neutropenia are common toxicities seen with brentuximab vedotin administration; these toxicities are common with other microtubule inhibitors.

Antibodies That Target CD33

Consisting of an IgG4 kappa antibody linked to a calicheamicin derivative, gemtuzumab ozogamicin is an ADC-targeting CD33, which is expressed on leukemic cells in AML. Gemtuzumab ozogamicin has a unique approval history. In 2000, gemtuzumab ozogamicin received an accelerated approval for the treatment of patients with AML but was removed from the market soon thereafter due to lack of benefit and excessive toxicity. However, since then, multiple studies have been completed using a modified dosing scheme resulting in the reapproval of gemtuzumab ozogamicin for the treatment of CD33-positive AML. Warnings associated with the use of this agent include hepatotoxicity (including veno-occlusive disease), infusion-related reactions, and hemorrhage. Other common toxicities are infection, fever, nausea, vomiting, constipation, headache, rash, and mucositis.

Antibodies That Target CD38

Daratumumab is a mAb that inhibits CD38-expressing tumor cells by inducing apoptosis directly through Fc-mediated cross-linking and immune-mediated tumor cell lysis through CDC, ADCC, and antibody-dependent cellular phagocytosis. Myeloid-derived suppressor cells and a subset of regulatory T-cells express CD38. Daratumumab is administered as an intravenous infusion and is also available in combination with hyaluronidase for subcutaneous injection. Both formulations are approved for the treatment of patients with multiple myeloma and are typically given in combination with other anticancer agents.

The most frequently reported adverse drug reactions are infusion-related reactions, fatigue, nausea, back pain, pyrexia, cough, upper respiratory tract infection, and myelosuppression. Premedications (corticosteroid, antipyretic, and an antihistamine) and a postinfusion medication (corticosteroid) are recommended to prevent acute and delayed infusion reactions. Daratumumab interferes with blood bank cross-matching by binding to CD38 on red blood cells possibly resulting in a positive indirect Coombs test. It is therefore recommended that a type and screen be performed prior to treatment initiation. If a blood transfusion is necessary, inform the blood bank that the patient has received daratumumab.

Isatuximab is a mAb-targeting CD38 that is indicated for the treatment of multiple myeloma in combination with dexamethasone and either pomalidomide or carfilzomib. Warnings associated with isatuximab are similar to those with daratumumab including infusion-related reactions and a false-positive indirect Coombs test. Additionally, patients receiving isatuximab are at risk of developing a second primary malignancy, such as skin cancer. In one study, the overall incidence of a second primary malignancy was 3.9% in patients receiving isatuximab, pomalidomide, and dexamethasone versus 0.7% in patients receiving only pomalidomide and dexamethasone.[48]

Daratumumab, isatuximab, and all other mAbs approved for the treatment of multiple myeloma (regardless of target) are associated with a warning for interference with the M-protein assay which is used for the clinical monitoring of patients with multiple myeloma. The interference is related to the assay being unable to distinguish between M-proteins and mAbs.

Antibodies That Target CD52

Alemtuzumab is a recombinant humanized mAb that is directed against CD52. CD52 is expressed on the surface of B and T lymphocytes, natural killer cells, monocytes, and macrophages. Its anticancer activity comes from binding to the CD52 antigen present on leukemic lymphocytes and inducing cell lysis and death. Alemtuzumab is indicated as a single agent for the treatment of B-cell CLL.

Alemtuzumab is associated with severe infusion-related reactions, hematologic toxicity, and opportunistic infections. Hematologic toxicity consisting of severe prolonged neutropenia and thrombocytopenia occurs in most patients. Health professionals should monitor complete blood counts before each dose to determine the need for dose modification. Since CD52 is expressed on lymphocytes, alemtuzumab can induce profound lymphopenia including a decrease in CD4 and CD8 counts. Patients should receive prophylaxis for *Pneumocystis jirovecii* pneumonia and herpes virus, which should be continued for a minimum of 2 months after completing alemtuzumab therapy or until recovery of CD4 counts. Alemtuzumab is only available through a restricted distribution program that allows access for patients deemed appropriate for treatment.

Antibodies That Target CD79B

While CD79B is present on the surface of most malignant B-cells, its expression on mature B-cells is restricted, thus making it an attractive target.[49] Polatuzumab vedotin is an ADC consisting of monomethylauristatin E conjugated to an anti-CD79B mAb. It is given in combination with bendamustine and rituximab for the treatment of diffuse large B-cell lymphoma. Toxicities include peripheral neuropathy, infusion-related reactions requiring premedications, myelosuppression, infections, multifocal leukoencephalopathy, TLS, and hepatotoxicity.

Antibodies That Target Chemokine Receptor

Mogamulizumab is a recombinant humanized IgG1 kappa mAb that targets CC chemokine receptor 4–expressing cells. CC chemokine receptors are a subfamily of chemokine receptors that possess four cysteine residues; chemokines are chemoattractants that facilitate the migration of cells. CC chemokine receptor 4 is involved in the trafficking of lymphocytes to various organs. Mogamulizumab is indicated for relapsed or refractory mycosis fungoides or Sézary syndrome. The most common adverse drug reactions are rash, infusion-related reactions, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection.

Antibodies That Target Folate Receptor Alpha

Folate receptor alpha is a cell surface protein that is overexpressed in epithelial ovarian carcinoma. Given the limited expression in healthy tissues and its ability to engulf large molecules, folate receptor alpha is an optimal target for an ADC. Mirvetuximab soravtansine is an ADC that consists of an antibody which targets folate receptor alpha and a payload of DM4 (a tubulin-targeting agent).[50] Prior to each dose, the following premedications are recommended: a corticosteroid, an antihistamine, an antipyretic, and an antiemetic. Severe ocular toxicities have been reported with mirvetuximab soravtansine which require baseline and periodic ophthalmic exams in addition to prophylactic artificial tears and ophthalmic topical steroids throughout treatment. Additional adverse drug reactions include pneumonitis, peripheral neuropathy, nausea, and fatigue.

Antibodies That Target GD2

Glycolipid GD2 is expressed primarily on the cell surface of neuroblastoma cells and on normal tissues, including neurons and peripheral sensory nerve fibers.[51] The function of the GD2 carbohydrate antigen is not completely understood, but it is thought to play a role in the attachment of tumor cells to extracellular matrix proteins.[51] Dinutuximab is a chimeric mAb that binds GD2, thereby inducing cell lysis through ADCC and CDC. This activity is thought to be enhanced when dinutuximab is given with granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-2. Dinutuximab is approved to be given with GM-CSF, interleukin-2, and 13-cis-retinoic acid for the treatment of pediatric patients with high-risk neuroblastoma. Serious toxicities associated with dinutuximab include infusion-related reactions and neurotoxicities. Patients should be monitored for infections, hypokalemia, hypotension, and capillary leak syndrome. Severe neuropathic pain occurs in most patients and intravenous opioids are required prior to, during, and immediately following administration.

Similar to dinutuximab, naxitamab binds to cell surface GD2 and induces ADCC and CDC. Naxitamab is indicated in combination with GM-CSF for the treatment of pediatric and adult patients with high-risk neuroblastoma. Serious toxicities include infusion-related reactions, neurotoxicity, and hypertension. To manage severe neuropathic pain, patients should receive a 12-day course of a neuropathic pain medication (eg, gabapentin) starting 4 days before initiation in addition to opioids before the start of the infusion.

Antibodies That Target Nectin-4

Using the microtubule-disrupting agent monomethylauristatin E as its payload, enfortumab vedotin is an ADC-targeting nectin-4 that is approved for the treatment of urothelial carcinoma. Nectin-4 is an adhesion protein on cell surfaces that is highly expressed in urothelial cancer and also reported in breast, lung, and pancreatic cancer. Serious adverse drug reactions associated with enfortumab vedotin include skin reactions, peripheral neuropathy, hyperglycemia, and ocular disorders. Patients, particularly those with diabetes mellitus, should monitor blood glucose levels closely, and enfortumab vedotin should be held if blood glucose is greater than 250 mg/dL (13.9 mmol/L). Patients should be monitored for vision changes, and prophylactic artificial tears may be considered for dry eyes.

Antibodies That Target EGFR

Cetuximab

Cetuximab is a chimeric mAb that binds specifically to the extracellular domain of EGFR on both normal and cancer cells, and competitively inhibits the binding of epidermal growth factor and other ligands, such as transforming growth factor-α. Binding of cetuximab to the EGFR inhibits cell growth, induces apoptosis, and inhibits VEGF production. Cetuximab is indicated for the treatment of metastatic KRAS wild-type colorectal cancer and for squamous cell head-and-neck cancer. Acneiform rash and skin reactions occur in most patients receiving cetuximab, as observed with other agents that inhibit EGFR. Multiple follicular or pustular lesions generally appear within the first 2 weeks of therapy and usually resolve after cessation of treatment. Resolution can be slow, continuing beyond 28 days in nearly half of cases. In patients who develop a severe rash, dose modifications may be necessary. Interestingly, a trend for improved responses with increasing severity of skin reactions has been suggested but additional research is required to confirm this association.[31]

Additionally, patients receiving cetuximab should be monitored for other serious adverse drug reactions including infusion-related reactions and electrolyte abnormalities. Hypomagnesemia may be severe and can occur within days or months after treatment. Cardiopulmonary arrest and sudden death have also been reported.

