Targeted Therapy: Attacking Cancer with Molecular and Immunological Targeted Agents

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ABSTRACT

Today, personalized cancer therapy with targeted agents has taken center stage, and offers individualized treatment to many. As the mysteries of the genes in a cell’s DNA and their specific proteins are defined, advances in the understanding of cancer gene mutations and how cancer evades the immune system have been made. This article provides a basic and simplified understanding of the available (Food and Drug Administration- approved) molecularly and immunologically targeted agents in the USA. Other agents may be available in Asia, and throughout the USA and the world, many more agents are being studied. Nursing implications for drug classes are reviewed.

Key words: Cancer, immunological, molecular, targeted agents, targeted therapy

Introduction

According to the World Health Organization (WHO), cancer continues to be a significant global public health problem. While in 2012, the number of new cancer cases was reported to be 14.1 million with 8.2 million deaths (2.9 million in developing countries and 5.3 in economically developing countries), this figure is expected to increase by 70% to 21.7 new cases and 13 million cancer deaths by 2030 due to an increase in the number and aging of the global population, and adoption of Western lifestyle habits.

“Cancer” refers to the many different types of malignancy that share common characteristics including abnormal cells which have uncontrolled cell division, and the ability to avoid programmed cell death (apoptosis). Normally, cell birth equals cell death, and this is tightly controlled by the cell. Scientists continue to decipher the complex layers of tumorigenesis and progression, and pharmaceutical companies seek specific, precise medicines to treat each cancer based on specific mutations and abnormalities.

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As the understanding of malignant transformation has increased, it is clear cancer involves changes in cell signaling, cell metabolism, ability to avoid apoptosis, and ability to spread or metastasize to a different site within the body. To do this, cancer cells can avoid immune surveillance or detection by the immune system. To develop targeted therapy, the targets should be identified. Hanrahan and Weinberg identify ten hallmarks of cancer that guide our understanding of the targets, that are shown below along with an example of agents (if known) that targets this hallmark (in parens):[3]

- Sustained proliferation signaling so that the cell can continue to divide without regard to the body’s needs (epidermal growth factor receptor [EGFR] inhibitors)
- Evading growth suppressors that would normally turn off cell division or cause the cell to undergo apoptosis (cyclin-dependent kinase [CDK] inhibitors)
- Avoiding immune destruction (programmed death [PD]-1 inhibitors)
- Enabling replicating immortality (investigational)
- Tumor-promoting inflammation (fosters multiple hallmark functions)(selective anti-inflammatory drugs)
- Activating invasion and metastasis (inhibitors of hepatocyte growth factor or its receptor kinase cMet)
- Inducing angiogenesis (vascular endothelial growth factor [VEGF] signaling inhibitors)
- Genome instability (allows for genetic diversity that accelerates the acquisition of the hallmarks)(poly [ADP-ribose] polymerase [PARP] inhibitors)
- Resisting cell death (inhibitors of the anti-apoptotic proteins such as BCL-2)
- Deregulating cellular energetics (allows cancer cells to use glucose as a fuel source exclusively) (enasidenib, an IDH2 (iso dehydrogenase) inhibitor, possibly metformin[4])

**Molecular Targeted Therapy**

Normally, cells are very careful to make more cells only if the body needs them, and hence that cell birth equals cell death. For example, when you wash your hands, you slough off many keratinized epidermal cells, that need to be replaced by underlying cells in the skin. They do this by controlling cell division. When the cell needs to make more cells like those lost, a growth factor or hormone binds to a receptor in the cell’s membrane and turns on a signaling cascade resulting in cell division. Two key groups of genes that regulate this controlled cell division are proto-oncogenes (turn on cell division) and tumor suppressor genes (turn off cell division). The binding of a ligand (growth factor or hormone) to the cell receptor initiates a signal that passes through the cell membrane, into the cell cytoplasm, and is sent through the cytoplasm from protein to protein like a bucket brigade, to the cell nucleus to tell the cell's DNA to start division. This is called cell signaling. There are many attractive anticancer targets in the abnormal cell signaling proteins in cancer cells. These abnormalities are discussed further.

To understand this therapy, it is important to understand what the cancer targets are. The proteins in the bucket brigade are usually protein kinases. In cancer, the cell membrane receptor (receptor tyrosine kinase) which is often a proto-oncogene, becomes an oncogene when mutated, such as the EGFR and VEGF receptor (VEGFR), and hence, the signal to divide is sent continually. A signaling pathway within the cell is a series of protein kinases (enzymes which add a phosphate group) which pass the message from inside the cell membrane, through the cytoplasm to the cell nucleus, or “downstream,” like a bucket brigade, from protein to protein. Once in the cell nucleus the message is transcribed (copied) to make a protein, and the cell is told to do something, such as to divide repeatedly, ignore death signals and survive, to migrate or metastasize, and to make new blood vessels. In cancer, one or more of these proteins in the bucket brigade is mutated, leading to sustained signaling to divide as the protein continually sends the message whether it receives it from another protein or not. In addition, other messages leading to the other hallmarks of cancer occur. Two important Food and Drug Administration (FDA) approved drugs are cetuximab which is an EGFR inhibitor, and bevacizumab, which is a VEGF angiogenesis inhibitor.

One important signaling pathway which often has mutations is the mitogen-activated protein kinase (MAPK) pathway that has the proteins Ras, Raf, MEK, and ERK in its cascade.[5] Ras acts as a switch to turn on signaling, taking the message from inside the cell membrane to the next protein kinase Ras, which then sends it to MEK, then ERK which in the cell nucleus makes the DNA genes turn on the cell cycle for cell division, make specific proteins, help the cell survive and move (migrate), and invade nearby tissues. Ras can be continually “turned on.” Raf, the next protein kinase in the cascade, includes B-raf, and its gene *BRAF* which is often mutated in malignant melanoma (the *BRAF* V600E mutation). These messages sent to the cell nucleus control cell proliferation, survival, migration, and angiogenesis, all functions important to a cancer cell.[6] Another important signaling pathway is the PI3K-Akt-mTOR pathway, which also helps to regulate cell growth and division, movement, death, and survival.[7] This pathway is often abnormal in cancers such as breast, lung, and prostate cancers, and each of the steps of the pathway is
an attractive anticancer targets. PI3K activates AKT, which then activates mTOR (mammalian target of rapamycin). mTOR is an important protein kinase that is often mutated; it can be thought of as a “Grand Central Station” as it integrates signals from multiple pathways, such as those regulating nutrient supply, growth factors, hormones, and stress (e.g. hypoxia, DNA damage). Other important genes that are mutated in cancer, and which make an abnormal or mutated protein kinase that controls cancer hallmark(s) are B-cell receptor (Bcr-ABL) (CML), and ALK (causing a type of nonsmall cell lung cancer (NSCLC)).

A key growth factor is VEGF and the receptor on the endothelial cell membrane is VEGFR. There are a number of types of VEGF receptors. Solid tumors cannot grow beyond 2 mm without requiring blood vessels to provide oxygen and remove cellular waste products. Cancer cells have abnormal blood vessels, some may be tortuous, and others end in a dead end. It is believed that the VEGF/VEGFR inhibitors, which block the growth factor on the outside (such as bevacizumab) or the protein kinase inside of the endothelial cell, not only block the ability of tumors to build new blood vessels but also normalize the existing tumor blood vessels, so that administered anticancer drugs can enter a patent tumor blood supply to kill the tumor.

