Review Article

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.[1] 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,[1] and adoption of Western lifestyle habits.[2]

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"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.[7] 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).[8] 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.[9] Cancer cells have abnormal blood vessels, some may be tortuous, and others end in a dead end.[10] 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.[11]

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.[12] 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.[12] 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.[13] Inhibition of the CDK/cyclin complex blocks pRb phosphorylation so the breast cancer cells stop dividing, resulting in aging of the cell and apoptosis.[14]

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).[15] 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).[16] 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.[17]

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.[15] The *TP53* gene is called the "guardian of the genome."[15] 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		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 Warnings: Hepatotoxicity, ILD, bradycardia, severe myalgia and creatine phosphokinase elevation, embryo-fetal toxicity
Brigatinib (Alunbrig®)[23]	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 Warnings: ILD, HTN, bradycardia, visual disturbances, CPK elevations, pancreatic enzyme elevation, hyperglycemia, embryo-fetal toxicity
Ceritinib (Zykadia®)[24]	RTK ALK, IGF-1R, InsR, ROS1; ALK+ metastatic NSCLC	Diarrhea, nausea, fatigue, vomiting, abdominal pain, decreased appetite, and weight loss Warnings: Severe/persistent GI toxicity, hepatotoxicity, ILD, QT interval prolongation, hyperglycemia, bradycardia, pancreatitis, embryo-fetal toxicity
Crizotinib (Xalkori®)[25]	RTK ALK, ROS-1; ALK+or ROS-1 positive metastatic NSCLC	Vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy Warnings: Hepatotoxicity, ILD, QT interval prolongation, bradycardia, severe visual loss, embryo-fetal toxicity
Angiogenesis inhibitors		Class effects: HTN, proteinuria, bleeding/hemorrhage, GI perforation/fistula, thrombotic events, impaired wound healing; embryo-fetal toxicity
Axitinib (Inlyta®)[26]	VEGF receptors on endothelial cells lining blood vessels; advanced RCC	Diarrhea, HTN, fatigue, decreased appetite, nausea, dysphonia, PPES (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation Warnings: HTN, arterial and venous thrombotic events, hemorrhage, cardiac failure, GI perforation/fistula, hypothyroidism, RPLS, proteinuria, elevated LFTs, embryo-fetal toxicity
Cabozantinib (Cabometyx™)[27]	VEGF 1, 2, 3; MET, RET, ROS1, others. Advanced RCC	Diarrhea, fatigue, nausea, decreased appetite, PPES, HTN, vomiting, decreased weight, constipation Warnings: Hemorrhage, GI perforation/fistula, HTN and hypertensive crisis, severe diarrhea, palmar-plantar erythrodysesthesia (hand-foot) syndrome, RPLS, embryo-fetal toxicity

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Table 1: Contd...

Class/drug	Target (s)/indication (s)	Common adverse effects/warnings
Cabozantinib (Cometriq™)[28]	MET, HGF; VEGFR 1, 2, 3; RET, KIT, FLT-3, others. Progressive, metastatic medullary thyroid cancer	Diarrhea, stomatitis, PPES, decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, HTN, abdominal pain, constipation, elevated LFTs, increased alkaline phosphatase, neutropenia, thrombocytopenia, hypocalcemia, hypophosphatemia Warnings: Thrombotic events, wound complications, HTN, osteonecrosis of the jaw, PPES, proteinuria, RPLS, embryo-fetal toxicity
Levatinib (Lenvima®)[29]	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, PPES, abdominal pain, and dysphonia Warnings: 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®)[30]	VEGFR 1, 2, 3; PDGF-R, FGFR; Advanced RCC; advanced soft tissue sarcoma	Diarrhea, HTN, hair color changes (depigmentation), nausea, anorexia, vomiting Warnings: Hepatotoxicity, prolonged QT intervals and torsades de pointes, cardiac dysfunction, hemorrhage, thrombotic events, thrombotic micro-angiopathy, GI perforation/fistula, ILD, RPLS, HTN, hypothyroidism, proteinuria, infection, embryo-fetal toxicity
Regorafenib (Stivarga™)[31]	VEGFR 2, 3; PDGF-R, RET, KIT, RAF; metastatic CRC; locally advanced unresectable or metastatic GIST, hepatocellular carcinoma previously treated with sorafenib	Pain, HFSR, asthenia/fatigue, diarrhea, decreased appetite/food intake, HTN, infection, dysphonia, fever, mucositis, hyperbilirubinemia, weight loss, rash, nausea Warnings: Hepatotoxicity, infections, hemorrhage, GI perforation or fistula, dermatologic toxicity, HTN, cardiac ischemia/MI, RPLS, sound healing complications, embryo-fetal toxicity
Sorafenib (Nexavar®)[32]	VEGFR2, PDGF, RAF; unresectable 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 Warnings: Cardiac ischemia/MI, bleeding, HTN, dermatologic toxicities, GI perforation, QT prolongation, drug-induced hepatitis, embryo-fetal toxicity, impairment of TSH suppression
Sunitinib (Sutent®)[33]	PDGF-R, VEGFR 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 Warnings: Hepatotoxicity, embryo-fetal toxicity, cardiovascular events, prolonged QT intervals and Tirsades 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®)[34]	VEGFR 2, EGFR 1; symptomatic or progressive medullary thyroid cancer in patients with metastatic or locally advanced unresectable disease	Diarrhea/colitis, rash, aneiform dermatitis, nausea, headache, HTN, URI, decreased appetite, abdominal pain Warnings: Prolonged QT, torsades de pointes, and sudden death; severe dermatologic toxicities; ILD; ischemic cerebrovascular events, hemorrhage, heart failure, diarrhea, HTN, RPLS; embryo-fetal toxicity
Ziv-aflibercept (Zaltrap®)[35] (Inravenous)	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, dysphonia, increased serum creatinine, headache Warnings: Fistula formation, HTN, arterial thromboembolic events, proteinuria, neutropenia and neutropenic complications, diarrhea and dehydration, RPLS, hemorrhage, GI perforation, compromised wound healing
Bcl-2 inhibitor (restores apoptosis)		Class effects: TLS; embryo-fetal toxicity; neutropenia, drug interactions
Venetoclax (Venclexta®)[17]	Bcl-2; CLL with 17p deletion mutation	Neutropenia, diarrhea, nausea, anemia, URI, thrombocytopenia, fatigue Warnings: TLS, neutropenia, embryo-fetal toxicity, live immunizations contraindicated
BCR-ABL kinase inhibitors		Class effects: CYP3A4 drug interactions, edema, bone marrow suppression; embryo-fetal toxicity
Bosutinib (Bosulif®)[36]	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 Warnings: GI toxicity, myelosuppression, hepatotoxicity, fluid retention, renal toxicity, embryo-fetal toxicity
Dasatinib (Sprycel®)[37]	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 Warnings: 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®)[38]	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, cardiogenic shock, bullous dermatologic reactions, hypothyroidism, embryo-fetal toxicity, growth retardation in children, TLS, renal toxicity, changes in mental status
Nilotinib (Tasigna®)[39]	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®)[40]	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®)[41] MEK inhibitor	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®)[42] BRAF inhibitor	Mutated *BRAF*; unresectable or metastatic melanoma with *BRAF V600E* mutation; metastatic NSCLC with *BRAF V600E* mutation	Hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, PPES, 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®)[43] MEK inhibitor	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, ILD, serious febrile reactions, serious skin toxicities, hyperglycemia, embryo-fetal toxicity
Vemurafenib (Zelboraf®)[44] BRAF inhibitor	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:** cytopenias (infection and hemorrhage); HTN; 2nd primary malignancies; TLS; embryo-fetal toxicity
Acalabrutinib (Calquence®)[45]	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®)[46]	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™)[14]	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
	women with HR+, HER-2-negative advanced or metastatic breast who have progressed on endocrine therapy or endocrine/ chemotherapy (when given as monotherapy)	
Palbociclib (Ibrance®)[47]	CDKs 4, 6 (which allow cells to progress through G1 and S phases of cell cycle); postmenopausal women with ER+, HER2- advanced BC, with letrozole or fulvestrant.	Neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, pyrexia Warnings: Neutropenia, embryo-fetal toxicity
Ribociclib (Kisqali) [48]	Cyclin Dependent Kinase (CDK) s 4, 6 (which allow cells to progress through G1 and S phases of cell cycle); postmenopausal women with ER+, HER2- advanced or metastatic BC, with an aromatase inhibitor	Neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, back pain Warnings: QT-interval prolongation on ECG, neutropenia, embryo-fetal toxicity
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 Metastatic NSCLC including EGFR with exon 19 deletions or exon 21 (L858R) substitution mutations	Diarrhea, rash/acneiform dermatitis, stomatitis, paronychia, dry skin, decreased appetite, nausea, vomiting, pruritus Warnings: Diarrhea, bullous and exfoliative skin disorders, ILD, hepatotoxicity, keratitis, embryo-fetal toxicity
Erlotinib (Tarceva®)[50]	EGFR with exon 19 deletions or exon 21 (L858R) substitution EGFR1-positive locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; EGFR1 positive locally advanced or metastatic pancreatic cancer, together with gemcitabine	Rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, vomiting Warnings: ILD, renal failure, 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 Metastatic NSCLC having EGFR exon 19 deletions or exon 21 (L858R) substitution mutations	Skin reactions, diarrhea Warnings: ILD, hepatotoxicity, GI perforation, diarrhea, ocular disorders, 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, diarrhea, ILD, prolonged QT interval, severe cutaneous reactions, embryo-fetal toxicity
Neratinib (Nerlynx®)[53]	HER-2 Extended adjuvant therapy of early stage HER-2 overexpressed/ amplified breast cancer to follow adjuvant trastuzumab-based adjuvant therapy	Diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, increased AST or ALT, nail disorder, dry skin, abdominal distention, decreased weight, UTI 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®)[55]	FLT3, KIT, PDGFRα/β, 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