Panitumumab

Panitumumab, the first human mAb approved to treat cancer, is an IgG2 antibody that binds to the cell surface EGFR. It is approved to treat RAS wild-type metastatic colon cancer. Adverse drug reactions are similar to cetuximab, although severe infusion-related reactions appear to be less common because panitumumab does not have a murine component.

Both cetuximab and panitumumab are more effective in patients with tumors that are RAS wild-type compared to tumors that are RAS mutation-positive. Therefore, patients with metastatic colorectal cancer should not receive anti-EGFR antibody therapy if a RAS mutation is detected. Genetic testing of colorectal cancers is discussed in further detail in Chapter 153, “Colorectal Cancer.”

Necitumumab

Necitumumab is a next-generation mAb that binds to the human EGFR and blocks the binding of EGFR to its ligands. It is approved for the treatment of patients with metastatic *squamous* NSCLC in combination with gemcitabine and cisplatin. Serious and clinically significant adverse drug reactions include cardiopulmonary arrest, hypomagnesemia, thromboembolic events, dermatologic toxicities, and infusion reactions. Since increased toxicity and mortality was observed when necitumumab was given with pemetrexed and cisplatin for the treatment of nonsquamous NSCLC, patients with metastatic nonsquamous NSCLC should not receive necitumumab.

Antibodies That Target EGFR and MET

Amivantamab is a bispecific antibody that binds both EGFR and MET. It is approved for the treatment of patients with NSCLC that harbors an EGFR exon 20 insertion mutation. These mutations are associated with de novo EGFR inhibitor resistance and a poor patient prognosis.[52] Due to the high incidence of amivantamab infusion-related reactions, the prescribing information recommends premedications and peripheral administration of the first two infusions. Other serious adverse drug reactions include interstitial lung disease, dermatologic toxicities, and ocular toxicities.

Antibodies That Target HER2

HER2-Targeting mAbs

Trastuzumab is a humanized mAb that selectively binds to HER2. HER2 is overexpressed in about 33% of breast cancers, in about 22% of gastroesophageal junction and gastric cancers, and to varying degrees in other malignancies. Trastuzumab inhibits cell-cycle progression by decreasing cells entering the S phase of the cell cycle, which leads to downregulation of HER2 receptors on cancer cells and decreased cell proliferation. Trastuzumab also leads to ADCC and CDC and directly induces apoptosis in cells overexpressing HER2. In addition, synergy between trastuzumab and chemotherapy has been demonstrated, resulting in trastuzumab often being used in combination regimens. Trastuzumab is administered via intravenous infusion and is approved for the treatment of HER2-positive breast cancer and metastatic gastric or gastroesophageal junction adenocarcinoma. The tumor should overexpress HER2 as measured by diagnostic tests that can quantify gene amplification or protein expression. Additionally, a trastuzumab and hyaluronidase subcutaneous injection formulation has been approved for the treatment of HER2-positive breast cancer.

The most serious adverse drug reactions associated with trastuzumab include cardiomyopathy, hypersensitivity reactions, and increased myelosuppression. An evaluation of cardiac function should be performed before administration and extreme caution should be exercised in patients with preexisting cardiac dysfunction and in those who have received prior anthracyclines. In patients who develop a clinically significant decrease in LVEF (defined as greater than 16% decrease in ejection fraction from pretreatment levels or an ejection fraction below normal limits and greater than 10% decrease from baseline), discontinuation of therapy should be considered. Myelosuppression is infrequent with trastuzumab alone, but the incidence of neutropenia and febrile neutropenia is higher when trastuzumab is given with myelosuppressive chemotherapy.

Pertuzumab is a humanized mAb that targets the HER2 receptor. It is synergistic with trastuzumab and is effective in tumors that have developed resistance to trastuzumab. Pertuzumab binds to the extracellular domain II of HER2, a site distinct from trastuzumab, and inhibits ligand-dependent HER2–HER3 dimerization, which subsequently decreases tumor proliferation and resistance pathways. Dual targeting of the HER2 receptor allows for increased efficacy against variant forms of the HER2 receptor, including truncated HER2 receptors. Similar to trastuzumab, it appears to induce ADCC in cancer cells. Pertuzumab is approved to treat HER2-overexpressed breast cancer in combination with trastuzumab and chemotherapy. Warnings and precautions are similar to those of trastuzumab, including a boxed warning for cardiotoxicity.

Because pertuzumab and trastuzumab are often administered as part of the same regimen in clinical practice, a subcutaneous formulation of these agents in combination with hyaluronidase was developed for the treatment of breast cancer. Warnings associated with this agent include cardiomyopathy, pulmonary toxicity, exacerbation of chemotherapy-induced neutropenia, and administration-related reactions.

Margetuximab, another HER mAb, binds to the same extracellular domain of HER2 as trastuzumab, but has a modified Fc region. The modified Fc is thought to allow for increased binding to the activating receptor and decreased binding to the inhibitory receptor, thus leading to greater ADCC compared to trastuzumab.[53] Margetuximab is approved for the treatment of HER2-positive metastatic breast cancer in combination with chemotherapy in patients who have received two or more prior anti-HER2 regimens. Similar to other agents in this class, the margetuximab product labeling contains a warning for left ventricular dysfunction.

HER2-Targeting ADCs

Ado-trastuzumab emtansine (sometimes referred to as T-DM1) is indicated for the treatment of HER2-positive breast cancer, whereas fam-trastuzumab deruxtecan is approved for the treatment of patients with HER2-positive breast cancer and gastric cancer. Ado-trastuzumab emtansine is an ADC that consists of the humanized anti-HER2 mAb trastuzumab covalently linked to the microtubule inhibitory drug derivative of maytansine 1. The adverse drug reactions associated with ado-trastuzumab emtansine are similar to those reported with trastuzumab and microtubule inhibitors.

Fam-trastuzumab deruxtecan is an ADC that consists of an anti-HER2 mAb covalently linked to DX-8951 derivative, a topoisomerase I inhibitor. Warnings on the product labeling include pneumonitis, neutropenia, and left ventricular dysfunction. Unlike most ADCs, nausea and vomiting are common with fam-trastuzumab deruxtecan, and it is associated with a moderate emetic risk. It is important to note that ado-trastuzumab emtansine, fam-trastuzumab deruxtecan, and trastuzumab are not interchangeable and should not be substituted for one another.

Monoclonal Antibodies That Target Signaling Lymphocytic Activation Molecule Family 7 (SLAMF7)

Elotuzumab is an IgG mAb directed against SLAMF7. SLAMF7 is expressed on multiple myeloma cells, natural killer cells, and other immune cells. The antitumor effects of elotuzumab are a result of ADCC and through blocking multiple myeloma and stromal cell interaction but it is not thought to induce CDC.[54] Elotuzumab is approved in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma. The most common adverse drug reactions reported include fatigue, diarrhea, constipation, pyrexia, peripheral neuropathy, decreased appetite, cough, and respiratory infections. Patients should also be monitored for infusion-related reactions, infections, second primary malignancies, and hepatotoxicity.

Antibodies That Target Tissue Factor

Tissue factor is a protein prevalent in various solid tumors, including cervical cancer. Tisotumab vedotin is an ADC with an antibody that targets tissue factor and a payload of monomethyl auristatin E (a microtubule inhibitor). Similar to other ADCs with the monomethyl auristatin E payload, tisotumab vedotin is associated with ocular toxicities and peripheral neuropathy. To aid in reducing the risk of severe ophthalmic reactions, the following instructions and premedications are recommended: topical corticosteroid ophthalmic drops starting prior to each infusion and continuing for 72 hours; topical vasoconstrictor ophthalmic drops immediately prior to each infusion; cooling eye packs during the infusion; topical lubricating ophthalmic drops during treatment and for 30 days after the last dose; and contact lenses should be avoided for the duration of the treatment. Additional adverse drug reactions include hemorrhage, pneumonitis, alopecia, fatigue, increased creatinine, diarrhea, and rash.

Antibodies That Target Trophoblast Cell-Surface Antigen 2 (TROP2)

Sacituzumab govitecan is an ADC-targeting TROP2, which is a transmembrane calcium signal transducer overexpressed in many epithelial cancers. The cytotoxic payload of sacituzumab govitecan is SN-38 which, as described above, is the active metabolite of the topoisomerase I inhibitor irinotecan. Therefore, precautions and adverse drug reactions are similar between these agents. Boxed warnings for sacituzumab govitecan include neutropenia and diarrhea. The management strategy for diarrhea is similar to that of irinotecan: atropine is used for acute diarrhea, whereas loperamide is the best option for delayed diarrhea. Patients homozygous for the UGT1A1*28 allele are at increased risk of neutropenia, febrile neutropenia, and anemia. Sacituzumab govitecan is approved for the treatment of triple negative breast cancer and urothelial carcinoma.

Antibodies That Target VEGF

Bevacizumab

Bevacizumab is a humanized mAb directed against circulating VEGF. It binds to all biologically active circulating isoforms of VEGF and prevents the activation and promotion of angiogenesis. Bevacizumab is approved for the treatment of patients with multiple types of solid tumors including the following: cervical cancer; colorectal cancer; glioblastoma; nonsquamous NSCLC; ovarian, fallopian tube, or primary peritoneal cancer; and renal cell carcinoma. A bevacizumab biosimilar, bevacizumab-awwb, was the first biosimilar approved for the treatment of cancer.