The normal cell controls cell division by making sure the cell division cycle (cell cycle) stops at a “Restriction Point” if there is inadequate nutrition for the cell to make the many necessary proteins to reproduce its DNA, or if the cell is abnormal. It does this by a special policeman gene called rhabdoblastoma (Rb) gene, which makes the policeman protein pRb. If pRb becomes phosphorylated (takes on an additional phosphate group), the cell cycle continues on; if it is unphosphorylated, the cell cycle stops in its tracks, and the cell undergoes apoptosis. Classically, cancer cells have unregulated Restriction Points, and continue going through the cell cycle regardless of how abnormal they are. In normal cells, they are identified as abnormal and made to undergo apoptosis. CDKs bind to a cyclin, and then the complex pushes pRb to phosphorylate, moving the cell first through the Restriction Point, and then through each phase of the cell cycle, with a different CDK/cyclin complex for each phase. Once a CDK/cyclin complex is used, it is broken down so the cell cannot keep cycling. In cancer cells, the gene(s) for one or more CDKs may be mutated, making the CDK hyperactive so that it continually moves the malignant cell through the cell cycle without stopping. The cancer cell does not leave the cell cycle so the cell continues to divide. In addition, the Rb gene may be mutated, so that the Restriction Point police are ineffective in preventing the malignant cell from entering the cell cycle or completing it. The cell cycle machinery is an excellent target as it is responsible for continual and unrestricted cell division. Three CDK inhibitors are currently FDA approved in the USA. For example, abemaciclib inhibits CDK 4 and CDK6, which are activated on binding to cyclin D, which is overexpressed in certain breast cancer cells. Inhibition of the CDK/cyclin complex blocks pRb phosphorylation so the breast cancer cells stop dividing, resulting in aging of the cell and apoptosis.

Once the cell moves through the cell cycle, the cell’s DNA is checked for errors. When found, DNA repair genes make proteins to repair the damage. If the damage cannot be repaired, the cell undergoes apoptosis as directed by the p53 protein (made by the TP53 gene). In over 50% of cancers, TP53 is mutated, so cancer cells evade apoptosis and the cell acquires replicative immortality (keeps dividing even if the DNA is flawed). To repair damaged DNA, the cell has two normal mechanisms, and one is controlled by DNA Repair genes such as BRCA-1 and BRCA-2. In some breast and other cancers, BRCA-1 and/or BRCA-2 genes are mutated, so the cell cannot use this pathway. Drugs called PARP inhibitors block the remaining DNA repair pathway, causing the cancer cell to die (synthetic lethality). Currently, three PARP inhibitors have been FDA approved. Apoptosis (programmed cell death) is an organized, systematic destruction of abnormal or unwanted cells, a normal physiologic process in each of our cells. Whether or not a cell undergoes apoptosis is determined by the balance of proapoptotic (propelling the cell into apoptosis) and antiapoptotic proteins (halting the cells from undergoing apoptosis). Cancer cells, however, want immortality, so they have developed ways to circumvent apoptosis. One way they do this is to commandeer more anti-apoptotic proteins, such as Bcl-2, so that the scales tip in favor of avoidance of apoptosis. One FDA approved drug is venetoclax, which inhibits Bcl-2, thus restoring apoptosis.

The receptor protein kinase inhibitors (on the outside of the cell) are large molecules, so require monoclonal antibodies to deliver them them to the target; once in the body, the drug can block the message from being sent from the abnormal receptor on the outside of the cell (in) to the cell. In contrast, the oral protein kinase inhibitors are small molecules that can be taken orally to block the message once it has entered the membrane and prevents it from being sent like a bucket brigade down through the cell’s cytoplasm to the nucleus. The tumor suppressor genes such as the TP53 gene, are often mutated so that they do not oppose unrestricted cell division. The TP53 gene is called the “guardian of the genome,” The TP53 gene mutation continues to be an attractive target, but no drug or gene therapy has yet proven successful.
Proteasomes are important in recycling proteins within the cell and are also an anticancer target in the treatment of malignancies such as multiple myeloma. Proteasomes are involved in controlling cell cycle progression (division) and programmed cell death (apoptosis) by removing recently used proteins so they cannot continue to work in the cell cycle or apoptotic apparatus. If a protein, say a CDK-cyclin complex, is allowed to stay available for a long time, it will continue to bring the cell through the cell cycle when more cells are not needed by the body. Hence, certain proteins need to be destroyed immediately after use so that they will not stay active. The proteasomes can be thought of as a large protein recycling plant in the cytoplasm of the cell: the proteins that are no longer needed or which are damaged are brought to the proteasome by an enzyme called ubiquitin, and then deposited in the proteasome, where the protein is broken down into peptides and amino acids. These building blocks can be recycled and used in the synthesis of more proteins. Cancer cells are more sensitive to blockade of the proteasome than normal cells, possibly because they use it for unlimited cell division and avoidance of apoptosis, and proteasome inhibition causes cancer cell death.[18]

All the processes discussed so far occur at the level of the cancer cell and generally involve genetic changes or abnormalities in the cell’s DNA. Epigenetics refers to heritable changes in our genes that do not involve changes in the actual DNA; rather there is a change in the expression of genes, for example, whether the gene is turned “on” or not.[19] Specifically, cancer can silence some of the tumor suppressor genes through controlling DNA methylation and histone modification. Anticancer therapy can decrease methylation to make the tumor suppressor gene turn on, or histone deacetylase (HDAC) inhibitors can loosen the tightly wound DNA, so that the tumor suppressor genes are expressed or turned on.[20]

Protein kinase inhibitors block the abnormal proteins and hence the extra messages telling the cell to divide, survive, or migrate do not get to the cell nucleus. In terms of nomenclature, the generic names of protein kinase inhibitors end in–tinib, proteasome inhibitors in–zomib, CDK inhibitors in–ciclib, PARP inhibitors in–parib, BRAF inhibitors in–fenib, and PI3K inhibitors in–lisib.[21] Monoclonal antibodies are discussed with immunological agents.

While molecular targets and targeted agents continue to be identified, those available today are shown in Table 1. There are common and significant adverse effects; the nurse needs to be knowledgeable to assess, intervene, and teach the patient and family self-care measures, as some adverse effects can be life-threatening.[22-72]

Table 1: Molecular targeted therapy agents (all oral except as indicated)

| Class/drug | Target (s)/indication (s) | Common adverse effects/warnings |
|------------|---------------------------|---------------------------------|
| ALK inhibitor | RTK ALK, RET and downstream, STAT3 and AKT; ALK-positive metastatic NSCLC that has progressed or patient is intolerant of crizotinib | Class effects: CYP3A4 drug interactions; GI symptoms; embryo-fetal toxicity; bradycardia; ILD; hepatotoxicity; QTc interval prolongation |
| Alectinib (Alecensa®)[22] | RTK ALK, RET and downstream, STAT3 and AKT; ALK-positive metastatic NSCLC that has progressed or patient is intolerant of crizotinib | Fatigue, constipation, edema, myalgia |
| Brigatinib (Alunbrig®)[24] | RTK ALK, ROS1; IGF-1R, FLT-3, as well as EGFR deletion and point mutations. Also EMLA4-ALK and NPM-ALK fusion proteins | Nausea, diarrhea, fatigue, cough, headache |
| Ceritinib (Zykadia®)[24] | RTK ALK, IGF-1R, InsR, ROS1; ALK+ metastatic NSCLC | Warnings: ILD, HTN, bradycardia, visual disturbances, CPK elevations, pancreatic enzyme elevation, hyperglycemia, embryo-fetal toxicity |
| Crizotinib (Xalkori®)[24] | RTK ALK, ROS-1; ALK+ or ROS-1 positive metastatic NSCLC | Diarrhea, nausea, fatigue, vomiting, abdominal pain, decreased appetite, and weight loss |
| Angiogenesis inhibitors | VEGF receptors on endothelial cells lining blood vessels; advanced RCC | Warnings: Severe/persistent GI toxicity, hepatotoxicity, ILD, QT interval prolongation, hyperglycemia, bradycardia, pancreatitis, embryo-fetal toxicity |
| Axitinib (Inlyta®)[26] | VEGF receptors on endothelial cells lining blood vessels; advanced RCC | Vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy |

Contd...
## Table 1: Contd...