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Table 1: Contd...

Class/drug	Target (s)/indication (s)	Common adverse effects/warnings
Sonidegib (Odomzo®)[56]	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 Warnings: Musculoskeletal adverse reactions with increased serum CK
Vismodegib (Erivedge®)[57]	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: Cytopenias (infection and bleeding); hepatotoxicity; TLS; embryo-fetal toxicity; GI symptoms; drug interactions	
Belinostat (Beleodaq®) (IV)[58]	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	Nausea, fatigue, pyrexia, anemia, vomiting Warnings: Thrombocytopenia, infection, hepatotoxicity, TLS, embryo-fetal toxicity
Panobinostat (Farydak®)[59]	HDAC; multiple myeloma, in combination with bortezomib and dexamethasone	Diarrhea, afatigue, nausea, peripheral edema, decreased appetite, pyrexia, vomiting Warnings: Hemorrhage, hepatotoxicity, embryo-fetal toxicity
Romidepsin (Isodax®)[60] (IV)	HDAC; CTCL; PTCL	Neutropenia, lymphopenia, thrombocytopenia, infections, nausea, fatigue, vomiting, anorexia, anemia, ECG T-wave changes Warnings: Myelosuppression, infections, ECG changes, TLS, embryo-fetal toxicity
Vorinostat (Zolinza®)[61]	HDAC; CTCL	Diarrhea, fatigue, nausea, thrombocytopenia (may be severe with GI bleeding if combined with another HDAC inhibitor), anorexia, dysgeusia Warnings: PE and DVT; thrombocytopenia and anemia; GI toxicity; hyperglycemia; clinical chemistry abnormalities; embryo-fetal toxicity
IDH2 inhibitor		Class effects: embryo-fetal toxicity, possible differentiation syndrome
Enasidenib (Idhifa®)[62]	Mutated IDH2; AML, refractory or relapsed, with IDH2 mutation	Nausea, vomiting, diarrhea, elevated BR, decreased appetite Warnings: Embryo-fetal toxicity
mTOR inhibitor		Class effects: CYP3A4 drug interactions; pneumonitis; embryo-fetal toxicity; GI symptoms; impaired wound healing; renal failure; hyperglycemia
Everolimus (Afinitor®)[63]	mTOR; postmenopausal advanced ER+HER2-breast cancer; advanced RCC; progressive unresectable PNET (adults); renal angiomyolipoma (adults)	Stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, asthenia, fever, cough, headache, decreased appetite, respiratory tract infection. Warnings: Noninfectious pneumonia, infections, angioedema, stomatitis, renal failure, impaired wound healing, laboratory test alterations, embryo-fetal toxicity, avoid live vaccinations and close contact with those who have received live vaccines
Temsirolimus (Torisel®) (IV) [64]	mTOR; advanced RCC	Rash, asthenia, mucositis, nausea, edema, anorexia, laboratory abnormalities Warnings: HSRs/infusion reactions; hepatic impairment, hyperglycemia and hyperlipidemia; infections, ILD, bowel perforation; renal failure; abnormal wound healing; embryo-fetal toxicity; elderly may have more diarrhea, edema, and pneumonia; avoid live vaccinations and close contact with those who have received live vaccines
PARP inhibitors		Class effects: MDS/AML transformation, embryo-fetal toxicity
Olaparib (Lynparza®)[65]	PARP-1, 2, 3; germline *BRCA* mutated recurrent or advanced ovarian cancer (actual or suspected)	Anemia, nausea, fatigue, vomiting, nasopharyngitis, URI/influenza, diarrhea, arthralgia/myalgia, dysgeusia, headache, dyspepsia, decreased appetite, constipation, stomatitis, laboratory abnormalities, CYP3A4 drug interactions Warnings: MDS/AML, pneumonitis, embryo-fetal toxicity
Niraparib (Zejula®)[66]	Maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR after platinum-based chemotherapy	Thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, nausea, constipation, vomiting, abdominal l pain/distention, mucositis/stomatitis, diarrhea, dyspepsia, dry mouth, fatigue/asthenia, decreased appetite, UTI, AST/ALT elevation, myalgia, back pain, arthralgia, headache, dizziness, dysgeusia, insomnia, anxiety, nasopharyngitis, dyspnea, cough, rash, HTN Warnings: MDS/AML, bone marrow suppression, cardiovascular effects, embryo-fetal toxicity
Rucaparib (Rubraca™)[67]	PARP-1, 2, 3; germline and/or somatic *BRCA* mutated advanced ovarian cancer, after 2 or more prior chemotherapies	Nausea, fatigue, vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, dyspnea, laboratory abnormalities Warnings: MDS/AML, embryo-fetal toxicity
PI3K inhibitor		Class effects: Neutropenia; severe cutaneous reactions; embryo-fetal toxicity