Several serious adverse drug reactions have been associated with bevacizumab, including hypertension, bleeding, and thrombotic events. Hypertension is more common in patients with a history of uncontrolled blood pressure, and it responds to oral antihypertensive medications. Although the most common bleeding episodes are transient epistaxis, fatal CNS and gastrointestinal hemorrhages have been reported. The product labeling includes warnings regarding the risk of gastrointestinal perforation, wound dehiscence, and hemorrhage. Bevacizumab is not recommended for use within 28 days of major surgery and patients should be instructed to report abdominal pain (an initial sign of gastrointestinal hemorrhage) to their health professionals immediately. Paradoxically, bevacizumab also has been associated with thrombotic events, including deep vein thrombosis, pulmonary embolism, and myocardial infarction, especially in elderly patients with a history of cardiac events. Another potentially serious adverse drug reaction associated with bevacizumab is proteinuria/nephrotic syndrome, and patients should be monitored for the development or worsening of proteinuria with serial urine dipsticks.

Ramucirumab

Ramucirumab is a human mAb that binds to VEGFR-2 resulting in the inhibition of ligand-induced proliferation. While bevacizumab binds the circulating ligand (ie, VEGF), ramucirumab inhibits angiogenesis through the specific blockade of VEGFR-2. Ramucirumab is approved for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma as a single agent or with paclitaxel. Other indications include the following: treatment of metastatic NSCLC in combination with erlotinib or docetaxel; treatment of hepatocellular carcinoma in patients who have an AFP of ≥400

ng/mL (mcg/L) following treatment with sorafenib; and for the treatment of metastatic colorectal cancer in the second-line setting. When administered as a single agent, the most common toxicities associated with ramucirumab are hypertension and diarrhea. Patients should also be monitored for thromboembolic events, hypertension, proteinuria, and thyroid dysfunction.

Bispecific T-Cell Engagers

Blinatumomab is a bispecific T-cell engaging antibody directed against a B-lymphocyte-specific molecule CD19. Through the formation of a synapse, blinatumomab serves as a linker between CD19 on malignant B-cells and CD3 on T-cells, thereby potentiating T-cell–induced cytotoxic cell killing. Blinatumomab is indicated for the treatment of CD19-positive B-cell precursor ALL.

Due to its short half-life (~2 hours) and mechanism of action, blinatumomab is administered as a continuous intravenous infusion over 28 days. In addition to possible decreased efficacy, early trials that utilized shorter infusion durations also reported a higher rate of neurologic toxicities and cytokine release syndrome (CRS). Patients receiving blinatumomab are usually hospitalized for initiation of cycles 1 and 2 to monitor for infusion-related reactions. Patients should also be monitored for CRS, neurological toxicities, and infections. Other common adverse drug reactions include fever, headache, peripheral edema, and rash.

Mosunetuzumab is a bispecific T-cell engager that binds CD20 on lymphoma cells and CD3 on T-cells, thereby releasing proinflammatory cytokines and inducing B-cell lysis. It is FDA-approved for the treatment of patients with relapsed or refractory follicular lymphoma. A step-up dosing schedule and premedications are recommended to reduce the risk of CRS and infusion-related reactions. Additional serious adverse drug reactions include neurologic toxicity, infections, cytopenias, and tumor flare.

Teclistamab is a bispecific B-cell maturation antigen-directed CD3 T-cell engager that is indicated for the treatment of patients with relapsed or refractory multiple myeloma. B-cell maturation antigen is overexpressed on multiple myeloma cells and is thought to play a role in cell survival. A REMS program is required to mitigate the risk of CRS and neurologic toxicity associated with teclistamab. As part of the REMS requirements, healthcare providers who prescribe teclistamab must be certified with the program and pharmacies must also be certified to dispense the medication. Serious toxicities including hepatotoxicity, infections, neutropenia, and hypersensitivity reactions have also been reported.

Fusion Proteins

Moxetumomab pasudotox is a CD-22-directed cytotoxin that is composed of a recombinant murine immunoglobulin variable domain fused to a truncated form of *Pseudomonas* exotoxin. It is approved for the treatment of relapsed or refractory hairy cell leukemia. The most common adverse drug reactions include infusion-related reactions, edema, nausea, headache, pyrexia, constipation, anemia, and diarrhea. Most patients develop anti-moxetumomab binding and neutralizing antibodies.

Ziv-aflibercept is a soluble recombinant fusion protein that was designed to block multiple signals that stimulate the angiogenic process. It was developed by fusing sections of the VEGFR-1 and VEGFR-2 immunoglobulin domains to the Fc portion of human IgG1. Ziv-aflibercept blocks VEGFA, VEGFB, and phosphatidylinositol-glycan biosynthesis class F by “trapping” the ligands before they get to the native transmembrane receptors and thus decreasing proangiogenic signaling and tumor growth. It is approved with chemotherapy for resistant or progressive metastatic colorectal cancer and has toxicities similar to other anti-VEGF therapies.

Recently, a new class of bispecific fusion proteins has been developed which has been named immune-mobilizing monoclonal T-cell receptors against cancer (also called ImmTAC). The novel technology uses an engineered high-affinity T-cell receptor to target a protein presented as a peptide-HLA complex. The engineered T-cell receptor is fused to an anti-CD3 fragment which is involved in the process of cytokine release after the molecule binds to the target peptide-HLA complex. The tebentafusp molecule consists of an HLA-A*02:01 restricted T-cell receptor that is specific for a glycoprotein 100 peptide.[55] Tebentafusp is FDA-approved for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. CRS is a potentially life-threatening toxicity associated with tebentafusp which requires close monitoring and a step-up dose escalation strategy. Additional serious adverse drug reactions include dermatologic toxicities and hepatotoxicity.

IMMUNOTHERAPY

Immune Checkpoint Inhibitors

As discussed earlier in the chapter, immune checkpoint inhibitors (including PD-1, PD-L1, and CTLA-4 inhibitors) reverse immune down-regulation, thereby unleashing T-cells to eliminate malignant cells. PD-L1 is overexpressed on multiple types of tumors, and it has been suggested that PD-L1 expression is associated with increased tumor aggressiveness. Unlike cytotoxic chemotherapy, which can elicit cell death immediately after administration, immune checkpoint inhibitors may have a slower onset based on their inherent mechanism of action. Furthermore, durable responses are more common with checkpoint inhibitors compared to cytotoxic chemotherapy as immune activation against the tumor may continue months after administration. Given their potential to activate the immune system, immune-related adverse events (irAEs) may occur. Immune checkpoint inhibitors should be avoided in patients with underlying autoimmune conditions or a history of transplant—see more details in Chapter 150 "Supportive Care."

CTLA-4 Inhibitor

Ipilimumab is a human mAb that blocks CTLA-4 and was the first FDA-approved immune checkpoint inhibitor. Another CTLA-4 inhibitor, tremelimumab, has since received FDA approval. CTLA-4 acts as a negative regulator of T-cell function, decreasing the ability of the immune system to mount an antitumor response. By binding to CTLA-4, these mAbs allow for enhanced T-cell stimulation, proliferation, and antitumor activity. Based on their ability to produce an enhanced immune response, ipilimumab and tremelimumab have been associated with several severe and fatal irAEs including enterocolitis, hepatitis, dermatitis, neuropathies, and endocrinopathies. Infusion-related reactions may occur. Ipilimumab is often administered in combination with nivolumab and is indicated for the treatment of MSI-H or dMMR colorectal cancer, melanoma, NSCLC, mesothelioma, hepatocellular carcinoma, and renal cell carcinoma. Tremelimumab is given in combination with durvalumab and is approved for the treatment of hepatocellular carcinoma and NSCLC.

PD-1 Inhibitors

As described earlier in the chapter, PD-1 inhibitors bind to the PD-1 receptor and block the interaction of its ligand resulting in the restoration of T-cell activity. The toxicity profile of all four medications in this class is similar and includes fatigue and irAEs, Common irAEs include dermatologic conditions and endocrine dysfunction. Patients should also be monitored for potentially fatal irAEs including colitis, pneumonitis, nephritis, hepatitis, myocarditis, and neurologic events.

Cemiplimab is a recombinant human IgG4 mAb approved for the treatment of advanced cutaneous squamous cell carcinoma, basal cell carcinoma, and NSCLC. Dostarlimab is a humanized IgG4 mAb approved for the treatment of dMMR recurrent or advanced endometrial cancer.

Nivolumab and pembrolizumab are IgG4 mAbs approved for Hodgkin lymphoma and for the treatment of numerous solid tumors. Both agents were originally studied in patients with metastatic cancer, but their use is now expanding to earlier in the disease course (eg, adjuvant setting). Depending on the indication, these agents may be given alone or in combination with chemotherapy or targeted therapy. Additionally, nivolumab is approved to be given in combination with ipilimumab, as described above.

Pembrolizumab received the FDA's first tissue/site agnostic approval for the treatment of MSI-H or dMMR solid tumors. It is also approved for tumor mutational burden-high cancer (≥10 mutations/megabase) in patients who have progressed following prior treatment and have no satisfactory alternate options. Tumor mutational burden is a measure of somatic mutations in a tumor and may help identify patients that may benefit from immunotherapy.[56]

PD-L1 Inhibitors

Unlike the PD-1 inhibitors which bind to the receptor, PD-L1 inhibitors bind to the associated ligand resulting in immune activation. Since PD-1 and PD-L1 inhibitors target the same pathway, adverse drug reactions and monitoring are the same.

Atezolizumab is an IgG1 mAb indicated for the treatment of SCLC, triple-negative breast cancer, NSCLC, hepatocellular carcinoma, melanoma, and urothelial carcinoma. Durvalumab, a human IgG1 mAb, is approved for patients with NSCLC and SCLC. Avelumab is a human IgG1 mAb approved for the treatment of Merkel cell carcinoma, urothelial carcinoma, and in combination with axitinib for renal cell carcinoma.