| Class/drug | Target (s)/indication (s) | Common adverse effects/warnings |
|------------|---------------------------|---------------------------------|
| **Cabozantinib (Cometriq™)** | MET, HGF; VEGFR 1, 2, 3; RET, KIT, FLT-3; others. Progressive, metastatic medullary thyroid cancer | Diarrhea, stomatitis, PPE, decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, HTN, abdominal pain, constipation, elevated LFTs, increased alkaline phosphatase, neuprolenia, thrombocytopenia, hypocalcemia, hypophosphatemia |
|           |                           | Preferences: Thromboembolic events, wound complications, HTN, osteonecrosis of the jaw, PPE, proteinuria, RPLS, embryo-fetal toxicity |
| **Levatinib (Lenvima®)** | VEGFR1, 2, 3; Locally recurrent or metastatic progressive, RAI-refractory differentiated thyroid cancer; RCC | HTN, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, PPE, abdominal pain, and dysphoria |
|           |                           | Preferences: HTN (control before treatment), cardiac failure, arterial thrombotic events, hepatotoxicity, proteinuria, severe diarrhea, renal failure, GI perforation/fistula, QT-interval prolongation, hypocalcemia, RPLS, hemorrhage, thyroid dysfunction, embryo-fetal toxicity |
| **Pazopanib (Votrient®)** | VEGFR 1, 2, 3; PDGF-R, FGR; Advanced RCC; advanced soft tissue sarcoma | Diarrhea, HTN, hair color changes (depigmentation), nausea, anorexia, vomiting |
|           |                           | Preferences: Hepatotoxicity, prolonged QT intervals and torsades de pointes, cardiac dysfunction, hemorrhage, thrombotic events, thrombotic micro-angiopathy, GI perforation/fistula, RPLS, sound healing complications, embryo-fetal toxicity |
| **Regorafenib (Stivarga®)** | VEGF 2, 3; PDGF-R, RET, KIT, RAF; metastatic CRC; locally advanced, unresetable or metastatic GIST, hepatocellular carcinoma previously treated with sorafenib | Pain, HFSR, asthemia/fatigue, diarrhea, decreased appetite/food intake, HTN, infection, dysphoria, fever, mucositis, hyperbilirubinemia, weight loss, rash, nausea |
|           |                           | Preferences: Hepatotoxicity, infections, hemorrhage, GI perforation or fistula, dermatologic toxicity, HTN, cardiac ischemia/MI, RPLS, sound healing complications, embryo-fetal toxicity |
| **Sorafenib (Nexavar®)** | VEGFR2, PDGF, RAF; unresetable hepatocellular cancer; advanced RCC; locally recurrent or metastatic, progressive differentiated thyroid carcinoma refractory to RAI | Diarrhea, fatigue, infection, alopecia, HFSR, rash, weight loss, decreased appetite, nausea, GI and abdominal pain, HTN, hemorrhage |
|           |                           | Preferences: Cardiac ischemia/MI, bleeding, HTN, dermatologic toxicities, GI perforation, QT prolongation, drug-induced hepatitis, embryo-fetal toxicity, impairment of TSH suppression |
| **Sunitinib (Sutent®)** | PDGF-R, VEGF 1, 2, 3; KIT, FLT-3; RET; GIST after disease progression or intolerance to imatinib mesylate; advanced RCC; progressive, well-differentiated pNET | Fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, HTN, peripheral edema, rash, HFSR, skin discoloration, dry skin, hair color changes, altered taste, headache, backpain, arthralgia, extremity pain, cough, dyspnea, anorexia, bleeding |
|           |                           | Preferences: Hepatotoxicity, embryo-fetal toxicity, cardiovascular events, prolonged QT intervals and Torsades de Pointes, HTN, hemorrhagic events, TLS, thrombotic microangiopathy, proteinuria, dermatologic toxicities, thyroid dysfunction, hypoglycemia, osteonecrosis of the jaw, impaired wound healing, adrenal hemorrhage |
| **Vandetanib (Caprelsa®)** | VEGF 2, EGFR 1; symptomatic or progressive medullary thyroid cancer in patients with metastatic or locally advanced unresectable disease | Diarrhea/colicis, rash, aneiform dermatitis, nausea, headache, HTN, URI, decreased appetite, abdominal pain |
|           |                           | Preferences: Prolonged QT, torsades de pointes, and sudden death; severe dermatologic toxicities; IBD; ischemic cerebrovascular events, hemorrhage, heart failure, diarrhea, HTN, RPLS; embryo-fetal toxicity |
| **Ziv-afibercept (Zaltrap®)** (Inavanes) | VEGF (recombinant fusion protein that is a decoy [VEGF trap]); metastatic CRC in combination with FOLFIRI | Leukopenia, diarrhea, neutropenia, proteinuria, increased ALT and AST, HTN, weight loss, stomatitis, fatigue, thrombocytopenia, decreased appetite, epistaxis, abdominal pain, dysphoria, increased serum creatinine, headache |
|           |                           | Preferences: Fistula formation, HTN, arterial thromboembolic events, proteinuria, neutropenia and neutrophenic complications, diarrhea and dehydration, RPLS, hemorrhage, GI perforation, compromised wound healing |
| **Bcl-2 inhibitor (restores apoptosis)** | Bcl-2; CLL with 17p deletion mutation | Class effects: TLS; embryo-fetal toxicity; neutropenia, drug interactions |
| **Venetoclax (Venclexta®)** | Neutropenia, diarrhea, nausea, anemia, URI, thrombocytopenia, fatigue |
|           |                           | Preferences: TLS, neutropenia, embryo-fetal toxicity, live immunizations contraindicated |
| **BCK-ABL kinase inhibitors** | Class effects: CYP3A4 drug interactions, edema, bone marrow suppression; embryo-fetal toxicity |
| **Bosutinib (Bosulif®)** | BCR-ABL kinase, most resistant forms; adults with Ph + CML with relapsed disease | Diarrhea, nausea, thrombocytopenia, rash, vomiting, abdominal pain, respiratory tract infections, anemia, pyrexia, LFT abnormalities, fatigue, cough, headache |
|           |                           | Preferences: GI toxicity, myelosuppression, hepatotoxicity, fluid retention, renal toxicity, embryo-fetal toxicity |
| **Dasatinib (Sprycel®)** | BCR-ABL kinase, other kinases including SRC; newly diagnosed PH + CML in chronic phase; chronic accelerated or myeloid or lymphoid blast phase PH + CML; resistant PH + ALL; pediatric PH + CML in chronic phase | Myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, musculoskeletal pain |
|           |                           | Preferences: Myelosuppression and bleeding events, fluid retention, cardiac dysfunction, pulmonary arterial HTN, QT prolongation, severe dermatologic reactions, TLS, embryo-fetal toxicity, adverse effect on growth and development in pediatric patients |

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### Table 1: Contd...