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Table 1: Contd...

Class/drug	Target (s)/indication (s)	Common adverse effects/warnings
Copanlisib (Aliqopa™)[68] [IV administration]	PI3K sends signals to B lymphocytes telling them where to find and attach to lymph nodes and bone marrow stroma. Drug inhibits PI3K; Relapsed follicular lymphoma after 2 prior therapies	Hyperglycemia, diarrhea, decreased general strength and energy, HTN, leukopenia, neutropenia, nausea, lower respiratory infection, thrombocytopenia Warnings/precautions: Severe infections, noninfectious pneumonitis, severe cutaneous toxicity, embryo-fetal toxicity; control hyperglycemia and HTN before treatment
Idelalisib (Zydelig®)[69]	PI3K sends signals to B lymphocytes telling them where to find and attach to lymph nodes and bone marrow stroma; Drug inhibits PI3K; relapsed CLL in combination with rituximab; relapsed follicular B-cell NHL; relapsed small lymphocytic lymphoma	Diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, rash, laboratory abnormalities, CYP3A drug interactions Warnings: Severe cutaneous reactions, anaphylaxis, neutropenia, hepatotoxicity, severe diarrhea or colitis, serious infections, intestinal perforation, embryo-fetal toxicity
Proteasome inhibitors		Class effects: GI toxicity; embryo-fetal toxicity; CYP3A4 drug interactions; TLS; hepatotoxicity; thrombocytopenia
Bortezomib (Velcade®)[70] (IV or subcutaneous injection)	26S proteasome; multiple myeloma; mantle cell lymphoma	Nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, anorexia, CYP3A4 drug interactions Warnings: Peripheral neuropathy, hypotension, cardiac toxicity, pulmonary toxicity, PRES, GI toxicity, thrombocytopenia/neutropenia, TLS, hepatotoxicity, embryo-fetal toxicity
Carfilzomib (Kyprolis®)[71] (Intravenous)	20S proteasome; relapsed or refractory multiple myeloma in combination with dexamethasone±lenalidomide, or as a single agent	Anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, edema (peripheral) Warnings: Cardiac toxicity, acute renal failure, TLS, pulmonary toxicity, pulmonary HTN, dyspnea, HTN, venous thrombosis, infusion reactions, hemorrhage, thrombocytopenia, hepatotoxicity, thrombotic microangiopathy, PRES, increased serious/fatal reactions in combination with melphalan/prednisone, embryo-fetal toxicity
Ixazomib (Ninlaro®)[72]	20S proteasome (beta 5 subunit); multiple myeloma having received 1 prior therapy, given with lenalidomide and dexamethasone	Diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, back pain, CYP3A inducer drug interaction Warnings: Thrombocytopenia, CI toxicities, peripheral neuropathy, peripheral edema, cutaneous reactions, hepatotoxicity, embryo-fetal toxicity

AML: Acute myeloid leukemia, ALK: Anaplastic lymphoma kinase, NSCLC: Nonsmall-cell lung cancer, RTK: Receptor tyrosine kinase, EGFR: Epidermal growth factor receptor, VEGF: Vascular endothelial growth factor, RCC: Renal cell cancer, PPES: Palmar-plantar erythrodysesthesia syndrome, CYP3A4: Cytochrome P enzyme system 3A4, RPLS: Reversible posterior leukoencephalopathy syndrome, RAI: Radioactive iodine, PDGF-R: Platelet-derived growth factor receptor, FGFR: Fibroblast growth factor receptor, CRC: Colorectal cancer, GIST: Gastrointestinal stromal tumor, pNET: Pancreatic neuroendocrine tumor, CLL: Chronic myelogenous leukemia, BCRs: B-cell receptors, CML: Chronic myeloid leukemia, ALL: Acute lymphoblastic leukemia, MDS: Myelodysplastic syndrome, TKIs: Tyrosine kinase inhibitor, TLS: Tumor lysis syndrome, BTK: Bruton's Tyrosine kinase, HDAC: Histone deacetylase, IDH2: Isocitrate dehydrogenase-2, mTOR: Mammalian target of rapamycin, PARP: Poly (ADP-ribose) polymerase, PI3K: Phosphatidylinositol 3-kinase, IV: Intravenous, MAPK: Mitogen-activated protein kinase, MCL: Mantle cell lymphoma, SLL: Small lymphocytic lymphoma, WM: Waldenstrom's macroglobulinemia, MZL: Marginal zone lymphoma, cGVHD: Chronic graft versus host disease, CDKs: Cyclin dependent kinase, HER 2: Human epidermal growth factor receptor-2, HR: Hormone receptor, ER: Estrogen receptor, PKC: Protein kinase C, SMO: Smoothened, RT: Radiotherapy, GI: Gastrointestinal, CTCL: Cutaneous T-cell lymphoma, PTLC: Peripheral T-cell lymphoma, CR: Complete responders, PR: Partial responders, NHL: Non-Hodgkin's Lymphoma, ILD: Interstitial lung disease, HTN: Hypertension, CPK: CPK: Creatine phosphokinase, LFTs: Liver function tests, MI: Myocardial infarction, TSH: Thyroid-stimulating hormone, URI: Upper respiratory infection, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CHF: Congestive heart failure, G-6-PD: Glucose-6-phosphate dehydrogenase deficiency, HSRs: Hypersensitivity reactions, UTI: Urinary tract infection, AST: Aspartate aminotransferase, PRES: Posterior reversible encephalopathy syndrome, CI: Confidence interval, CK: Creatine kinase, QTc interval: Time during heart beat when there is ventricular activity, both depolarization and repolarization; it is measured as the distance between the beginning of the Q wave (beginning of QRS complex) to the end of the T wave on the ECG. The value is corrected for differences in heart rate (c). If the QTc interval is prolonged it increases the risk of ventricular arrhythmias, including Torsades de Pointes, and sudden death, ECG: Electrocardiogram, BR: bilirubin, CVA: Cerebrovascular accident, DVT: Deep venous thrombosis, P-pg: P-glycoprotein, a cellular drug efflux pump, PE: pulmonary embolus, PH: Philadelphia-chromosome, RET: -a proto-oncogene with a frequently mutated tyrosine kinase; RET=Rearranged during Transfection, AKTProtein-kinase B which plays a large role in glucose metabolism, apoptosis, cell proliferation, and transcription, ROS1: Proto-oncogene that encodes a protein kinase that is often mutated in cancer, IGF-1R: Insulin-like growth factor-1 is a transmembrane receptor that is implicated in certain cancers, FLT-3:Receptor tyrosine kinase important in hematologic stem/progenitor cell survival, and mutated in some patients with AML, EMLA4:stands for echinoderm micro-tubule associated protein-like 4, and genetically fuses with ALK to cause a certain type of NSCLC, NPM: Nucleophosmin is important in cellular functions, and the gene which makes it is mutated in some patients with AML, MET: Receptor tyrosine kinase that may be mutated in cancer, HGF: Hepatocyte growth factor aslo called scatter factor, which binds to MET and is often abnormal in cancer, HFSR: Hand Foot Skin Reaction, RAF: Protein kinase that is overexpressed in many cancers, SRC: Proto-oncogene whose tyrosine kinase is overexpressed in many cancers, BRAF: Proto-oncogene that is often mutated in cancer