Unlike the other PD-L1 inhibitors, infusion-related reactions are common with avelumab, and premedications are required prior to the first four infusions at minimum. The development of antidrug antibodies has been shown to reduce avelumab exposure, and exploratory analyses suggest that the development of these antidrug antibodies may reduce the effectiveness in some populations. The development of antidrug antibodies does not

appear to affect the incidence or severity of adverse drug reactions.

PD-1 And Lymphocyte-activation Gene 3 (LAG-3) Combination Inhibitor

As described above, nivolumab is an IgG4 mAb targeting PD-1. In addition to the single agent product, nivolumab is also FDA-approved as a combination product with relatlimab, a LAG-3 inhibitor. Similar to PD-1, LAG-3 is an inhibitory immune checkpoint whose function is restored in the presence of a blocking antibody. LAG-3 is upregulated in various solid tumors, including melanoma, and dual inhibition with PD-1 has been shown to be synergistic.[57] Nivolumab/relatlimab is indicated for the treatment of unresectable or metastatic melanoma. Adverse drug reactions are similar to those reported with other immune checkpoint inhibitors including irAEs.

Cytokines

Interleukin-2 (Aldesleukin)

Interleukin-2 is a cytokine produced by recombinant DNA technology that promotes B- and T-cell proliferation and differentiation and initiates a cytokine cascade with multiple interacting immunologic effects. The interleukin-2 receptor is expressed in increased amounts on activated T-cells and mediates most of the effects of aldesleukin. Anticancer activity depends on proliferation of cytotoxic immune cells that can recognize and destroy cancer cells without damaging normal cells. Some of these cytotoxic cells are natural killer cells, lymphokine-activated killer cells, and tumor-infiltrating lymphocytes. Aldesleukin is approved for the treatment of metastatic renal cell carcinoma and melanoma.

Aldesleukin is a toxic therapy that requires vigorous supportive care under the supervision of experienced healthcare professionals. The most common dose-limiting toxicities are hypotension, fluid retention, and renal dysfunction. Aldesleukin decreases peripheral vascular resistance, producing peripheral vasodilation, tachycardia, and hypotension. A characteristic vascular or capillary leak syndrome produces fluid retention, which in turn can cause respiratory compromise. These toxicities require administration of vasopressors in most patients, judicious use of fluid support and diuretics, and supplemental oxygen. Patients with underlying cardiovascular or renal abnormalities are more susceptible to these toxicities, making careful patient selection important. Most patients treated with aldesleukin experience thrombocytopenia, anemia, eosinophilia, reversible cholestasis, and skin erythema with burning and pruritus; some patients have neuropsychiatric changes, hypothyroidism, and bacterial infections. In general, the toxicities from aldesleukin reverse quickly after therapy is stopped and can be managed or prevented by careful monitoring and supportive care.

Therapeutic Vaccines

Sipuleucel-T was the first therapeutic vaccine approved by the FDA. It is classified as an autologous cellular immunotherapy and is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer. Through leukapheresis, a patient's dendritic cells are collected and isolated, then cultured ex-vivo. The fusion protein is composed of prostate acid phosphatase, or PAP, and GM-CSF. Prostate acid phosphatase is selectively expressed on prostatic tissues and GM-CSF is included to enhance the immune response. Antigen-presenting cells take up this antigen and are then reinfused into the donor patient to stimulate a T-cell response.

Treatment with sipuleucel-T consists of three infusions separated by approximately 2 weeks. Due to the leukapheresis, ex-vivo cell manipulation, and reinfusion, treatment with sipuleucel-T can be logistically challenging. Premedication consisting of acetaminophen and an antihistamine should be given prior to each infusion to decrease the risk of an infusion-related reaction. Common toxicities include chills, fatigue, back pain, nausea, joint ache, and headache.

Talimogene laherparepvec is an oncolytic viral therapy based on a modified herpes simplex virus type 1. Talimogene laherparepvec is modified through the deletion of two herpes simplex virus genes, ICP34.5 and ICP47, and is designed to lyse tumor cells and promote antitumor immunity. It is indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery and is injected directly into the lesion. The most common toxicities are fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. Pyrexia, chills, and influenza-like illness can occur any time during treatment but are more frequent during the first 3 months. Cellulitis is the most commonly reported serious adverse drug reaction.

CAR T-Cell Therapies

CAR T-cell therapies were the first FDA-approved genetically modified autologous T-cell immunotherapies and are also known as adoptive T-cell

therapies. Peripheral blood mononuclear cells are harvested from a patient via apheresis. The T-cells are then reprogrammed with a transgene encoding a CAR, which consists of a binding domain and signaling domains. Following lymphodepletion with a conditioning regimen (often fludarabine and cyclophosphamide), the CAR T-cells are then reinfused into the patient.

The design of CAR T-cells has evolved over the years primarily to improve the signaling capability. Four anti-CD19 CARs are currently FDA-approved: axicabtagene ciloleucel (second-generation agent) for the treatment of follicular lymphoma and large B-cell lymphoma; brexucabtagene autoleucel (second-generation agent) for the treatment of mantle cell lymphoma; tisagenlecleucel (second-generation agent) for the treatment of ALL and diffuse large B-cell lymphoma; and lisocabtagene maraleucel (third-generation agent) for the treatment of large B-cell lymphoma. Binding the CD19-expressing cell activates downstream signaling through the costimulatory signaling domains, resulting in cytokine and chemokine secretion and ultimate destruction of the B-cell. Although all four agents are similar in mechanism, they differ in their costimulatory signaling domains. Axicabtagene ciloleucel and brexucabtagene autoleucel both include a CD28 and CD3-zeta signaling domain, whereas tisagenlecleucel contains a 4-1BB and CD3-zeta domain. Lisocabtagene maraleucel is considered a next-generation CAR T-cell because it contains multiple costimulatory domains, including CD28 and 4-1BB in addition to CD3-zeta.

Additionally, idecabtagene vicleucel, a second-generation CAR therapy targeting B-cell maturation antigen, is approved for the treatment of relapsed or refractory multiple myeloma. Similar to tisagenlecleucel, the idecabtagene vicleucel CAR construct contains signaling domains 4-1BB and CD3-zeta. After binding to the B-cell maturation antigen, the signaling domains will activate cytokine and chemokine secretion, resulting in destruction of the targeted cell.

Toxicities associated with CAR T-cell therapies can be severe and life-threatening. As a result, a REMS program has been implemented which, among other requirements, mandates hospitals and clinics be certified before administering these agents.

Cytokine-associated toxicities are common and include CRS, which manifests with hypotension, tachycardia, fever, and hypoxia. Organ dysfunction may also be present. The typical time to onset of CRS is 2 to 3 days and the usual duration is 7 to 8 days.[58] Immune effector cell-associated neurotoxicity syndrome, or ICANS, is the terminology used for neurotoxicities associated with CAR T-cell treatment. CAR T-cell-related neurotoxicities can be fatal or life-threatening. The typical time to onset is 4 to 10 days after treatment, and symptoms last approximately 14 to 17 days.[58] Common neurotoxicities include encephalopathy, headache, tremor, dizziness, and aphasia, but serious events, such as seizures and cerebral edema, have also been reported. See Chapter 150 “Supportive Care” for management of CRS and ICANS.

RESPONSE CRITERIA

The response to anticancer agents and other treatment modalities could be described as a cure; complete response, or CR; partial response, or PR; stable disease, or SD; or progression. A cure implies that the patient is entirely free of disease and has the same life expectancy as a cancer-free individual. Because of our inability to detect small numbers of cancer cells, we can never be absolutely certain that an individual patient is cured. Cancers that are curable with treatment are characterized by a stable plateau in the survival curve where the risk of relapse is very low. For most curable cancers, the survival curve has plateaued by about 5 years. Therefore, patients with a curable cancer who are alive 5 years from the time of diagnosis without disease recurrence are often considered “cured,” but patients with some malignancies, such as breast cancer and melanoma, are still at significant risk for relapse after 5 years.

Response Criteria for Solid Tumors

In an attempt to simplify and unify response definitions in clinical practice, clinical trials, and published reports, the response evaluation criteria in solid tumors (RECIST) criteria were developed in 2000 and revised in 2009 (RECIST 1.1).[59] At baseline, overall tumor burden and measurable disease is assessed. Target lesions are identified and measured at baseline and are later re-evaluated to determine objective tumor response. Nontarget lesions are also assessed. A CR means disappearance of all target lesions and any pathological lymph nodes must be reduced in short axis to less than 10 mm. A PR is defined as a 30% or greater decrease in the sum of diameters of target lesions from baseline. Overall, objective response rates for a given treatment are calculated by adding the CR and PR rates. Progressive disease is defined as a 20% or greater increase in the sum of diameters of target lesions when compared to the smallest sum since treatment initiation. The development of one or more new lesions while receiving treatment is also considered progressive disease. A patient whose tumor size neither grows nor shrinks by the above criteria is termed to have stable disease. Some patients may experience subjective improvement in cancer-related symptoms without a defined response. Although clinically important, this does not

indicate an objective response. RECIST 1.1 is the most widely accepted criteria for the assessment of tumor response in solid tumors but it does not come without shortcomings. The modified RECIST, or mRECIST, assessment may be more accurate for the evaluation of tumor burden in some cancers.[60]