| Class/drug                       | Target (s)/indication (s)                                                                 | Common adverse effects/warnings                                                                 |
|----------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| **Imatinib mesylate (Gleevec®)** | BCR-ABL kinase; newly diagnosed Ph+ CML in chronic phase (adult, children); Ph+ CML in blast crisis/accelerated phase/chronic phase; relapsed refractory Ph+ ADD (adults); newly diagnosed Ph+ ALL children; certain MDS in adults | Edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, abdominal pain  
Warnings: Edema and severe fluid retention, cytopenias, severe CHF and left ventricular dysfunction, severe hepatotoxicity, severe hemorrhage, GI perforation, cardiacogenic shock, bullous dermatologic reactions, hypothyroidism, embryo-fetal toxicity, growth retardation in children, TLS, renal toxicity, changes in mental status |
| **Nilotinib (Tasigna®)**         | BCR-ABL kinase; newly diagnosed Ph+ CML in chronic phase (adult); Ph+ CML in chronic/accelerated phases (adult) | Nausea, rash, headache, fatigue, pruritus, vomiting, diarrhea, cough, constipation, arthralgia, nasopharyngitis, pyrexia, night sweats, myelosuppression  
Warnings: Myelosuppression, cardiac and arterial vascular occlusive events, pancreatitis, hepatotoxicity, electrolyte abnormalities, TLS, hemorrhage, drug interactions, caution in patients with total gastrectomy, embryo-fetal toxicity, fluid retention (effusions) |
| **Ponatinib (Iclusig®)**        | BCR-ABL kinase; CML in chronic/accelerated/blast phase or Ph+ for whom no other TKI inhibitor is indicated; adults with T3151-positive CML or Ph+ ALL | Abdominal pain, rash, constipation, headache, dry skin, fatigue, HTN, pyrexia, arthralgia, nausea, diarrhea, increased serum lipase, vomiting, myalgia, extremity pain  
Warnings |
| **BRAF and MEK inhibitors**     |                                                                                           | Class effects: New primary malignancies, hemorrhage, HTN, eye problems, GI symptoms, CYP3A4 drug interactions, embryo-fetal toxicity |
| **Cobimetinib (Cotellic®)**     | Mutated BRAF; reversible inhibitor of MAPK/extracellular signal regulated kinase 1 (MEK1, MEK2); unresectable or metastatic melanoma with BRAF V600E or V600K mutation in combination with vemurafenib | Diarrhea, photosensitivity reaction, nausea, pyrexia, vomiting, increased LFTs, increased CPK, hypophosphatemia, hyponatremia, lymphopenia  
Warnings: New primary malignancies, hemorrhage, cardiomyopathy, severe dermatologic reaction, serous retinopathy and retinal vein occlusion, hepatotoxicity, rhabdomyolysis, embryo-fetal toxicity |
| **Dabrafenib (Tafinlar®)**      | Mutated BRAF; unresectable or metastatic melanoma with BRAF V600E mutation; metastatic NSCLC with BRAF V600E mutation | Hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, PPS, decreased appetite, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, hemorrhage  
Warnings: New primary malignancies, tumor promotion in BRAF wild-type tumors, hemorrhage, cardiomyopathy, uveitis, serious febrile reactions, serious skin toxicity, hyperglycemia, risk of hemolytic anemia in patients with G-6-PD, embryo-fetal toxicity |
| **Trametinib (Mekinist®)**      | MEK pathway; unresectable metastatic melanoma with BRAF V600E or V600K mutation, in combination with dabrafenib; metastatic NSCLC with BRAF V600E mutation | Rash, diarrhea, lymphedema, pyrexia, nausea, rash, chills, diarrhea, vomiting, HTN, peripheral edema, dry skin, decreased appetite, hemorrhage  
Warnings: New primary malignancies, hemorrhage, colitis and GI perforation, venous thromboembolism, cardiomyopathy, ocular toxicities, IILD, serious febrile reactions, serious skin toxicities, hyperglycemia, embryo-fetal toxicity |
| **Vemurafenib (Zelboraf®)**     | Mutated BRAF; malignant melanoma with BRAF V600E mutation; erdheim-Chester disease with BRAF V600 mutation | Arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, skin papilloma, prolonged QT-interval  
Warnings: New primary cutaneous malignancy, new noncutaneous squamous cell carcinoma, other malignancies, tumor promotion in BRAF wild-type melanoma, serious hyper-sensitivity reactions including anaphylaxis, severe dermatologic reactions, QT-prolongation, hepatotoxicity, photosensitivity, serious ophthalmologic reactions, embryo-fetal toxicity, radiation sensitization/recall, renal failure, Dupuytren’s contracture and plantar fascial fibromatosis |
| **BTK inhibitor**               |                                                                                           | Class effects: cytope尼亚s (infection and hemorrhage); HTN; 2nd primary malignancies; TLS; embryo-fetal toxicity |
| **Acalabrutinib (Calquence®)**  | Bruton’s tyrosine kinase (signaling molecule of the B-cell antigen receptor); Mantle cell lymphoma | Anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, bruising  
Warnings: Hemorrhage, infections, cytopenias, second primary malignancies, atrial fibrillation, and flutter |
| **Ibrutinib (Imbruvica®)**      | Bruton’s tyrosine kinase (signaling molecule of the B-cell antigen receptor); MCL, CLL/SLL, CLL/SLL with 17p deletion mutation; WM, MZL, cGVHD | Neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, pyrexia, muscle spasms  
Warnings: Hemorrhage, cytopenias, atrial fibrillation, HTN, second primary malignancies, TLS, embryo-fetal toxicity |
| **Cyclin-dependent kinase inhibitor** |                                                                                               | Class effects: Neutropenia; embryo-fetal toxicity; CYP3A4 drug interactions; GI symptoms |
| **Abemaciclib (Verzenio®)**     | CDKs 4, 6 (which allow cells to progress through G1 and S phases of cell cycle); together with fulvestrant, or as a single agent in | Diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, thrombocytopenia  
Warnings: Diarrhea, neutropenia, hepatotoxicity, venous thromboembolism, embryo-fetal toxicity |

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### Table 1: Contd...

| Class/drug                  | Target (s)/indication (s)                                                                 | Common adverse effects/warnings                                                                 |
|-----------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Palbociclib (Ibrance®[^47]) | CDKs 4, 6 (which allow cells to progress through G1 and S phases of cell cycle); postmenopausal women with ER+ | Neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea,  |
|                            | and HER2-negative advanced or metastatic breast who have progressed on endocrine therapy  | thrombocytopenia, rash, vomiting, decreased appetite, asthenia, pyrexia. Warnings: Neutropenia, |
|                            | or endocrine/chemotherapy (when given as monotherapy)                                     | embryo-fetal toxicity                                                                           |
| Ribociclib (Kisqali)        | Cyclin Dependent Kinase (CDK) s 4, 6 (which allow cells to progress through G1 and S | Neutropenia, nausea, fatigue, diarreha, leukopenia, alopecia, vomiting, constipation, headache, |
|                            | phases of cell cycle); postmenopausal women with ER+, HER2- advanced or metastatic       | back pain. Warnings: QT-interval prolongation on ECG, neutropenia, embryo-fetal toxicity           |
|                            | BC, with an aromatase inhibitor                                                          |                                                                                                 |
| Epidermal growth factor TKIs, small molecule |                                                                                          | Class toxicity: skin rash, diarrhea, ILD, embryo-fetal toxicity, CYP3A4 and/or P-gp drug interactions |
| Afatinib (Gilotrif®[^49])   | EGFR with exon 19 deletions or exon 21 (L858R) substitution                              | Diarrhea, rash/acneiform dermatitis, stomatitis, paronychia, dry skin, decreased appetite, nausea, |
|                            | Metastatic NSCLC including EGFR                                                         | vomiting, pruritus. Warnings: Diarrhea, bullous and exfoliative skin disorders, ILD, hepatotoxicity, |
|                            | with exon 19 deletions or exon 21 (L858R) substitution mutations                         | keratitis, embryo-fetal toxicity                                                                 |
| Erlotinib (Tarceva®[^54])   | EGFR with exon 19 deletions or exon 21 (L858R) substitution                              | Rash, diarrhea, anorexia, fatigue, dyspea, cough, nausea, vomiting. Warnings: ILD, renal failure, |
|                            | EGFR1-positive locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations | hepatotoxicity, GI perforation, bullous and exfoliative skin disorders, CVA, microangiopathic hemolytic anemia, ocular disorders, hemorrhage in patients taking warfarin, embryo-fetal toxicity |
| Gefitinib (Iressa®[^51])    | EGFR with exon 19 deletions or exon 21 (L858R) substitution                              | Skin reactions, diarrhea. Warnings: ILD, hepatotoxicity, GI perforation, diarrhea, ocular disorders, |
|                            | Metastatic NSCLC including EGFR                                                          | bullous and exfoliative skin disorders, embryo-fetal toxicity                                    |
| Lapatinib (Tykerb®[^52])    | EGFR1, EGFR2 (HER-2); advanced or metastatic HER2+ breast cancer with capecitabine, or with letrozole | With Capecitabine, diarrhea, PPES, nausea, rash, vomiting, fatigue; when given with letrozole, diarrhea, rash, nausea, fatigue. Warnings: Decreased LVEF, hepatotoxicity, diarreha, ILD, prolonged QT interval, severe cutaneous reactions, embryo-fetal toxicity |
| Neratinib (Nerlynx®[^53])   | HER-2                                                                                   | Diarrhea, nausea, abdominal pain, fatigue, vomiting, stomatitis, decreased appetite, muscle spasms, dyspepsia, increased AST or ALT, nail disorder, dry skin, abdominal distention, decreased weight, URI. Warnings: Diarrhea, hepatotoxicity, embryo-fetal toxicity |
| Osimertinib (Tagrisso®[^54])| EGFR1 with T790M mutation Metastatic NSCLC having EGFR T790M mutation                   | Diarrhea, rash, dry skin, nail toxicity, fatigue. Warnings: ILD, QTc interval prolongation, cardiomyopathy, keratitis, embryo-fetal toxicity |
| FLT3 kinase inhibitor       |                                                                                         | Class effects: Nausea, vomiting, diarrhea, embryo-fetal toxicity                                  |
| Midostaurin (Rydapt®[^57])  | FLT3, KIT, PDGFRαβ, VEGFR2, members of the serine/threonine kinase PKC family; newly diagnosed FLT3 mutation positive AML, together with standard chemotherapy; aggressive systemic mastocytosis; systemic mastocytosis with hematologic neoplasm; mast cell leukemia | Febrile neutropenia, nausea, mucositis, vomiting, headache, petechiae, musculoskeletal pain, epistaxis, device-related infection, hyperglycemia, URI, diarrhea, edema, abdominal pain, fatigue, constipation, pyrexia, headache, dyspnea. Warnings: Pulmonary toxicity, embryo-fetal toxicity |
| Hedgehog pathway inhibitors |                                                                                         | Class effects: Embryo-fetal toxicity (negative pregnancy test before starting drug, effective contraception, no donation of blood, sperm); muscle spasms; risk of increased CK, GI symptoms |