Immunologically Targeted Therapy

The cancer cell can evade immune surveillance or identification by the immune system as abnormal or foreign, and this is a hallmark of cancer.[3] The immune system is very effective in preventing invading microorganisms from injuring the body. There are two principal types of immunity: innate and adaptive. We are born with innate immunity, and the body responds to any microbial attack with an army of neutrophils, macrophages, Natural killer lymphocytes (NK cells, which can kill the invading virus, other invading microorganisms), and other elements of the immune system, killing the invader.[73] There may be inflammation and fever. There is no antigen recognition. The response is immediate, and there is no immunologic memory. An example is an influenza for which an individual has to get a flu shot each year, as the body will not recall any microorganism from the previous influenza infection.

The second type, *adaptive*, takes more time to develop and involves recognition of an antigen.[73] It is a response

involving lymphocytes. Amazingly, the immune system can recognize millions of different antigens. An antigen is a substance that can trigger an immune response.[73] The immune response involves the B (bursa equivalent) lymphocytes which make antibody, called the humoral response, and the T (Thymus-dependent) lymphocytes which are responsible for cell-mediated immunity, to kill the invading or abnormal cell which has the antigen. In the adaptive immune response, the body compares the antigen(s) of the invading microorganism or abnormal cell (e.g. cancer) to the HLA (human leukocyte antigen) which identifies cells as belonging to "self." If 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.[73] 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.[74]

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.[73] 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 micro-organism 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.[73] 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.[75] 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.[75] 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.[75] The response in some patients has been astounding with significant tumor regression that is long-acting.[76] 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.[77] 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.[78] 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.[79] 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.[78] 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).[78] 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.[80] The biosimilar drugs, however, are not interchangeable.[80] 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.[81]

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).[82] 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.[83]

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.[84]

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 reinjected into the patient.[85]

Immunologically targeted agents, including monoclonal antibodies, are shown in Table 2, along with their targets, common and significant adverse effects.[86-117]

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,[118] and the American Society of Clinical Oncology is developing guidelines with the National Comprehensive Cancer Network.[119] In addition, CAR-T cell therapy has a unique CRS that may be severe and fatal, and nurses should understand the treatment implications.[120] 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		Class effects: HTN, proteinuria, bleeding/hemorrhage, impaired wound healing, embryo-fetal toxicity
Bevacizumab (Avastin®)[86]	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 Warnings: Perforation or fistula; arterial thromboembolic events; HTN; venous thromboembolic events; PRES; proteinuria, infusion reactions, embryo-fetal toxicity, ovarian failure
Bevacizumab-awwb (Mvasi®)[87] Avastin® Biosimilar not interchangeable with avastin (bevacizumab)	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 disorder, back pain, exfoliative dermatitis Warnings: Perforation or fistula; arterial thromboembolic events; HTN; venous thromboembolic events; PRES; proteinuria, infusion reactions, embryo-fetal toxicity, ovarian failure
Ramucirumab (Cyramza®)[88]	VEGFR-2; advanced gastric/GEJ cancer, metastatic NSCLC, mCRC	HTN, diarrhea; when combined with chemotherapy, neutropenia, fatigue, stomatitis/mucosal inflammation, decreased appetite Warnings: ATEs, HTN, infusion-related reactions, impaired wound healing, clinical deterioration in patients with cirrhosis, RPLS, proteinuria, thyroid dysfunction, embryo-fetal risk
Autologous cellular vaccine		
Sipuleucel-T (Provenge®)[85]	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®)[79]	Target is CD19 protein on lymphocytes. CD-19-CD3 bi-specific 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-lymphocte) directed MAb		Infections, infusion reactions, embryo-fetal toxicity, HSRs TLS
Ibritumomab tiuxetan (Zevalin®)[89]	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 (Gazyvz®)[90]	CD20; follicular lymphoma, CLL	Infusion reactions, neutropenia, thrombocytopenia, diarrhea, cough, constipation, pyrexia, URI, UTI, arthralgia, sinusitis, asthenia, 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®)[91]	CD20; CLL	Infusion reactions, neutropenia, febrile neutropenia, URIs, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, rash, nausea, URI Warnings: Hepatitis B virus reactivation, PML, infusion reactions, TLS, cytopenias
Rituximab (Rituxan®)[92] 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, UTI, 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® Hycela)[93] 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

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Table 2: Contd...