Furthermore, the emergence of immunotherapy in oncology has led to the need for revised response criteria that accounts for the mechanism of immunotherapeutic agents. RECIST neglects to take into account pseudoprogression (ie, "flare") associated with these agents, which may inadvertently result in the premature discontinuation of an effective therapy. Pseudoprogression refers to apparent tumor growth on imaging, resulting from an immunotherapy treatment-related effect rather than malignant cell proliferation. The apparent progression is thought to be a result of immune infiltrates and is followed by tumor regression. Immune-related response criteria, or irRC, and immune-related RECIST, or irRECIST, have been proposed to overcome the challenges of RECIST 1.1 with immunotherapy.[61,62]

Response Criteria for Hematologic Malignancies

The response definitions described above are applicable to solid tumors, but leukemias and multiple myeloma are not characterized by discrete, measurable masses. Responses in these cancers are measured by elimination of abnormal cells (eg, return to normal hematology parameters and normal bone marrow in leukemia), return of tumor markers to normal levels (eg, normal serum protein electrophoresis in multiple myeloma), or improved function of affected organs (eg, improved renal function after obstructive uropathy). Cytogenetic markers and molecular techniques have an increasingly important role in determining whether all cancer has been truly eliminated. For example, in CML, the Ph can be detected by polymerase chain reaction techniques even when no leukemia is evident in the bone marrow or bloodstream. Patients without evidence of the Ph are classified as having a complete cytogenetic response. Measuring cytogenetic responses is increasingly common in patients with known cytogenetic abnormalities, and the absence of a complete cytogenetic response may be predictive of disease relapse. Minimal residual disease (MRD) is a prognostic factor used to guide treatment in ALL and AML. Data regarding MRD is still emerging, but it is now recommended that MRD be monitored in patients with AML as MRD positivity is associated with higher relapse rates and shorter survival.[63]

FACTORS AFFECTING TREATMENT RESPONSE

9 Factors affecting response include tumor burden, cancer cell heterogeneity, drug resistance, dose intensity, and patient-specific factors, such as pharmacogenomics. The significance of tumor burden was discussed earlier in the chapter. Tumors consist of a heterogeneous population of cells. Because of the genetic instability of cancer cells compared with normal cells, genetic alterations commonly occur during cell division. Large tumors have therefore undergone many cell divisions and express multiple genetic alterations, resulting in genetically varied populations. In 1979, Goldie and Coldman proposed that these cytogenetic changes were not completely random and were highly associated with the ability of tumors to develop drug resistance. The probability of developing resistant cell populations increases as tumor size increases. It is believed that a small percentage of resistant cancer cells may survive initial therapy. Resistant populations later proliferate and eventually become the dominant population, which could explain the common pattern of an initial response to therapy followed by progressive tumor regrowth despite continuing the same treatment.

Drug Resistance

Drug resistance may be either acquired or inherited. Mechanisms of drug resistance include altered drug transport systems, metabolism, and target enzymes; ability to repair drug-induced damage; and insensitivity to drug-induced apoptosis.[2] For example, multidrug resistance has been observed with natural chemotherapies (eg, anthracyclines, vinca alkaloids, epipodophyllotoxins, taxanes), and it occurs when some cancer cells are exposed to increasing concentrations of a specific chemotherapy. Surprisingly, these same cells also become resistant to other structurally unrelated chemotherapies and are therefore considered multidrug resistant. The resistant cancer cells may overexpress the drug transporter P-gp, which enhances the export of these chemotherapies. Other potential mechanisms of drug resistance include inactivation of chemotherapy by glutathione metabolism, upregulation of drug targets, alternative intracellular signaling pathways, and decreased apoptosis. The last mechanism can be mediated by overexpression of BCL-2 or loss of TP53, as discussed earlier in the chapter.

Dose Intensity

The relationship between dose and response has been extensively explored for chemotherapy agents, because dose is believed to be a critical factor in determining response for many cancers. Dose intensity is defined as the dose delivered to the patient over a specified period of time. The three main

variables that determine delivered dose intensity are the dose per course, the interval between doses, and the total cumulative dose. Dose density refers to shortening of the usual interval between doses (eg, every 2 weeks instead of every 3 weeks) and is designed to maximize the effects of therapy on tumor growth kinetics. This strategy has been extensively studied in breast cancer. The delivery of optimal dose intensity is often compromised by the toxicities of the anticancer agent. Treatment cycles are commonly delayed because of inadequate recovery from toxicity, especially myelosuppression. Subsequent doses of the anticancer agents are often reduced to prevent or minimize the severity of these toxicities. The impact on patient outcome has been proven in studies showing reduced rates of response and survival in individuals receiving less-than-optimal doses. Understanding the pathophysiology of toxicities has led to the development of more effective agents to prevent and manage these toxicities. The development of chemoprotective agents has facilitated application of dose-intensity principles. For example, CSFs minimize neutropenia and permit delivery of dose-intensive or dose-dense regimens that are myelosuppressive. The concept of dose intensity is particularly important in the setting of high-dose chemotherapy with autologous hematopoietic stem cell support. Although lethal myelosuppression is avoided through HSCT, other severe end-organ toxicities emerge as doses of the anticancer agents are increased.

Molecular Biomarkers

A molecular biomarker is a molecular characteristic of the tumor that influences prognosis or predicts response to a specific therapy. Many of these molecular biomarkers are somatic mutations that contribute to the development of the cancer. Prognostic biomarkers inform the risk of clinical outcomes such as disease progression or recurrence. Numerous tests are currently available that measure tumor gene expression and may provide information on a patient's risk of recurrence. For example, the Oncotype Dx® Breast Cancer Assay measures 21 genes associated with breast cancer recurrence and chemotherapy benefit in select patients with breast cancer. A predictive biomarker predicts response to a specific therapeutic intervention. For example, EGFR and ALK mutations predict response to EGFR and ALK inhibitors in NSCLC. Similarly, HER2 overexpression predicts response to trastuzumab in breast cancer. Molecular testing of cancer at the time of diagnosis allows for personalized therapy with targeted agents.

Patient-Specific Factors

Patient-specific factors create unpredictable variability in response to anticancer therapy. For example, interindividual variations in absorption, distribution, or elimination could lead to sub- or supratherapeutic levels of anticancer agents and their metabolites. The genetic alterations that resulted in the cancer can also affect response. For example, breast cancers that overexpress HER2 are often sensitive to anthracycline-based regimens. As a result, both efficacy and tolerability can be affected. Healthcare professionals in oncology may preemptively modify doses based on variations in body size, blood counts, and organ function to optimize the effectiveness of therapy and minimize toxicity. However, more specific tools are becoming available as we learn how to identify and apply genetic differences. Pharmacogenomics is the study of the role of inheritance in individual variation of drug response. In oncology, several clinically relevant genetic polymorphisms or variations have been identified that can affect pharmacokinetics and pharmacodynamics. Examples include polymorphisms in genes responsible for the activity of the enzymes DPD (responsible for fluorouracil metabolism), TPMT and NUDT15 (responsible for thiopurine metabolism), UGT1A1 (responsible for irinotecan metabolism), and cytochrome P450 2D6 (responsible for tamoxifen metabolism). Patients with deficiencies in these enzymes can experience significant and possibly life-threatening toxicity. Identifying these genetic variants could permit individualization of regimens to reduce toxicity. Furthermore, pharmacokinetic and pharmacodynamic modeling is associated with improved responses and decreased toxicity in children with ALL.

The presence of other disease states (eg, comorbidities) may also affect response to treatment by limiting treatment options. The overall functional status of a patient may be assessed using performance status scales, such as the Karnofsky Performance Status and the Eastern Cooperative Oncology Group or ECOG scales (see Table 149-8). These scales can be used to predict patient tolerance of anticancer therapy and to assess the effects of therapy on the patient's level of activity and quality of life. For many cancers, performance status at diagnosis is the most important prognostic indicator.

TABLE 149-8

Assessing the Performance Status of Patients with Cancer

Eastern Cooperative Oncology Group (ECOG) Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	**Percent**	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self; unable to carry on normal activity or to do active work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance but is able to care for most of personal needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very ill, hospitalization and active supportive care necessary.
		10	Moribund.
5	Dead.	0	Dead.

Adapted from ECOG-ACRIN Cancer Research Group. ECOG Performance Status [cited 2021 July 18]. Available at: https://ecog-acrin.org/resources/ecog-performance-status.

Today's oncology healthcare professionals have a wealth of information to consider when designing a personalized treatment approach. Patient-specific factors (eg, performance status, comorbidities, organ function, and pharmacogenomics), tumor-specific factors (eg, pathology, stage, and biomarkers), and treatment goals (eg, palliation and cure) are all considered when determining the best treatment option. Treatment cost can also be an important consideration.

DRUG ADMINISTRATION

Dosage and Administration

Healthcare professionals should monitor all clinical and laboratory values that are affected by a specific anticancer agent at baseline and periodically during treatment. For example, a complete blood count should be evaluated weekly or before each cycle while receiving anticancer agents associated with myelosuppression. In general, an absolute neutrophil count, or ANC of 1,500 cells/mm^3 (1.5×10^9/L) or above, and a platelet count of 100,000 cells/mm^3 (100×10^9/L) or above are usually required before administering myelosuppressive agents. In addition, a chemistry panel is drawn to assess organ function, especially for agents eliminated or metabolized via those routes.

Anticancer agents might be dosed based on body size (such as body weight or body surface area [BSA]) or as a fixed (ie, flat) dose. Cytotoxic chemotherapy is generally dosed based on BSA. BSA is commonly used as an estimate of cardiac output and subsequent distribution to the liver and kidneys, the primary determinants of drug elimination. The most common methods used to determine BSA are the Mosteller and DuBois formulas. Traditionally, body-sized dosing has been used for mAbs but some agents, such as some immune checkpoint inhibitors, may use a flat dose. In contrast, most oral targeted agents are based on a fixed-dose approach.