Contd...
| Class/drug | Target (s)/indication (s) | Common adverse effects/warnings |
|-----------|------------------------|--------------------------------|
| Sonidegib (Odomzo®)①② | SMO, a transmembrane signal transduction protein; adults with locally advanced basal cell carcinoma, recurrent after surgery, RT or in unresectable patients | Muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased appetite and weight, myalgia, abdominal pain headache, pain, vomiting, pruritus |
| Vismodegib (Erivedge®)③ | SMO, a transmembrane signal transduction protein; locally advanced or metastatic basal cell carcinoma | Muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, ageusia. Warnings: Teach patient not to donate blood during or for 24 months after drug; teach male patient not to donate semen during or for 3 months after therapy; premature fusion of epiphyses |
| HDAC inhibitors | Class effects: Myelosuppression, infections and bleeding; hepatotoxicity; TLS; embryo-fetal toxicity; GI symptoms; drug interactions | Nausea, fatigue, pyrexia, anemia, vomiting |
| Belinostat (Beleodaq®) (IV)④ | HDAC (enzyme that prevents uncoiling of DNA strand so genes can be transcribed), so inhibition leads to cell-cycle arrest and apoptosis; Relapsed or refractory peripheral T-cell lymphoma | Diarrhea, afatigue, nausea, peripheral edema, decreased appetite, pyrexia, vomiting |
| Panobinostat (Farydak®)⑤⑥ | HDAC; multiple myeloma, in combination with bortezomib and dexamethasone | Neutropenia, lymphopenia, thrombocytopenia, infections, nausea, fatigue, vomiting, anemia, anorexia, anemia, ECG T-wave changes |
| Romidepsin (Isosdax®)⑥⑦ (IV) | HDAC; CTCL; PTCL | Diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, vomiting |
| Vorinostat (Zolinza®)⑧⑨ | HDAC; CTCL | Neutropenia, lymphopenia, thrombocytopenia, infections, nausea, fatigue, vomiting, anemia, anorexia, anemia, ECG T-wave changes |
| IDH2 inhibitor | Mutated IDH2; AML, refractory or relapsed, with IDH2 mutation | Class effects: embryo-fetal toxicity, possible differentiation syndrome |
| Enasidenib (Idhifa®)⑩⑪ | Neutropenia, lymphopenia, thrombocytopenia, infections, nausea, fatigue, vomiting, anemia, anorexia, anemia, ECG T-wave changes |
| mTOR inhibitor | Class effects: CYP3A4 drug interactions; pneumonitis; embryo-fetal toxicity; GI symptoms; impaired wound healing; renal failure; hyperglycemia | Nausea, vomiting, diarrhea, elevated BR, decreased appetite |
| Everolimus (Afinitor®)⑪⑫ | mTOR; postmenopausal advanced ER + HER2-breast cancer; advanced RCC; progressive unresectable PNET (adults); renal angiomylipoma (adults) | Neutropenia, lymphopenia, thrombocytopenia, infections, nausea, fatigue, vomiting, anemia, anorexia, anemia, ECG T-wave changes |
| Temsirolimus (Torisel®) (IV)⑬⑭ | mTOR; advanced RCC | Neutropenia, lymphopenia, thrombocytopenia, infections, nausea, fatigue, vomiting, anemia, anorexia, anemia, ECG T-wave changes |
| PARP inhibitors | Mutated BRCA1, 2, 3; germline BRCA1 mutated recurrent or advanced ovarian cancer (actual or suspected) | Class effects: embryo-fetal toxicity |
| Olaparib (Lynparza®)⑮ | Class effects: MDS/AML transformation, embryo-fetal toxicity | Class effects: MDS/AML transformation, embryo-fetal toxicity |
| Niraparib (Zejula®)⑯ | Maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who are in a CR or PR after platinum-based chemotherapy | Class effects: MDS/AML transformation, embryo-fetal toxicity |
| Rucaparib (Rubraca®)⑰⑱ | PARP-1, 2, 3; germline and/or somatic BRCA mutated advanced ovarian cancer, after 2 or more prior chemotherapies | Class effects: MDS/AML transformation, embryo-fetal toxicity |

Contd...
The immune system is a complex network of cells, tissues, and organs that work together to protect the body from infections and cancers. It contains different types of white blood cells, including B cells, T cells, and natural killer (NK) cells. The immune system also includes immune organs such as the thymus, lymph nodes, spleen, and bone marrow. It is divided into two main parts: the innate immune system and the adaptive immune system.

### Innately Recognized Pathogens

These are pathogens that are recognized by both the innate and adaptive immune systems. Examples include bacteria, fungi, and viruses.

### Pathogen-Specific Immunity

This is where the immune system mounts a specific response to a particular pathogen. This can be either through the innate immune system or the adaptive immune system.

### Induced Immunity

This is a state of immune protection that occurs after successful infection or vaccination. It is mediated by the adaptive immune system and can be either humoral (B cells and antibodies) or cellular (T cells).

### Immuno-Targeted Therapy

This is a targeted approach to control cancer growth and progression. It includes genetic and epigenetic modifications, identification of protein, and development of vaccines and therapeutic vaccines. It can be divided into three types: immunogenic, immune evasion, and immune suppression.

### Genetic Alterations in Cancer

These are alterations in the genome of cancer cells, which can include point mutations, deletions, translocations, and amplifications. These alterations can be targeted by immunotherapy to induce an immune response against cancer cells.

### Epigenetic Modifications in Cancer

These are changes in gene expression that do not involve changes in DNA sequence. They include DNA methylation, histone modifications, and microRNA expression. These modifications can be targeted by immunotherapy to induce an immune response against cancer cells.

### Immune Checkpoints in Cancer

These are regulatory checkpoints that control the immune response. They include the PD-1/PD-L1 and CTLA-4 pathways. Inhibitors of these pathways can be used to enhance the immune response against cancer cells.

### Future Directions

The future of cancer immunotherapy is promising. New immunotherapies are being developed that target specific cancer antigens, and new methods of delivering vaccines are being explored. There is also a growing interest in combining immunotherapy with other forms of therapy, such as chemotherapy and targeted therapy.

### Conclusion

Cancer immunotherapy is a rapidly evolving field that has the potential to revolutionize the treatment of cancer. It is a promising approach to controlling cancer growth and progression, and it is likely to play a central role in the treatment of cancer in the future.
Some tumors produce the PD-L1 and inhibit the helper T cell. The antibody functions like a guided missile to locate and destroy the cells with the antigen. Unfortunately, the invading cell is not identified as “self,” then the B-lymphocytes begin an antibody-dependent cytotoxic reaction, and the T-lymphocytes go through a process to kill the antigen-containing cell(s).

Looking first at the B-cell (antibody) response, called the humoral response, B-cells mature in the bone marrow and develop many BCRs, one for each antigen it might encounter. Once mature, they enter the lymph system and start looking for their specific antigen (on a microorganism or abnormal cell). Once the specific antigen is found, the BCR binds to the antigen. Then, a helper T-cell or interleukin (IL) (a chemical messenger) binds to the complex, acting as a co-stimulator, activating the B-cell, and inducing the B-cell to divide rapidly producing an army of many thousands of identical B-cells. The B-cells make a clone of identical plasma cells, each becoming antibody-producing factories, making an antibody against the specific antigen. The antibody is shaped like a Y, where the top of the Y is the variable region that will bind the antigen, and the bottom is the constant region, which will recruit immune cells to kill the cell with the identified antigen. The antibody functions like a guided missile to locate and destroy the cells with the antigen. Some of the B-cells become memory cells so that when the same antigen is encountered in the future, the immune response will be swift and antibodies made rapidly after the encounter.