Class/drug	Target (s)/indication (s)	Common adverse effects/warnings
CD22 (protein on B-lymphocte) directed MAb		
Inotuzumab ozogamicin (Besponsa™)[94]	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 Warnings: Hepatotoxicity, higher post-HCST nonrelapse mortality rate, myelosuppression, infusion-related reactions, QT interval prolongation, embryo-fetal toxicity
CD30 (protein on B-lymphocte) directed MAb		
Brentuximab vedotin (Adcetris®)[95]	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 Warnings: JC virus infection resulting in PML, peripheral neuropathy, anaphylaxis and infusion reactions, hematologic toxicities, serious infections and opportunistic infections, TLS, hepatotoxicity, pulmonary toxicity, serious dermatologic reactions, GI complications, embryo-fetal toxicity
CD33 (protein on B-lymphocyte) directed MAb		
Gemtuzumab ozogamicin (Mylotarg™)[96]	CD33; newly diagnosed CD33-positive AML adults, or treatment of relapsed CD33+AML in adults and children	Hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased AST/ALT laboratory tests, rash, mucositis Warnings: Hepatotoxicity, infusion-related reactions, hemorrhage (severe and potentially fatal), embryo-fetal toxicity
CD38 (protein on B-lymphocte) directed MAb		
Daratumumab (Darzalex®)[97]	CD38; multiple myeloma	Infusion reactions, neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, constipation, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy, URI Warnings: Infusion reactions, interference with red blood cell cross-matching and antibody screening, neutropenia, thrombocytopenia
CD52 (protein on B-lymphocte) directed MAb		
Alemtuzumab (Campath®)[98]	CD52 protein on B-cell CLL cells	Cytopenias, prolonged lymphopenia with increased risk for infection, infusion reactions, CMV infection and other infections, nausea, vomiting, diarrhea, insomnia. Embryo-fetal toxicity Warnings: Hematologic toxicity which may be fatal, infusion reactions, infections including opportunistic infections. Patient should receive prophylaxis for PCP while receiving the drug. Do not administer live vaccines while receiving or who have recently received the drug
EGFR inhibitors includes HER1 (EGFR1) and HER2 (EGFR2)		Dermatologic toxicity, infusion reactions, magnesium wasting (hypomagnesemia), diarrhea, embryo-fetal toxicity
Ado-trastuzumab emtansine (Kadcyla®)[99]	HER2 (EGFR2); metastatic HER2+breast cancer	Fatigue, nausea, musculoskeletal pain, hemorrhage, thrombocytopenia, headache, increased hepatic transaminase values, constipation, epistaxis Warnings: Do not substitute drug for trastuzumab, hepatotoxicity with liver failure and death, reduced LVEF, embryo-fetal toxicity
Cetuximab (Erbitux®)[100]	EGFR1; mCRC (wild type), HNSCC	Cutaneous reaction (rash, pruritus, nail changes), headache, diarrhea, infection Warnings: Infusion reactions which may be fatal, cardiopulmonary arrest/sudden death occurred in 2%-3% of study patients with HNSCC also receiving RT
Necitumumab (Portrazza®)[101]	EGFR1; squamous NSCLC, with gemcitabine and cisplatin	Rash, hypomagnesemia Warnings: Cardiopulmonary arrest/sudden death (likely related to hypo-magnesemia), hypomagnesemia, VTE, ATE, dermatologic toxicities, infusion-related reactions, increased toxicity and mortality if given to a patient with nonsquamous NSCLC, embryo-fetal toxicity
Panitumumab (Vectibix®)[102]	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 Warnings: Dermatologic toxicities occurred in 90% of study patients, severe in 13% receiving monotherapy; increased progression/mortality or lack of benefit in patents with mutant *RAS* gene; electrolyte depletion; pulmonary fibrosis/ILD; ocular toxicities; embryo-fetal toxicity
Pertuzumab (Perjeta®)[103]	HER2 (EGFR2); HER2+breast cancer (neoadjuvant, metastatic)	In combination with other drugs: Diarrhea, alopecia, neutropenia, nausea, fatigue, rash, peripheral neuropathy, vomiting, thrombocytopenia, anemia Warnings: LVEF decrease, embryo-fetal toxicity, infusion-related reactions, HSRs including anaphylaxis

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Table 2: Contd...

Class/drug	Target (s)/indication (s)	Common adverse effects/warnings
Trastuzumab (Herceptin®)[104]	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®)[105] Herceptin® Biosimilar not interchangeable with herceptin (trastuzumab)	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		Immune-related toxicities, embryo-fetal toxicity
Atezolizumab (Tecentriq®)[106]	PD-L1; 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
Avelumab (Bavencio®)[107]	PD-L1; 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™)[108]	PD-L1; 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
Ipilimumab (Yervoy®)[109]	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®)[110]	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®)[111]	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
IECT		
Axicabtagene ciloleucel (Yescarta®)[112]	Chimeric antigen receptor T-cell therapy; CD19 directed genetically modified autologous T-cell immunotherapy producing superior immune fighting cells against patient tumor; refractory or relapsed large B-cell lymphoma in adults	CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections, hypoxia, tremor, cough, vomiting, dizziness, constipation, cardiac arrhythmias Warnings: CRS, which may be fatal, neurologic toxicities, which may be fatal, HSRs, serious infections, prolonged cytopenias, hypogammaglobulinemia, secondary malignancies, impairment of ability to drive or operate machinery during and for 8 weeks after drug treatment. Drug is available only through a restricted Yescarta REMS program
Tisagenlecleucel (Kymriah®)[113]	Chimeric antigen receptor T-cell therapy; CD19 directed genetically modified autologous T-cell immunotherapy producing superior immune fighting cells against patient tumor; refractory B-cell precursor ALL	CRS, hypogammaglobulinemia, infections, pyrexia, decreased appetite, headache, encephalopathy, hypotension, bleeding episodes, tachycardia, nausea, diarrhea, vomiting, viral infection, hypoxia, fatigue, acute kidney injury, delirium Warnings: CRS that may be fatal, neurological toxicities which may be severe, HSRs, prolonged cytopenias, serious infections, hypogammaglobulinemia, secondary malignancies, impairment of ability to drive or operate machinery during and for 8 weeks after drug treatment. Drug is available only through a restricted Kymriah REMS program
iMIDs		Class effects: Embryo-fetal toxicity

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Table 2: Contd...