Other dosing methods are being used to improve tolerability and anticancer activity. For example, carboplatin is dosed based on the patient's estimated glomerular filtration rate or GFR. This method is known as the Calvert formula and has been demonstrated to achieve adequate levels of carboplatin while minimizing excessive toxicity.

Molecular diagnostic tests are required prior to administration of some targeted agents (eg, trastuzumab, vemurafenib, and crizotinib), which are indicated only for patients whose tumors express a specific protein or gene. Additionally, health professionals must know how to interpret the findings from the various diagnostic tests. For example, some tests may identify if a tumor is mutation positive or negative, whereas other tests may identify the specific genetic alteration present in the tumor.

Safety and Handling

All anticancer agents regardless of the route of administration should be handled with care to avoid inadvertent exposure to healthcare professionals and caregivers. Consequently, all healthcare facilities should have written procedures for safely handling these agents, and all personnel should be oriented to these procedures. Healthcare professionals should provide information about safe handling and disposal to patients and their families when a patient is prescribed an oral anticancer agent. Patients should be informed of proper methods for disposing of potentially contaminated body excreta and cytotoxic waste. Safe handling includes avoiding skin contact and inhalation, but patient-centered guidelines regarding safe handling of oral anticancer agents have not been developed.

The United States Pharmacopeia regulates the preparation of extemporaneously compounded sterile preparations and should be used by healthcare professionals that prepare intravenous chemotherapy. Chapter 800 provides standards for the safe handling of hazardous agents in the healthcare setting. The most common avenue of exposure is via inhalation or skin absorption. Individuals preparing intravenous chemotherapy should work in an International Organization for Standardization, or ISO Class 5 biologic safety cabinet and wear appropriate personal protective equipment including a gown, face mask, eye protection, hair covers, shoe covers, and double sterile chemotype gloves. Closed-system vial-transfer devices should be used when possible. Negative-pressure techniques should be used in drug preparation to minimize aerosolization. Health professionals administering chemotherapy should take similar precautions to avoid exposure. Double chemotherapy-tested gloves, protective gowns, and protective eyewear (if there is potential for splashing) should be worn whenever handling or administering hazardous drugs. Kits for cleaning up chemotherapy spills should be located in all areas where chemotherapy is handled and cytotoxic waste should be disposed of properly.

ABBREVIATIONS

ABL	Abelson
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ALL	acute lymphoblastic leukemia

ALK	anaplastic lymphoma kinase
αKG	alpha-ketoglutarate
AML	acute myeloid leukemia
ATP	adenosine triphosphate
BCL-2	B-cell lymphoma 2
BCR-ABL	breakpoint cluster region-Abelson
BRCA	breast cancer gene
BTK	Bruton's tyrosine kinase
CAR	chimeric antigen receptor
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CDK	cyclin-dependent kinase
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CNS	central nervous system
CRS	cytokine release syndrome
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte–associated antigen 4
DHFR	dihydrofolate reductase
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DNMT	DNA methyltransferase
DPD	dihydropyrimidine dehydrogenase
ECG	electrocardiogram
EGFR	epidermal growth factor receptor
EML4	echinoderm microtubule-like protein 4

ER	estrogen receptor
ErbB	erythroblastic leukemia viral oncogene
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FLT3	FMS-like tyrosine kinase 3
GEP-NET	gastroenteropancreatic neuroendocrine tumors
GIST	gastrointestinal stromal tumor
HBV	hepatitis B virus
HDAC	histone deacetylase
HER2	human epidermal growth factor receptor 2
HPV	human papilloma virus
HSCT	hematopoietic stem cell transplant
IDH	isocitrate dehydrogenase
irAE	immune-related adverse event
JAK	Janus kinase
KIT	stem-cell factor receptor
KRAS	kirsten ras
LAG-3	lymphocyte-activation gene 3
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MDS	myelodysplastic syndrome
MEK	mitogen-activated protein kinase\extracellular signal-regulated kinase
MET	mesenchymal-epithelial transition
MRD	measurable residual disease

MSI-H	microsatellite instability-high
mTOR	mammalian target of rapamycin
NF-κB	nuclear factor-κB
NHL	non-Hodgkin lymphoma
NSCLC	non-small cell lung cancer
NTRK	neurotrophic receptor tyrosine kinase
NUDT15	nudix (nucleoside diphosphate linked moiety X)-type motif 15
PARP	poly ADP ribose polymerase
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
P-gp	p-glycoprotein
Ph	Philadelphia chromosome
Ph^+	Philadelphia chromosome-positive
PI3K	phosphatidylinositide 3-kinases
PPE	palmar-plantar erythrodysesthesia
RECIST	response evaluation criteria in solid tumors
REMS	risk evaluation and mitigation strategy
RET	rearranged during transfection
RNA	ribonucleic acid
SCLC	small cell lung cancer
STAMP	specifically targeting the ABL myristoyl pocket
SLAMF7	signaling lymphocytic activation molecule family 7
STAT	signal transducers and activators of transcription
TLS	tumor lysis syndrome

TNF-α	tumor necrosis factor-alpha
TPMT	thiopurine methyltransferase
TRK	tropomyosin receptor kinase
TROP2	trophoblast cell-surface antigen 2
UGT1A1	uridine diphosphate-glucuronosyl transferase 1A1
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	von Hippel-Lindau
VTE	venous thromboembolism

REFERENCES

1. Siegel RL, Miller KD, Wagel NS, et al. Cancer Statistics. *Ca Cancer J Clin.* 2023;73(1):17–48. 10.3322/caac.21763.

2. Clark JW, Longo DL. Cancer cell biology. In: Jameson J, Fauci A, Kasper D, Hauser S, Longo D, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 20th ed. McGraw Hill; 2018.

3. Moasser MM, Ai WZ. Neoplasia. In: Hammer G, McPhee S, eds. *Pathophysiology of Disease: An Introduction to Clinical Medicine*. 8th ed. McGraw Hill; 2019.

4. FDA U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/.

5. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. *Cell*. 2011;144(5):646–674. doi: 10.1016/j.cell.2011.02.013.

6. Chan CY, Tan KV, Cornelissen B. PARP inhibitors in cancer diagnosis and therapy. *Clin Cancer Res.* 2021;27:1585–1594. doi: 10.1158/1078-0432.CCR-20-2766.

7. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* 2015;372. doi: 10.1056/NEJMoa1500596.

8. Clark O, Yen K, Mellinghoff IK. Molecular pathways: Isocitrate dehydrogenase mutations in cancer. *Clin Cancer Res.* 2016;22(8):1837–1842. doi: 10.1158/1078-0432.CCR-13-1333.

9. Stricker TP, Kumar V. Neoplasia. In: Kumar V, Abbas A, Aster J, Fausto N, eds. *Robbins and Cotran Pathologic Basis of Disease*. 8th ed. Philadelphia, PA: Saunders; 2010:259–330.

10. National Cancer Institute. Training Modules Tumor List [cited 2021 July 18]. Available at: https://training.seer.cancer.gov/disease/categories/tumors.html.

11. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. *Ca Cancer J Clin.* 2019;69(3):184–210. [PubMed: 30875085]

12. Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 Guideline update from the American Cancer Society. *CA Cancer J Clin.* 2020;70(5):321–346. doi: 10.3322/caac.21628.

13. American Cancer Society study communicating cancer information through mass distribution leaflets: An American Cancer Society study. *Ca Cancer J Clin.* 1967;17:291–293. [PubMed: 4966094]

14. Saliba AN, John AJ, Kaufmann SH. Resistance to venetoclax and hypomethylating agents in acute myeloid leukemia. *Cancer Drug Resist*. 2021;4:125–142. doi: 10.20517/cdr.2020.95.

15. Rubin EH, Hait WN. Drugs that target DNA topoisomerase. In: Waun K, Bast R, Hait W, eds. *Cancer Medicine*. 8th ed. Shelton, CT: People's Medical Publishing House-USA; 2010:645–654.

16. Colvin M. Alklating agents and platinum antitumor compounds. In: Waun K, Bast R, Hait W, eds. *Cancer Medicine*. 8th ed. Shelton, CT: People's Medical Publishing House-USA; 2010:633–644.

17. Kost SEF, Bouchard EDJ, LaBossiere E, et al. Cross-resistance and synergy with bendamustine in chronic lymphocytic leukemia. *Leuk Res* 2016;50:63–71. 10.1016/j.leukres.2016.09.016.

18. Colvin M. Alkylating agents and platinum antitumor compounds. In: Waun K, Bast R, Hait W, eds. *Cancer Medicine*. 8th ed. Shelton, CT: People's Medical Publishing House_USA; 2010:633–644.

19. Loprinzi CL, Qin R, Dakhil SR, et al. Phase III randomized, placebo-controlled, double-blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity. *J Clin Oncol.* 2014;32(10):997–1005. doi: 10.1200/JCO.2013.52.0536.

20. Turck R. Radio-pharmaceuticals for cancer treatment: Are they ready for prime time yet. *Ann Oncol.* 2018;29(7):1594–1597. doi: 10.1093/annonc/mdy142.

21. Shaw AT, Kim D, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med.* 2014;370:1189–1197. doi: 10.1056/NEJMoa1311107.

22. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. *Lancet Oncol.* 2018;19(12):1654–1667. doi: 10.1016/S1470-2045(18)30649-1.

23. Anderson MA, Deng J, Seymour JF, et al. The BCL2 selective inhibitor venetoclax induces rapid onset apoptosis of CLL cells in patients via a TP53-independent mechanism. *Blood*. 2016;127(25):3215–3224. doi: 10.1182/blood-2016-01-688796.

24. Réa D, Mauro MJ, Boquimpani C, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021;138:2031–2041. 10.1182/blood.2020009984.

25. My Cancer Genome. Biomarkers/BRAF. Vanderbilt-Ingram Cancer Center; [cited 2021 July 21]. Available at: https://www.mycancergenome.org/content/gene/braf/.

26. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med.* 2014;371:1877–1888. 10.1056/NEJMoa1406037.

27. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study. *Lancet Oncol.* 2015;16(1):25–35. doi: 10.1016/S1470-2045(14)71159-3.

28. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): A randomised phase 3 trial. *Lancet*. 2019;394(10197):478–487. doi: 10.1016/S0140-6736(19)30764-0.

29. Jordan EJ, Kim HR, Arcila ME, et al. Prospective Comprehensive Molecular Characterization of Lung Adenocarcinomas for Efficient Patient Matching to Approved and Emerging Therapies. Cancer Discov. 2017;7:596–609. 10.1158/2159-8290.cd-16-1337.

30. Ricordel C., Friboulet L., Facchinetti F., et al. Molecular mechanisms of acquired resistance to third-generation EGFR-TKIs in EGFR T790M-mutant lung cancer. Ann Oncol. 2018;29:i28–i37. 10.1093/annonc/mdx705.

31. Li T, Perez-Soler R. Skin toxicities associated with epidermal growth factor receptor inhibitors. *Target Oncol.* 2009;4(2):107–119. doi: 10.1007/s11523-009-0114-0.

32. Ricordel C, Friboulet L, Facchinetti F, et al. Molecular mechanisms of acquired resistance to third-generation EGFR TKIs in EGFR T790M-mutant lung cancer. *Ann Oncol* 2018;29:i28–i37. 10.1093/annonc/mdx705.

33. Gonzalvez F, Vincent S, Baker TE., et al. Mobocertinib (TAK-788): a targeted inhibitor of *EGFR* exon 20 insertion mutants in non–small cell lung cancer. Cancer Discov. 2021;11:1672–1687. 10.1158/2159-8290.cd-20-1683.

34. Patani H, Bunney TD, Thiyagarajan N, et al. Landscape of activating cancer mutations in FGFR kinases and their differential responses to inhibitors in clinical use. *Oncotarget*. 2016;7(17):24252–24268. doi: 10.18632/oncotarget.8132.

35. Meric-Bernstam F, Bahleda R, Hierro C, et al. Futibatinib, an irreversible FGFR1–4 inhibitor, in patients with advanced solid tumors harboring *FGF*/*FGFR* aberrations: A phase I dose-expansion study. Cancer Disc. 2021;12:402–415. 10.1158/2159-8290.cd-21-0697.

36. Schaid DJ, Spraggs CF, McDonnel SK, et al. Prospective validation of HLA-DRB1*07:01 allele carriage as a predictive risk factor for lapatinib-induced liver injury. *J Clin Oncol.* 2014;32(22):2296–2303. doi: 10.1200/JCO.2013.52.9867.

37. Hasanov E, Jonasch E MK-6482 as a potential treatment for von Hippel-Lindau disease-associated clear cell renal cell carcinoma. Expert Opin Investig Drugs. 2021;30:495–504. 10.1080/13543784.2021.1925248.

38. Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. *N Engl J Med.* 2020;382:1430–1442. doi: 10.1056/NEJMoa1912735.

39. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, an dexamethasone versus twice-per-week boretzomib and dexamethasone in patients with multiple myeloma (BOSTON): A randomised, open-label, phase 3 trial. *Lancet*. 2020;396(10262):1563–1573. doi: 10.1016/S0140-6736(20)32292-3.

40. Paul J, Soujon M, Wengner AM, et al. Simultaneous inhibition of PI3Kδ and PI3Kα induces ABC-DLBCL regression by blocking BCR-dependent and -independent activation of NF-κB and AKT. *Cancer Cell*. 2017;31(1):64–78. 10.1016/j.ccell.2016.12.003.

41. Juric D, Rodon J, Tabernero J, et al. Phosphatidylinositol 3-kinase α-selective inhibition with alpelisib (BYL719) in PI3KCA-altered solid tumors: Results from the first-in-human study. *J Clin Oncol.* 2018;36(13):1291–1299. doi: 10.1200/JCO.2017.72.7107.

42. Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med.* 2021;384:2371–2381. doi: 10.1056/NEJMoa2103695.

43. Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non–small-cell lung cancer harboring a *KRAS*^{G12C} mutation. N Eng J Med 2022;387:120–131. 10.1056/nejmoa2204619.

44. Bekaii-Saab TS, Ou F, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): A randomised, multicentre, open-label, phase 2 study. *Lancet Oncol.* 2019;20(8):1070–1082. doi: 10.1016/S1470-2045(19)30272-4.

45. U.S. Food and Drug Administration. Biosimilars and interchangeable products [cited 2018 December 18]. Available at:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm.

46. Salles G, Duell J, Barca EG, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): A multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol.* 2020;21(7):978–988. doi: 10.1016/S1470-2045(20)30225-4.

47. Tobinai K, Klein C, Oya N, et al. A review of Obinutuzumab (GA101), a Novel Type II Anti-CD20 Monoclonal Antibody, for the treatment of patients with B-cell malignancies. *Adv Ther.* 2017;34:324–356. doi: 10.1007/s12325-016-0451-1.

48. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): A randomized, multicentre, open-label, phase 3 study. *Lancet*. 2019;394:2096–2107. doi: 10.1016/S0140-6736(19)32556-5.

49. Palanca-Wessels MC, Czuczman M, Salles G, et al. Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: A phase 1 study. *Lancet Oncol.* 2015;16(6):704–715. doi: 10.1016/S1470-2045(15)70128-2.

50. Moore KN, Oza AM, Colombo N, et al. Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I. Ann Oncol. 2021;32:757–765. 10.1016/j.annonc.2021.02.017.

51. Nazha B, Inal C, Owonikoko TK. Disialoganglioside GD2 expression in solid tumors and role as a target for cancer therapy. *Front Oncol.* 2020;10:1000. doi: 10.3389/fonc.2020.01000.

52. Vyse S, Huang PH. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. *Sig Transduct Target Ther.* 2019;4(5). doi: 10.1038/s41392-019-0038-9.

53. Rugo HS, Im S, Cardoso F, et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer. *JAMA Oncol.* 2021;7(4):573–584. doi: 10.1001/jamaoncol.2020.7932.

54. van de Donk NW, Moreau P, Plesner T, et al. Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma. *Blood*. 2016;127(6):681–695. doi: 10.1182/blood-2015-10-646810.

55. Nathan P, Hassel JC, Rutkowski P, et al. Overall survival benefit with tebentafusp in metastatic uveal melanoma. N Engl J Med. 2021;385:1196–1206. 10.1056/nejmoa2103485.

56. McNamara MG, Jacobs T, Lamarca A, et al. Impact of high tumor mutational burden in solid tumors and challenges for biomarker application. *Cancer Treat Rev.* 2020;89:102084. 10.1016/j.ctrv.2020.102084.

57. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386:24–34. 10.1056/nejmoa2109970.

58. The NCCN Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities (version 3.2021). National Comprehensive Cancer Network. Available at: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. [cited May 16, 2021].

59. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. doi: 10.1016/j.ejca.2008.10.026.

60. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis.* 2010;30(1):52–60. 10.1055/s-0030-1247132.

61. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria.

Clin Cancer Res. 2009;15(23):7412–7420. doi: 10.1158/1078-0432.CCR-09-1624.

62. Bohnsack O, Hoos A, Ludajic K. Adaptation of the immune related response criteria: irRECIST. Abstract presented at: ESMO 2014 Congress; 2014 September 26-30; Madrid, Spain.

63. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: A consensus document from the European LeukemiaNet Working Party. *Blood*. 2018;131(12):1275–1291. doi: 10.1182/blood-2017-09-801498.

SELF-ASSESSMENT QUESTIONS

1. Which of the following steps is part of the multistage process of carcinogenesis that involves further genetic alterations and increased cell proliferation?

   A. Transformation

   B. Promotion

   C. Propagation

   D. Progression

2. Which key characteristic allows cancer cells to become “immortal”?

   A. Activation of angiogenesis

   B. Undergoes apoptosis

   C. Activation of multiple oncogenes

   D. Activation of tumor suppressor genes

3. Which of the following statements *best* describes why cancer is difficult to treat?

   A. Homogeneous tumors with epigenetic mutations

   B. Heterogeneous tumors with multiple genetic and epigenetic mutations

   C. Homogeneous tumors with abnormal cytogenetics

   D. Heterogeneous tumors with normal cytogenetics

4. A 71-year-old individual is diagnosed with NSCLC. Tumor mutational analysis reveals an ALK mutation. Which of the following *best* describes the importance of the tumor mutational analysis result?

   A. Provides information on treatment strategies

   B. Predicts tolerability of therapy

   C. Provides information on ECOG performance status

   D. Provides information on stage of cancer

5. A 64-year-old individual is diagnosed with triple negative breast cancer (hormone receptor–negative and HER2-negative). The primary tumor in her left breast is 2 cm and she has 6 of 12 positive nodes. CT scan reveals a 2-cm tumor in her liver. MRI of brain is negative. Which of the following is the correct stage of cancer and goal of care?