Once the antibody finds the antigen, it binds to it and may kill it outright by blocking cell signaling within the antigen-containing cell, like the drug trastuzumab killing HER2-positive breast cancer cells, and/or may call in immune elements such as macrophages or NK cells which kill the antigen-containing cell in a process called antibody-dependent cellular cytotoxicity (ADCC). The B-cells may also stimulate the complement pathway, a part of the innate immune response, where complement coats the antigen-containing cell and kills it. Unfortunately, cancer cells have developed a way to avoid being killed by complement.

The cell-mediated immune response involves T-lymphocytes (T-cells), which circulate through the blood and lymphoid tissue. For the T-cells to locate and destroy invading microorganisms or abnormal cells identified as nonself (no MHC molecule), it needs to know what it looks like (what antigen it carries). Professional antigen presenting cells (APCs) are the dendritic cells and macrophages which mount a fragment of the antigen on their cell surface. The dendritic cell then goes to a nearby lymph node where it matures, as it should before it can activate the T-cells. Mounting the MHC together with the antigen, the APC binds to the T-lymphocyte and activates it, resulting in a rapid proliferation of T-cells which can recognize the antigen. The T-cells that can be activated are the cytotoxic T-cells, which can kill the invading microorganism or abnormal tumor cells with the antigen, helper T-cells, and memory T-cells which will turn on the immune response later when exposed to the same antigen. A co-stimulatory molecule helps increase the rapid expansion of the cytotoxic T-cell population. B-cells are also stimulated and are given the shape of the antigen to make antibody. The APC secretes IL-1, a chemical messenger, and displays the antigen fragments along with MHC molecules, to bring more helper T-cells into the fight. The helper T cell responds to the IL-1, and secretes more ILs, including IL-2 which enhances the production of cytotoxic T-cells. In addition, helper-T cells stimulate the production of nonspecific fighters such as NK cells and macrophages, to assist in killing the antigen-carrying invaders or abnormal cells. The response is a powerful response and needs to be turned down and off before normal tissue can be attacked, as in autoimmune disease. Other T-lymphocytes that are activated are the regulatory T-cells, which are released at immune checkpoints to turn down the immune response. Unfortunately, cancer cells have acquired the ability to co-opt the patient’s immune checkpoints to turn off the activation of cytotoxic T cells, so that the tumor is not detected, and can continue manifesting the hallmarks of cancer.

Immune checkpoints that are co-opted are many, but two are significant at this time: the CTLA-4 “on” “off” switch which controls cytotoxic T-cell activation; and the PD-1 receptor, and its ligand PD-L1 (binds to PD-1), which modulates and turns off the immune activity in peripheral tissues to prevent injury. Many tumors, such as malignant melanoma, can express CTLA-4 (CD152) receptors and turn down the immune response so the cancer cells become invisible, and escape immune surveillance. By blocking the CTLA-4 receptor, cytotoxic T-cell activation continues, and the tumor cells are killed by the patient’s own immune cells. Some tumors produce the PD-L1 and...
PD-L2 ligands that bind to the PD-1 receptor on cytotoxic T-cells, which turns cytotoxic T-cell activity down or off, as well as preventing further activation of cytotoxic T-cells in the tumor microenvironment. This results in cancer cells again being invisible to the immune system. Immune checkpoint inhibitors for CTLA-4 and PD-1/PD-L1 have been developed to stop tumor control, and to turn back on the activation of cytotoxic T-cells. The response in some patients has been astounding with significant tumor regression that is long-acting. However, as this benefit does not occur in all patients, research is underway to identify patient factors, such as high levels of PD-L1 or PD-L2, that predict response to immune checkpoint inhibitors. Currently, there are six approved immune checkpoint inhibitors.

Monoclonal antibodies (mAbs) are included in this section of immunologically targeted agents, as their mechanism is immunological. An antibody is a Y-shaped protein made by B-cells that has a receptor that recognizes a specific antigen. It is synthesized once its antigen has been detected and presented by the APC, and will only bind that antigen. Binding activates complement, and recruits immune cells to destroy and remove the invading antigen-bearing cell. Antibody production represents a very powerful immune response and has led to the development and engineering of more effective antibodies. For example, a mAb is a clone of antibodies to a specific antigen produced in the laboratory with DNA hybridization technology, and when administered to a patient with a specific cancer antigen, such as HER-2 in breast cancer, the mAb directly interferes with cell signaling from the outside of the cell going to the cell nucleus, and stops cancer cell division. MAbs can also kill the cell through ADCC by injecting proteins and enzymes to destroy the cancer cell with that antigen; in addition, it sends out a call to recruit cell killing immune elements such as NK cells, macrophages, and monocytes. Complement-dependent cytotoxicity can also kill the antigen carrying cancer cell as antigen-antibody binding causes activation of the complement cascade. Complement then coats the antigen-carrying cell and destroys it. MAbs can be “naked” with no attached armament to kill the cancer cell such as trastuzumab, or it can be conjugated with a cellular poison or radionucleotide like ibritumomab tiuxetan. New versions of engineered mAbs may be a combination of two antibodies, one of which engages or brings the cytotoxic T-cell directly to the antigen-containing cancer cell. An example of this is blinatumomab which is a bispecific CD-19 directed CD3 T-cell engager. One mAb identifies and attaches to CD-19, the malignant lymphocyte protein antigen, and the second binds to CD3, which is the receptor on T-cell.

There is a specific nomenclature for mAbs reflecting how much human protein the mAb contains and this is communicated in the ending of the name followed by -mab. Knowledge of the amount of mouse protein in the mAb is significant for nurses as the more mouse protein the mAb contains, the more likely the patient will have a hypersensitivity reaction (HSR), ranging from grade 1 with rash, fever to grade 4 life-threatening anaphylaxis. MAbs can be: murine (100% mouse, ending in-momab), chimeric (mouse and human, -ximab), humanized (mostly human, -zumab) or human (100% human, -mumab). If the mAb is human, the likelihood of an HSR is low, but it can still occur. Whenever an mAb is administered, the nurse must know how to assess, intervene, and anticipate orders from the physician or mid-level practitioner if an HSR occurs. In addition, each class of mAbs has specific side-effects that the nurse must be familiar with, anticipate, know intervention strategies, and how to teach the patient and family self-care as discussed below. Recently, biosimilars for bevacizumab and trastuzumab have been FDA approved. A biosimilar is a biological product that is highly similar to another FDA-approved biological product, without any clinically meaningful differences, and which has undergone rigorous testing and evaluation by the biosimilar drug manufacturer. The biosimilar drugs, however, are not interchangeable. It is hoped that biosimilars will stimulate competition which may lower the cost of the drugs specifically, and health-care costs in general.

The EGFR inhibitors and angiogenesis inhibitors that block the cell signal from entering the cell are too big to be administered orally, so are carried to the cell by mAbs. Many lymphomas can be defined by what CD protein (a name-tag, cluster of differentiation) is malignant, such as CD20, and the mAb is then developed against that protein. Another target is platelet-derived growth factor receptor-alpha, a receptor for PDGF, which is found on cells of mesenchymal origin that make up connective tissue. Its cell signaling helps cells to grow, move (chemotaxis), and differentiate (stem cells). When found on cancer cells, such as soft-tissue sarcoma cells, this receptor stimulates continual cell division, metastases, and the maintenance of the surrounding tumor microenvironment.

The immune checkpoint inhibitors are mAbs whose function is not to kill the cancer cells, but to remove the block placed on the activation of cytotoxic T-cells by the cancer cells which have taken control of the immune checkpoint. This allows the immune system to be turned back on and kill the cancer cells. Immune effector cell therapy is a recently developed immunotherapy where a patient’s T-cells are removed, the
T-cell receptors are genetically engineered to make them better able to (1) find the tumor antigen, (2) stimulate an aggressive immune response against the tumor cells with that antigen, and (3) replicate in the body so it is a “living drug” that continues to attack these tumor cells after the cells are reinfused into the patient’s body. It is also called chimeric antigen receptor T-cell therapy (CAR-T). Two agents are commercially available and offer truly individualized, precision cancer care.