Class/drug	Target (s)/indication (s)	Common adverse effects/warnings
Lenalidomide (Revlimid®)[114]	Anti-angiogenic mechanisms, T-cell costimulatory functions, stimulation of NK cells and T-cells; MM with dexamethasone; transfusion dependent anemia due to MDS due to deletion of 5q; relapsed MCL, maintenance therapy in MM after ASCT	Diarrhea, fatigue, anemia, constipation, neutropenia, peripheral edema, insomnia, muscle cramp/spasm, abdominal and back pain, nausea, asthenia, pyrexia, URI, nasopharyngitis, gastroenteritis, cough, rash, dyspnea, dizziness, decreased appetite, thrombocytopenia, tremor, pruritus, arthralgia, epistaxis, anemia Warnings: Embryo-fetal toxicity (causes birth defects or embryo-fetal death), hematologic toxicity, VTE, ATE, increased mortality if drug is used for CLL (not an indication), hepatotoxicity, cutaneous reactions, TLS, tumor flare reactions, impaired stem cell mobilization, early mortality in MCL. Only available through Revlimid REMS program
Pomalidomide (Pomalyst®)[115]	Anti-angiogenic mechanisms, T-cell costimulatory functions, stimulation of NK cells and T-cells; relapsed MM together with dexamethasone	Fatigue, asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, URI, back pain, pyrexia Warnings: Embryo-fetal toxicity (causes birth defects or embryo-fetal death), hematologic toxicity, VTE, ATE, hepatotoxicity, HSRs, TLS. Only available through Pomalyst REMS program
Thalidomide (Thalomid®)[116]	Anti-angiogenic mechanisms, T-cell costimulatory functions, stimulation of NK cells and T-cells; newly diagnosed MM, with dexamethasone, other conditions	Fatigue, hypocalcemia, edema, constipation, neuropathy (sensory and motor), dyspnea, muscle weakness, neutropenia, rash/desquamation, confusion, anorexia, nausea, anxiety/agitation, asthenia, tremor, fever, weight loss, thrombosis/embolism, weight gain, dizziness, dry skin, somnolence Warnings: Embryo-fetal toxicity (causes birth defects or embryo-fetal death), hematologic toxicity, VTE, ischemic heart disease, drowsiness and somnolence, peripheral neuropathy, dizziness and orthostatic hypotension, neutropenia, thrombocytopenia, increased HIV viral load, bradycardia, Stevens-Johnson syndrome, seizures, TLS, HSRs. Only available through Thalomid REMS program
Oncolytic viral therapy		
Talimogene laherparepved (T-vec®, Imlygic®)[83]	Genetically modified oncolytic viral therapy. Patient's tumor cells, when injected into tumor locally, destroys tumor cells so antigens can be fragmented and mounted on dendritic APC's which then can activate T-cells to kill the tumor antigen-containing cells elsewhere in the body; stimulates local and systemic immune responses. Local treatment of unresectable, cutaneous, subcutaneous, and nodal melanoma lesions that have recurred after initial surgery	Fatigue, chills, pyrexia, nausea, influenza-like illness, injection site pain Warnings: Accidental exposure to drug may cause transmission of drug and herpetic infection; herpetic infection; injection site complications; immune-mediated events; plasmacytoma at injection site; objective airway disorder requiring careful injection of lesions near major airways
PDGF-α		
Olaratumumab (Lartruvo®)[81]	Platelet-derived growth factor receptor alpha; soft tissue sarcoma, in combination with doxorubicin	Nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neuropathy, headache Warnings: Infusion-related reactions, embryo-fetal toxicity
SLAMF-7		
Elotuzumab (Empliciti®)[117]	SLAMF-7 protein on multiple myeloma and NK cells, promotes myeloma cell death from NK cells (immunostimulatory); multiple myeloma with lenalidomide/dexamethasone	Fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy, nasopharyngitis, URI, decreased appetite, pneumonia, embryo-fetal toxicity Warnings: Infusion reactions, infections, second primary malignancies, hepatotoxicity, interference with determination of a complete response (interferes with M-protein)

HTN: Hypertension, VEGF: Vascular endothelial growth factor, mCRC: Metastatic colorectal cancer, NSCLC: Nonsmall cell lung cancer, PRES: Posterior reversible encephalopathy syndrome, VEGFR: VEGF receptor, GEJ: Gastroesophageal junction, ATEs: Arterial thromboembolic events, RPLS: Reversible posterior leukoencephalopathy syndrome, PAP: Prostatic acid phosphatase, GM-CSF: Granulocyte-macrophage-colony stimulating factor, PH: Philadelphia-chromosome negative, ALL: Acute lymphoblastic leukemia, NHL: Non-Hodgkin's lymphoma, MDS: Myelodysplastic syndrome, CLL: Chronic myelogenous leukemia, URIs: Upper respiratory infections, UTI: Urinary tract infection, PML: Progressive multifocal leukoencephalopathy, HSRs: Hypersensitivity reactions, TLS: Tumor lysis syndrome, GI: Gastrointestinal, AML: Acute myeloid leukemia, AST: Aspartate aminotransferase, CD: Cluster of differentiation, identifying specific proteins on B-cell lymphocytes, e.g., CD20, ALT: Alanine aminotransferase, CMV: Cytomegalovirus, PCP: *Pneumocystis jiroveci* (formerly *carinii*) pneumonia, LVEF: Left ventricular ejection fraction, HNSCC: Head and neck squamous cell cancer, VTE: Venous thromboembolic event, CHF: Congestive heart failure, PD-L1: Programmed death ligand-1, CTLA4: Cytotoxic T-lymphocyte antigen 4, HCC: Hepatocellular carcinoma, IECT: Immune effector cell therapy, CRS: Cytokine release syndrome, REMS: Risk evaluation and mitigation strategy, iMIDs: Immunomodulatory drugs, MM: Multiple myeloma, NK: Natural killer cell: Type of lymphocyte that can kill invading virus or cancer cells without using antigen detection (uses enzymatic granules to kill the other cell) and is part of the innate immune system, MCL: Mantle cell lymphoma, 5q: Short arm of chromosome 5, ASCT: Autologous stem cell transplant, APCs: Antigen presenting cell, such as dendritic cells, PDGFR: Platelet-derived growth factor receptor, SLAMF-7: Signaling lymphocytic activation molecule family member 7 protein on multiple myeloma and NK cells, leading to death of myeloma cells by NK cells, PD-1: Programmed death receptor-1, dMMR: Mismatch repair (gene) deficient, MSI-1: microsatellite instability-high, HER2: Human epidermal growth factor receptor, HSCT: Hematopoietic stem cell transplant, , RT: Radiation therapy, MSH-1: mismatch repair protein

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, and enabling patients and their family to manage self-care.

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Conflicts of interest

There are no conflicts of interest.