A. Stage I and goal of care is palliative.

B. Stage II and goal of care is curative.

C. Stage III and goal of care is curative.

D. Stage IV and goal of care is to prolong survival.

6. Chemotherapy is resistant in which of the following phases of the cell cycle?

A. S phase

B. M Phase

C. G_2 phase

D. G_0 Phase

7. Small-molecule targeted agents interfere with which of the following?

A. Extracellular receptors

B. Signal transduction

C. Cell cycle

D. Immune response

8. A 33-year-old individual diagnosed with AML is admitted to the hospital for chemotherapy. After treatment, a bone marrow biopsy reveals the patient is in remission. Which of the following best describes the chemotherapy treatment?

A. Initial chemotherapy is considered induction therapy with a goal to put him in remission.

B. Initial chemotherapy is considered neoadjuvant therapy with a goal to make him a candidate for surgery.

C. Initial chemotherapy is considered adjuvant therapy with a goal to put him in remission.

D. Initial chemotherapy is considered consolidation therapy with a goal to put him in remission.

9. An average risk 50-year-old postmenopausal individual with no smoking history should be counseled regarding the following procedures as a part of routine cancer screening?

A. Cytology with HPV DNA test, every 5 years

B. Mammography, every 5 years

C. Colonoscopy, annually

D. Low-dose helical CT scan, annually

10. A 70-year-old individual is diagnosed with metastatic colon cancer. The oncologist recommends a chemotherapy regimen that consists of fluorouracil, oxaliplatin, leucovorin, and bevacizumab for 12 cycles. Which of the following statements describes characteristics of combination chemotherapy?

A. Incorporate agents with similar mechanisms of action and similar toxicity profiles.

B. Incorporate agents with different mechanisms of action and similar toxicity profiles.

C. Incorporate agents with similar mechanisms of action and different toxicity profiles.

D. Incorporate agents with different mechanisms of action and different toxicity profiles.

11. Which of the following *best* describes the difference between fam-trastuzumab deruxtecan and trastuzumab?

A. Trastuzumab is an antibody-drug conjugate and associated with more cardiotoxicity compared to fam-trastuzumab deruxtecan.

B. Fam-trastuzumab deruxtecan is an antibody-drug conjugate and associated with more cytotoxicity compared to trastuzumab.

C. Trastuzumab is a mAb and associated with more cytotoxicity compared to fam-trastuzumab deruxtecan.

D. Fam-trastuzumab deruxtecan is a mAb associated with similar cardiotoxicity compared to trastuzumab.

12. VEGFR inhibitors are commonly associated with which of the following adverse reactions?

A. Hypotension, QTc prolongation

B. Hypomagnesemia, acne-form rash

C. Hypothyroidism, bleeding

D. Hypertension, proteinuria

13. Which of the following agents is fatal if administered intrathecally?

A. Hydrocortisone

B. Cytarabine

C. Vincristine

D. Methotrexate

14. Which of the following immunotherapies mechanism of action includes: T-cell stimulation and proliferation?

A. Ipilimumab

B. Talimogene laherparepvec

C. Sipuleucel-T

D. Interleukin-2

15. Immune-related toxicities are reported with which of the following?

A. Pembrolizumab

B. Cetuximab

C. Bevacizumab

D. Talimogene laherparepvec

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** The first step in carcinogenesis is initiation, which requires exposure of normal cells to carcinogens. During the second step, known as

promotion, carcinogens or other factors alter the environment to favor growth of the altered cell population compared to normal cells. At some point, the altered cell becomes cancerous (ie, transformation). The final stage, called progression, involves further genetic alterations that lead to increased cell proliferation. Propagation is not a step in the process of carcinogenesis. See the section "Etiology of Cancer."

2. **C.** Uncontrolled proliferation of cancer cells is due to genetic alterations that impact strict regulation of cell cycle, activation of oncogene, or suppression of tumor suppressor genes. Angiogenesis is the development of new blood vessels, which is a characteristic that supports growth of some cancers. See the section "Pathology of Cancer."

3. **B.** Malignant tumors are formed as a result of several genetic alterations that accumulate over time. The accumulation of genetic alterations leads to different genetic and/or epigenetic mutations which result in the heterogeneity of cancer. Heterogeneity of cancer leads to resistance to anticancer therapy. See the section "Etiology of Cancer" and "Systemic Therapy" subsections "Chemotherapy" and "Combination Therapy."

4. **A.** ALK is an oncogene that leads to uncontrolled proliferation. NSCLC that harbors an ALK mutation has specific treatment options available that target the ALK mutation and are associated with improved outcomes compared to other subtypes of NSCLC. Tumor mutational analysis does not provide information on stage of disease or predict tolerability of therapy. See the section "Diagnosis of Cancer" subsection "Clinical Presentation" and section "Targeted Agents: Small Molecules", subsection "Anaplastic Lymphoma Kinase (ALK) Inhibitors."

5. **D.** The patient has locally advanced cancer (positive lymph nodes) as well as distant metastasis in her liver. Therefore, she has stage IV cancer given the distant spread to the liver. The goal of care in stage IV disease is to prolong survival or provide palliation. See the section "Diagnosis of Cancer" subsection "Staging" and section "Treatment Modalities" subsection "Goals of Care."

6. **D.** The cells that are most sensitive to the effects of chemotherapy are rapidly dividing cells. These cells are always in the cell cycle. Chemotherapy interferes with cellular division. Cells in the G_0 phase are not dividing and therefore resistant to the effects of chemotherapy. See the section "Pathology of Cancer" and "Systemic Therapy" subsection "Chemotherapy."

7. **B.** Small-molecule targeted agents inhibit kinases or enzymes responsible for activating various proteins involved in the intracellular signaling cascade. Monoclonal antibodies target extracellular receptors on the cell and chemotherapy targets cellular division via the cell cycle. Generally, the mechanism of action of a small-molecule inhibitor does not influence the immune system. See the section "Systemic Therapy" subsection "Targeted Agents" and section "Targeted Agents: Small Molecules."

8. **A.** Induction chemotherapy is high-dose combination chemotherapy with the intent to induce a remission or complete response. However, if chemotherapy is not continued then relapse will occur. Therefore, consolidation therapy is typically given after induction to maintain remission. Adjuvant therapy is systemic therapy administered to eradicate micrometastatic disease after local therapy (surgery or radiation). Neoadjuvant chemotherapy applies to tumors that are too large for surgical resection. AML is a hematologic malignancy; therefore, neoadjuvant therapy does not apply. See the section "Treatment Modalities."

9. **A.** Co-testing (cytology [Papanicolaou, or Pap, smear test] with HPV test) every 5 years, an annual mammogram, and a colonoscopy every 10 years would be appropriate for routine cancer screening in this patient. This patient should not be offered a low-dose helical CT scan as this lung cancer screening test should only be offered to current or former smokers 55- to 74-years old in good health with at least a 30-pack-year smoking history. See the section "Diagnosis of Cancer" and Table 149-4.

10. **D.** Combination chemotherapy is administered to treat cancer because of cancer heterogeneity and inherent resistance. Agents selected for combination regimens have demonstrated single agent activity and have different mechanism of actions to overcome different resistance patterns. In addition, agents selected should not have overlapping toxicity to avoid tolerability challenges. See the section "Systemic Therapy" subsection "Chemotherapy."

11. **B.** Fam-trastuzumab deruxtecan is an antibody-drug conjugate that consists of three components: antibody, linker, and cytotoxic payload. The cytotoxic payload contributes to the different adverse reaction profile compared to a mAb. Specifically, toxicity associated with the antibody-drug conjugate is a result of the cytotoxic payload as well as toxicity associated with the mAb. Fam-trastuzumab has a similar cardiotoxicity profile as trastuzumab; however, fam-trastuzumab is also associated with myelosuppression, given its cytotoxic payload. See the section "Targeted Agents: Antibodies" subsection "Antibodies That Target HER2."

12. **D.** VEGFR inhibitors are associated with proteinuria and hypertension. Other toxicities associated with VEGF inhibitors include wound healing

complications, bleeding, VTE, and gastrointestinal perforation. See the section "Targeted Agents: Small Molecules" subsection "VEGFR multikinase inhibitors."

13. **C.** Vincristine is an antimicrotubule agent. It is fatal if given intrathecally, and the World Health Organization recommends administering it as an intravenous infusion. Methotrexate, cytarabine, and hydrocortisone are safe to be administered intrathecally. See section "Chemotherapy" subsection "Vinca Alkaloids" and Table 149-7.

14. **A.** Ipilimumab is a CTLA-4 inhibitor. CTLA-4 acts as a negative regulator of T-cell function, decreasing the ability of the immune system to mount an antitumor response. By binding to CTLA-4, ipilimumab allows for enhanced T-cell stimulation, proliferation, and antitumor activity. Talimogene laherparepvec is an oncolytic viral therapy based on a modified HSV type 1. Sipuleucel-T is a vaccine that does not regulate T-cell function. Interleukin-2 is a cytokine produced by recombinant DNA technology that promotes B- and T-cell proliferation and differentiation and initiates a cytokine cascade with multiple interacting immunologic effects. See the section "Immunotherapy."

15. **A.** Pembrolizumab is an immune checkpoint inhibitor. Immune checkpoint inhibitors release the breaks on the immune system and are therefore known to cause immune-related adverse events. See the section "Immunotherapy."