Genetic modification is also used in creating a locally active herpes virus to infect and kill melanoma cells directly, and to stimulate an immune response against the melanoma cells. An example is talimogene laherparepvec. Once injected into the patient’s skin lesions, the herpes virus replicates (makes more copies of itself) causing the cell to rupture and die. In addition, it stimulates the patient’s own immune system to attack the melanoma cells.

The immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide have anti-angiogenic mechanisms, alter cytokine production (chemical messengers), regulate T-cell co-stimulation to stimulate cytotoxic T-cells and helper-T cells, and increase NK activity to kill cancer cells.

Ideally, a vaccine would be produced to stimulate the immune system so that cancer cells would be identified and destroyed before a tumor can form. Vaccines have been developed to prevent HPV-related cervical cancer and hepatitis B virus-related hepatomas. Sipuleucel-T is an autologous cellular vaccine to treat prostate cancer and combines the prostate cancer antigen with granulocyte-macrophage colony-stimulating factor together with the patient’s dendritic cells to stimulate an immune response against the prostate cancer cells once reinfused into the patient.

Immunologically targeted agents, including monoclonal antibodies, are shown in Table 2, along with their targets, common and significant adverse effects.

### Nursing Implications – Understanding Class Effects

All drugs in a class share a common mechanism of action so that there are some predictable adverse effects. By understanding the drug and mechanism of action/class effects and anticipated adverse effects, the nurse can assess the patient for potential toxicity, collaborate with physician/midlevel practitioner and intervene, as well as to give accurate patient/family education in self-care. These are indicated on each of the tables. It is important that the nurse look up each drug before administering it, as many drugs sound alike to identify drug-specific nursing care management strategies. If HSRs are possible, the nurse should be able to assess and intervene in an emergency. In addition, all signs and symptoms are not equal. For example, the nurse should understand that diarrhea from the EGFR inhibitor erlotinib is very different from diarrhea from the PD-1 inhibitor nivolumab, which may be symptomatic of immune-related colitis and may be life-threatening. The broad nursing care strategies need to be evidence-based, and that science is still emerging. As immunotherapy is quickly developing, guidelines are now being written, such as the European Society of Medical Oncology clinical practice guidelines for management of immunotherapy toxicities, and the American Society of Clinical Oncology is developing guidelines with the National Comprehensive Cancer Network. In addition, CAR-T cell therapy has a unique CRS that may be severe and fatal, and nurses should understand the treatment implications. Most drugs will cause embryo-fetal toxicity, and it is important to teach women of child-bearing age to use highly effective contraception. In addition, as the cost of many of these therapies is significant, the nurse involves others or assists the patient in identifying resources to allow the patient to receive the agent. By class, the following adverse effects are predictable:

- **EGFR inhibitors** will affect the skin, resulting in a nonacne skin rash, and diarrhea. Patients are taught expert skin care, to avoid sun exposure, and how to manage diarrhea.
- **Angiogenesis inhibitors** can cause hypertension (HTN), proteinuria, bleeding/hemorrhage, impaired wound healing, gastrointestinal (GI) perforation/fistula.
- **BCR-ABL protein kinase inhibitors** can cause edema, bone marrow suppression, CYP3A4 drug interactions.
- **The bcl-2 inhibitor** can cause such rapid lysis of tumor cells that the patient is at risk for developing tumor lysis syndrome (TLS).
- **BRAF and MEK inhibitors** can cause a new primary malignancy, hemorrhage, HTN, eye problems, GI symptoms, and CYP3A4 drug interactions.
- **HDACs may cause** cytopenias, infection, hepatotoxicity, and TLS.
- **mTOR inhibitors** may cause drug interactions, pneumonitis, GI symptoms, impaired wound healing, laboratory abnormalities.
- **Proteasome inhibitors may cause** GI toxicity, drug interactions, thrombocytopenia, and TLS.
- **mAbs may cause** cytokine release syndrome when the lymphocytes are lysed releasing the cytokines. In addition, HSRs may occur.
- **Immune checkpoint inhibitors may cause** immune-related adverse effects: endocrine abnormalities, pneumonitis, colitis, skin rash, and others.
Table 2: Immune (modulation) targeted therapy

| Class/drug | Target(s)/indication(s) | Common adverse effects/warnings |
|------------|-------------------------|---------------------------------|
| Angiogenesis inhibitors | | |
| Bevacizumab (Avastin)™ | VEGF; mCRC, nonsquamous NSCLC with carboplatin/paclitaxel, recurrent ovarian cancer, metastatic renal cell cancer, cervical cancer, recurrent glioblastoma | Epistaxis, headache, HTN, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation dis-order, back pain, exfoliative dermatitis |
| Bevacizumab-awwb (Mvasi)®™ | VEGF; mCRC, recurrent nonsquamous NSCLC with carboplatin/paclitaxel, recurrent ovarian cancer, metastatic renal cell cancer, cervical cancer, recurrent glioblastoma | Epistaxis, headache, HTN, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis |
| Ramucirumab (Cyramza)™ | VEGFR-2; advanced gastric/GEJ cancer, metastatic NSCLC, mCRC | HTN, diarrhea; when combined with chemotherapy, neutropenia, fatigue, stomatitis/mucosal inflammation, decreased appetite |

| Autologous cellular vaccine | | |
| Sipuleucel-T (Provenge)™ | Prostate cancer antigen; prostate cancer, asymptomatic or minimally symptomatic metastatic, castration-resistant. Drug is combined prostate cancer antigen (PAP) plus GM-CSF plus patient’s dendritic cells, used to stimulate an immune response against the tumor antigen | Chills, fatigue, fever, back pain, nausea, joint ache, headache |
| | Warnings: Drug is intended only for autologous use; acute infusion reaction; combination of vaccine plus chemotherapy and immunosuppressive drugs has not been studied; vaccine is not routinely tested for transmissible infectious diseases |

| Bispecific CD19-directed CD3 T-cell engager | | |
| Blinatumomab (Blincyto)™ | Target is CD19 protein on lymphocytes. CD19-CD3 bivalent as binds together cytotoxic T-cells and tumor cell antigen; PH-relapsed/refractory B-cell precursor ALL (adults and children) | Infections, pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, neutropenia |
| | Warnings: Infections, reduced ability to drive and use machines, pancreatitis, preparation and administration errors, risk of serious adverse reactions in children if alcohol containing diluent is used; cytokine release syndrome may be life-threatening, neurological toxicities |

| CD20 (protein on B-lymphocyte) directed MAb | | |
| Ibritumomab tiuxetan (Zevalin)™ | CD20; low-grade or follicular NHL | Cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, pyrexia |
| | Warnings: Serious infusion reactions, prolonged and severe cytopenias, severe cutaneous and mucocutaneous reactions, altered biodistribution, development of leukemia and MDS, extravasation, do not administer live viral vaccines, embryo-fetal toxicity |
| Obinutuzumab (Gazyva)™ | CD20; follicular lymphoma, CLL | Infusion reactions, neutropenia, thrombocytopenia, diarrhea, cough, constipation, pyrexia, URI, UTL, arthralgia, sinusitis, asthma, headache, herpesvirus infection, pneumonia, decreased appetite, alopecia, pruritus |
| | Warnings: Hepatitis B virus reactivation, PML, infusion reactions, HSRS, TLS, infections, neutropenia, thrombocytopenia, do not administer live viral vaccines before or during therapy |
| Ofatumumab (Arzerra)™ | CD20; CLL | Infusion reactions, neutropenia, febrile neutropenia, URTIs, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, rash, nausea, URI |
| | Warnings: Hepatitis B virus reactivation, PML, infusion reactions, TLS, cytopenias |
| Rituximab (Rituxan)™ IV only | CD20 + low grade or follicular NHL, CLL, rheumatoid arthritis, Wegener’s granulomatosis and microscopic polyangiitis | Infusion reactions, fever, lymphopenia, chills, infection, asthenia, neutropenia, URI, nasopharyngitis, UTL, bronchitis, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema |
| | Warnings: Infusion reactions that are fatal, severe mucocutaneous reactions which may be fatal, hepatitis B reactivation, PML, TLS, infections, cardiac arrhythmias and angina, bowel obstruction and perforation, cytopenias, do not administer live virus vaccines before or during therapy |
| Rituximab and hyaluronidase human (Rituxan® Hycefa)™ SQ only | CD20 + follicular NHL, diffuse large cell lymphoma, CLL | Infections, neutropenia, nausea, constipation, cough, fatigue, alopecia, anemia, thrombocytopenia, pyrexia, vomiting, injection site erythema |
| | Warnings: Severe mucocutaneous reactions which may be fatal, hepatitis B reactivation, PML, HSRS, TLS, infections, cardiac adverse events, renal toxicity, bowel obstruction and perforation, do not administer live virus vaccines before or during therapy, embryo-fetal toxicity |