References

1. World Health Association. Cancer Fact Sheet. February, 2017. Available from: http://www.who.int/mediacentre/factsheets/fs297/en/. [Last accessed on 2017 Nov 27].
2. American Cancer Society. Global Cancer Facts and Figures 3rd ed. American Cancer Society; 2015. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-3rd-edition.pdf. [Last retrieved on 2017 Oct 20; Last accessed on 2017 Nov 27].
3. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144:646-74.
4. Yu X, Mao W, Zhai Y, Tong C, Liu M, Ma L, *et al.* Anti-tumor activity of metformin: From metabolic and epigenetic perspectives. Oncotarget 2017;8:5619-28.
5. Santarpia L, Lippman SM, El-Naggar AK. Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. Expert Opin Ther Targets 2012;16:103-19.
6. Martinelli E, Morgillo F, Troiani T, Ciardiello F. Cancer resistance to therapies against the EGFR-RAS-RAF pathway: The role of MEK. Cancer Treat Rev 2017;53:61-9.
7. Porta C, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR signaling in cancer. Front Oncol 2014;4:64.
8. Watanabe R, Wei L, Huang J. MTOR signaling, function, novel inhibitors, and therapeutic targets. J Nucl Med 2011;52:497-500.
9. Folkman J. Angiogenesis. Annu Rev Med 2006;57:1-8.
10. Baluk P, Hashizume H, McDonald DM. Cellular abnormalities of blood vessels as targets in cancer. Curr Opin Genet Dev 2005;15:102-11.
11. Huang Y, Goel S, Duda DG, Fukumura D, Jain RK. Vascular normalization as an emerging strategy to enhance cancer immunotherapy. Cancer Res 2013;73:2943-8.
12. Malumbres M, Barbacid M. Milestones in cell division to cycle or not to cycle: A critical decision in cancer. Nat Rev Cancer 2001;1:222-3.
13. Xu XL, Chen SZ, Chen W, Zheng WH, Xia XH, Yang HJ, *et al.* The impact of cyclin D1 overexpression on the prognosis of ER-positive breast cancers: A meta-analysis. Breast Cancer Res Treat 2013;139:329-39.
14. Verzenio™ (Abemaciclib). Indianapolis, IN: Eli Lilly and Co.; 2017.
15. Nguyen D, Liao W, Zeng SX, Lu H. Reviving the guardian of the genome: Small molecule activators of p53. Pharmacol Ther 2017;178:92-108.
16. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science 2017;355:1152-8.
17. Venclexta™ (Venetoclax). North Chicago, IL: Abbvie Inc, and Genentech USA, Inc.; 2016.
18. Crawford LJ, Walker B, Irvine AE. Proteasome inhibitors in cancer therapy. J Cell Commun Signal 2011;5:101-10.
19. Deans C, Maggert KA. What do you mean, "epigenetic"? Genetics 2015;199:887-96.
20. Gryder BE, Sodji QH, Oyelere AK. Targeted cancer therapy: Giving histone deacetylase inhibitors all they need to succeed. Future Med Chem 2012;4:505-24.
21. Abramson RG. Overview of Targeted Therapies for Cancer. My Cancer Genome. Available from: https://www.mycancergenome.org/content/molecular-medicine/overview-of-targeted-therapies-for-cancer/. [Last accessed on 2017 Dec 01].
22. Alescensa® (Alectinib). South San Francisco, CA: Genentech USA, Inc.; 2016.
23. Alunbrig® (Brigatinib). Cambridge, MA: Ariad Pharmaceuticals, Inc.; 2017.
24. Zykadia® (Ceritinib). East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2017.
25. Xalkori® (Crizotinib). New York: Pfizer Laboratories; 2017.
26. Inlyta® (Axitinib). New York: Pfizer Laboratories; 2014.
27. Cometriq™ (Cabozantinib). South San Francisco, CA: Exelixis Inc; 2012.
28. Cabometyx™ (Cabozantinib). South San Francisco, CA: Exelixis Inc.; 2016.
29. Lenvima® (Lenvatinib). Woodcliff Lake, NJ: Eisai Inc.; 2017.
30. Votrient® (Pazopanib). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
31. Stivarga™ (Regorafenib). Whippany, NJ: Bayer Healthcare Pharmaceuticals, Inc.; 2017.
32. Nexavar™ (Rsorafenib). Whippany, NJ: Bayer Healthcare Pharmaceuticals, Inc.; 2013.
33. Sutent® (Sunitinib). New York: Pfizer Laboratories; 2015.
34. Caprelsa® (Vandetanib). Cambridge, MA: Sanofi Genzyme; 2016.
35. Zaltrap (Ziv-Aflibercept). Bridgewater, NJ: Sanofi-Aventis US LLC; 2016.
36. Bosulif® (Bosutinib). New York: Pfizer Laboratories; 2017.
37. Sprycel®(Dasatinib). Princeton, NJ: Bristol-Myers Squibb Co.; 2017.
38. Gleevec® (Imatinib Mesylate). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
39. Tasigna® (Nilotinib). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
40. I® Iclusig (Ponatinib). Cambridge, MA: Ariad Pharmaceuticals, Inc.; 2016.
41. Cotellic® (Cobimetinib). South San Francisco, CA: Genentech USA, Inc.; 2016.
42. Tafinlar® (Dabrafenib). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
43. Mekinist® (Trametinib). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
44. Zelboraf® (Vemurafenib). South San Francisco, CA: Genentech USA, Inc.; 2017.
45. Calquence (Acalabrutinib). Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.
46. Imbruvica® (Ibrutinib). Sunnyvale, CA: Pharmacyclics, LLC; 2017.
47. Ibrance® (Palbociclib). New York: Pfizer Laboratories; 2017.
48. Kisqali® (Ribociclib). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
49. Gilotrif® (Afatinib). Ridggefield, CT: Boehringer Ingelheim Pharamceuticals, Inc.; 2017.
50. Tarceva® (Erlotinib). South San Francisco, CA: Genentech USA, Inc.; 2016.