Contd...
### Table 2: Contd...

| Class/drug | Target (s)/indication (s) | Common adverse effects/warnings |
|------------|---------------------------|--------------------------------|
| CD22 (protein on B-lymphocyte) directed MAb | Inotuzumab ozogamicin (Besponsa®) | CD22; relapsed/refractory B-cell ALL | Thrombocytopenia, neutropenia, infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, increased hepatic transaminase laboratory values, abdominal pain, hyperbilirubinemia |
| | Brentuximab vedotin (Adcetris®) | CD30; Hodgkin's lymphoma (consolidation after auto-HSCT or high risk of relapse); systemic or cutaneous anaplastic large cell lymphoma | Peripheral sensory neuropathy, fatigue, nausea, diarrhea, neutropenia, URI, pyrexia |
| | Daratumumab (Darzalex®) | CD38; multiple myeloma | Infusion reactions, neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, constipation, vomiting, muscle spasm, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy, URI |
| | Alemtuzumab (Campath®) | CD52 protein on B-cell CLL cells | Cytopenias, prolonged lymphopenia with increased risk for infection, infection reactions, CMV infection and other infections, nausea, vomiting, diarrhea, insomnia, Embryo-fetal toxicity |
| | EGFR inhibitors includes HER1 (EGFR1) and HER2 (EGFR2) | HER2 (EGFR2); metastatic HER2+ breast cancer | Dermatologic toxicity, infusion reactions, magnesium wasting (hypomagnesemia), diarrhea, embryo-fetal toxicity |
| | Ado-trastuzumab emtansine (Kadcyla®) | HER2 (EGFR2); metastatic HER2+ breast cancer | Fatigue, nausea, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased hepatic transaminase values, constipation, epistaxis |
| | Cetuximab (Erbitux®) | EGFR1; mCRC (wild type), HNSCC | Cutaneous reaction (rash, pruritus, nail changes), headache, diarrhea, infection |
| | Necitumumab (Portrazza®) | EGFR1; squamous NSCLC, with gemcitabine and cisplatin | Rash, hypomagnesemia |
| | Panitumumab (Vectibix®) | EGFR1; mCRC (wild-type RAS gene) | Skin rash, paronychia, fatigue, nausea, diarrhea. In combination with FOLFOX chemotherapy, also stomatitis, mucosal inflammation, asthenia, anorexia, hypomagnesemia, hypokalemia, acneiform dermatitis, pruritus, dry skin |
| | Pertuzumab (Perjeta®) | HER2 (EGFR2); HER2+ breast cancer (neoadjuvant, metastatic) | In combination with other drugs: Diarrhea, alopecia, neutropenia, nausea, fatigue, rash, peripheral neuropathy, vomiting, thrombocytopenia, anemia |

**Contd...**
| Class/drug                          | Target (s)/indication (s)                                                                 | Common adverse effects/warnings                                                                 |
|----------------------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Trastuzumab (Herceptin®)
[34] | HER2; HER-2 overexpressing adjuvant or metastatic breast cancer, metastatic gastric or GEJ adenocarcinoma | Headache, diarrhea, nausea, chills, fever, CHF, infection, insomnia, cough, rash, weight loss, URI, fatigue, thrombocytopenia, nasopharyngitis, dysgeusia, anemia, mucosal inflammation. Warnings: Cardiomyopathy, infusion reactions, embryo-fetal toxicity, pulmonary toxicity, exacerbation of chemotherapy-induced neutropenia. |
| Trastuzumab-dkst (Ogivri®)
[61] | HER2; HER-2 overexpressing adjuvant or metastatic breast cancer or metastatic gastric or gastroesophageal adenocarcinoma | Headache, diarrhea, nausea, chills, fever, CHF, infection, insomnia, cough, rash, weight loss, URI, fatigue, thrombocytopenia, nasopharyngitis, dysgeusia, anemia, mucosal inflammation. Warnings: Cardiomyopathy, infusion reactions, embryo-fetal toxicity, pulmonary toxicity, exacerbation of chemotherapy-induced neutropenia. |
| Immune checkpoint inhibitors     | PD-1; locally advanced/metastatic urothelial cancer, metastatic NSCLC                      | Fatigue, decreased appetite, nausea, constipation, UTI, diarrhea, pyrexia, musculoskeletal pain. Warnings: Immune-related: Hepatitis, colitis, pneumonitis, endocrinopathies, neurologic syndromes (e.g., myasthenic syndrome); ocular inflammatory toxicity; infection; infusion reaction; embryo-fetal toxicity. |
| Atezolizumab (Tecentriq®)
[63] | PD-1; advanced/metastatic urothelial cancer; metastatic Merkel cell carcinoma             | Fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, peripheral edema, UTI. Warnings: Immune-mediated: Pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, and renal dysfunction; infusion-related reactions, embryo-fetal toxicity. |
| Durvalumab (Imfinzi®)
[64]   | PD-1; locally advanced or metastatic urothelial cancer                                    | Fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, UTI. Warnings: Immune-mediated: Pneumonitis, hepatitis, colitis, endocrinopathies, nephritis; infection, infusion-related reactions, embryo-fetal toxicity. |
| Ivelimunab (Yervoy®)
[59]   | CTLA4; adjuvant melanoma, metastatic melanoma                                             | Fatigue, diarrhea, pruritus, rash, colitis; adjuvant dose: In addition to above, nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, insomnia. Warnings: Immune-mediated adverse events (hepatitis, endocrinopathies, colitis; embryo-fetal toxicity. |
| Nivolumab (Opdivo®)
[50]   | Programmed death receptor-1; metastatic NSCLC, melanoma alone or in combination with ipilimumab, renal cell cancer, HNSCC, urothelial cancer, CRC with dMMT/MSH-1, HCC, classical Hodgkins lymphoma | Fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, URI, pyrexia; with ipilimumab: Fatigue, rash, diarrhea, nausea, pyrexia, vomiting, dyspnea. Warnings: Immune-mediated: Pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction; skin adverse reaction, encephalitis; infusion reactions; complications of allogeneic HSCT after nivolumab; embryo-fetal toxicity. |
| Pembrolizumab (Keytruda®)
[71] | PD-1; unresectable or metastatic melanoma; metastatic NSCLC, HNSCC, urothelial cancer, solid tumors with dMMT/MSH-1, gastric cancer; classical Hodgkin's lymphoma | Fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation. Warnings: Immune-mediated: Pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, skin adverse reactions, other immune-related toxicities; infusion-related reactions; complications of allogeneic HSCT after pembrolizumab; embryo-fetal toxicity. |
| iMIDs                            |                                                                                          | Class effects: Embryo-fetal toxicity.                                                                 |

Contd...
In conclusion, significant advances have occurred in the development of molecularly and immunologically targeted agents to treat cancer by targeting mutations and abnormalities in the patient's tumor cells. This enables effective personalized, individualized cancer care for some patients. As the understanding of tumor biology continues, more targets and therapies will be identified and added to the present armamentarium. The nurse plays a significant role in assessing patients for potential adverse events, collaborating with the health-care team to provide the best care possible.
care, and enabling patients and their family to manage self-care.

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Conflicts of interest
There are no conflicts of interest.

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