51. Iressa® (Gelfitinib). Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.
52. Tykerb® (Lapatinib). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
53. Nerlynx™ (Neratinib). Los Angeles, CA: Puma Biotechnology, Inc.; 2017.
54. Tagrisso® (Osimertinib). Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.
55. Rydapt® (Midostaurin). East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2017.
56. Odomzo® (Sonidegib). Cranbury, NJ: Sun Pharaceutical Industries, Inc.; 2017.
57. Erivedge® (Vismodegib). South San Francisco, CA: Genentech USA, Inc.; 2017.
58. Beleodaq® (Belinostat). Irvine, CA: Spectrum Pharmaceuticals, Inc.; 2014.
59. Farydak® (Panobinostat). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2016.
60. Isodax® (Romidepsin). Summit, NJ: Celgene Corporation; 2016.
61. Zolinza® (Vorinostat). Whitehouse Station, NJ: Merck and Co., Inc.; 2015.
62. Idhifa® (Enasidenib). Summit, NJ: Celgene Corp; 2017.
63. Afinitor® (Everolimus). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
64. Torisel® (Temsirolimus). Philadelphia, PA: Wyeth Pharmaceuticals, Inc., A Division of Pfizer, Inc.; 2017.
65. Lynparza® (Olaparib). Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.
66. Zejula® (Niraparib). Waltham, MA: Tesaro, Inc.; 2017.
67. Rubraca™ (Rucaparib). Boulder, CO: Clovis Oncology; 2017.
68. Aliqopa™ (Copanlisib). Whippany, NJ: Bayer Healthcare Pharmaceuticals, Inc.; 2017.
69. Zydelig® (Idelalisib). Foster City, CA: Gilead Sciences, Inc.; 2016.
70. Velcade® (Bortezomib). Cambridge, MA: Millennium Pharmaceuticals, lnc, Subsidiary of Takeda Pharmaceuticals; 2017.
71. Kyprolis® (Carfilzomib). Thousand Oaks, CA: Amgen; 2017.
72. Ninlaro® (Ixazomib). Cambridge, MA: Millennium Pharmaceuticals, lnc, Subsidiary of Takeda Pharmaceuticals; 2016.
73. Murphy K. Janeway's Immunobiology. 8th ed. New York: Garland Science; 2011.
74. Weinberg RA. The Biology of Cancer. 2nd ed. New York: Garland Science; 2014.
75. Wolchok JD, Saenger Y. The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. Oncologist 2008;13 Suppl 4:2-9.
76. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.
77. Shields BD, Mahmoud F, Taylor EM, Byrum SD, Sengupta D, Koss B, *et al.* Indicators of responsiveness to immune checkpoint inhibitors. Sci Rep 2017;7:807.
78. Wilkes GM, Barton Burke M. Oncology Nursing Drug Handbook. Burlington, MA: Jones and Bartlett Learning; 2017. p. 728-32.
79. Blincyto® (Blinatumomab). Thousand Oaks, CA: Amgen Inc.; 2017.
80. Food and Drug Administration (USA). What is a Biosimilar? Available from: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM585738.pdf. [Last accessed on 2017 Dec 03].
81. Lartruvo™ (Olaratumab). Indianapolis, IN: Eli Lilly and Co.; 2017.
82. Maus MV, Nikiforow S. The why, what and how of the new FACT standards for immune effector cells. J Immunol Ther Cancer 2017;5:36-46.
83. Imlygic® (Talimogene Laherparepvec). Thousand Oaks, CA: Amgen Inc.; 2017.
84. Kotla V, Goel S, Nischal S, Heuck C, Vivek K, Das B, *et al.* Mechanism of action of lenalidomide in hematological malignancies. J Hematol Oncol 2009;2:36.
85. Provenge® (Sipuleucel-T). Seattle WA: Dendreon Pharmaceuticals, Inc.; 2010.
86. Avastin® (Bevacizumab). South San Francisco, CA: Genentech, Inc., Genentech USA, Inc.; 2016.
87. MVASI® (Bevacizumab-Awwb). Thousand Oaks, CA: Amgen Inc.; 2017.
88. Cyramza™ (Ramucirumab). Indianapolis, IN: Eli Lilly and Co.; 2017.
89. Zevalin® (Ibritumomab). Irvine, CA: Spectrum Pharmaceuticals, Inc.; 2013.
90. Gazyva® (Obinutuzumab). South San Francisco, CA: Genentech, Inc., Genentech USA, Inc.; 2017.
91. Arzerra® (Ofatumumab). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2016.
92. Rituxan® (Rituximab). South San Francisco, CA: Genentech USA, Inc.; 2016.
93. Rituxan Hycela® (Rituximab and Hyaluronidase Human). South San Francisco, CA: Genentech USA, Inc.; 2017.
94. Besponsa™ (Inotuzumab Ozogamicin). Philadelphia, PA: Wyeth Pharmaceuticals Inc.; 2017.
95. Adcetris® (Brentuximab Vedotin). Seattle, WA: Seattle Genetics, Inc.; 2017.
96. Mylotarg™ (Gemtuzumab Ozogamicin). Philadelphia, PA: Wyeth Pharmaceuticals Inc.; 2017.
97. Darzalex® (Daratumumab). Horsham, PA: Janssen Biotech Inc.; 2017.
98. Campath® (Alemtuzumab). Cambridge, MA: Genzyme Corp; 2007.
99. Kadcyla® (Ado-Trastuzumab Emtansine). South San Francisco, CA: Genentech, Inc. Genentech USA, Inc.; 2016.
100. Erbitux® (Cetuximab). Branchburg, NJ: ImClone LLC, a Subsidiary of Eli Lilly and Company; 2016.
101. Portrazza™ (Necitumumab). Indianapolis, IN: Eli Lilly and Co.; 2015.
102. Vectibix® (Panitumomab). Thousand Oaks, CA: Amgen Inc.; 2017.
103. Robert NJ, Goertz HP, Chopra P, Jiao X, Yoo B, Patt D, *et al.* HER2-positive metastatic breast cancer patients receiving pertuzumab in a community oncology practice setting: Treatment patterns and outcomes. Drugs Real World Outcomes 2017;4:1-7.
104. Herceptin® (Trastuzumab). South San Francisco, CA: Genentech, Inc., Genentech USA, Inc.; 2017.
105. Ogivri® (Trastuzumab-Dkst). Zurich, Switzerland: Mylan GmbH; 2017.
106. Tecentriq® (Atezolizumab). South San Francisco, CA: Genentech USA, Inc.; 2017.
107. Bavencio® (Avelumab). Rockland, MA: EMD Serono, Inc.; 2017.

108. Imfinzi™ (Durvalumab). Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.
109. Yervoy® (Ipilimumab). Princeton, NJ: Bristol Myers Squibb Company; 2017.
110. Opdivo® (Nivolumab). Princeton, NJ: Bristol Myers Squibb Company; 2017.
111. Keytruda® (Pembrolizumab). Whitehouse Station, NJ: Merck and Co., Inc.; 2017.
112. Yescarta™ (Axicabtagene Ciloleucel). Santa Monica, CA: Kite Pharma, Inc.; 2017.
113. Kymriah™ (Tisagenlecleucel). East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
114. Revlimid® (Lenalidomide). Summit, NJ: Celgene Corporation; 2017.
115. Pomalyst® (Pomalidomide). Summit, NJ: Celgene Corporation; 2016.
116. Thalomid® (Thalidomide). Summit, NJ: Celgene Corporation; 2017.
117. Empliciti™ (Elotuzumab). Princeton, NJ: Bristol Myers Squibb Company; 2017.
118. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, *et al.* Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv119 42.
119. ASCO. Guidelines Planned on Management of Immunotherapy Side Effects: ASCO and NCCN to Collaborate on Development; 16 February, 2017. Available from: https://www.asco.org/advocacy-policy/asco-in action/guidelines-planned-management-immunotherapy-side-effects-asco-and. [Last accessed on 2017 Dec 03].
120. Smith L, Venella K. Cytokine release syndrome: Inpatient care for side effects of CAR T-cell therapy . Clin J Oncol Nurs 2017;21:29-34.