Review

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Targeted Therapies: A Molecular Overview

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Abstract

Cancer remains a major health issue and our understanding of its etiopathogenesis needs to be improved. Cancer cells have specific abilities such as uncontrolled proliferation, differentiation, progression, and metastasis. Improved interpretation of intracellular molecular pathways and the development of new genetic or immunological diagnostic techniques have facilitated novel treatment modalities for cancer. These therapeutic agents generally have antiproliferative properties and regulate molecular mechanisms on the intracellular pathways. Small molecule inhibitors, monoclonal antibodies, and some gene-editing treatments have been suggested due to the discovery of new molecular mechanisms. However, limited and transient efficacy, and drug resistance generated by mutations are among the disadvantages of these treatments. Multi-functional inhibitors have highly side effects, but benefit from greater efficacy and evading resistance while the recent specific inhibitors possess increased potency and less toxicity. Furthermore, the combination of therapeutic modalities may potentiate the outcome.
Considering the actual literature, this review summarized targeted therapies for treating cancer patients in urology as an overview.
Keywords: Cancer, small molecules, urology, monoclonal antibodies

Introduction

Targeted therapies identify specific targets at the cancer cells and attack them. Tamoxifen is the oldest targeted therapeutic agent acting as a selective estrogen receptor modulator to treat hormone receptor-positive patients. Presently, numerous targeted therapy agents have been in us for cancer treatment owing to the evolution of molecular medicine and advances in drug technologies. The size of the global drug market for cancer patients has reached almost 200 million dollars. Nowadays, hundreds of targeted therapy agents are undergoing clinical trials and some of them are approved for cancer treatment. Mainly, these drugs either block the molecules involved in oncogenesis, such as enzymes and proteins, or help the immune system to kill the cancer cells. These agents can be classified as small molecule drugs, monoclonal antibodies, or gene editing agents. Inhibitory small molecule drugs have "-ib" and monoclonal antibodies have "-mab" as a suffix.

Targeted therapies generally have fewer side effects than other types of cancer treatment and are less harmful to a normal cell. These drugs act on molecular targets in the cancer cells and inhibit tumor cell proliferation (cytostatic). In contrast, other chemotherapeutic agents act on all cells with have high proliferation capability and kill the tumor cells (cytotoxic). Normally, the receptor is activated after binding to its ligand, and the signal is transmitted down for cell response. Some compounds are agonists that can bind to the receptor and activate it. In contrast, an antagonist blocks the agonistic effect on the receptor (1).

There are still some challenges, such as drug resistance based on gene mutations and low efficiency. Hence, the development of advanced drug design techniques is essential along with the identification of distinct targets such as epigenetic regulatory proteins, microRNA (miRNAs), and cancer stem cells (CSCs). For instance, successful outcomes are expected with antibody-drug conjugate (ADC) drugs and proteolysis targeting chimera (PROTAC) techniques in the future. The evolution of novel agents that act on intracellular mechanisms or genes can entail personalized medicine, using individual information on genes and proteins for treating cancer. Considering the current literature, this review aims to outline targeted cancer therapies for urologists.

Small Molecule Therapies

Small molecule therapies can affect many intracellular pathways during oncogenesis by changing enzymatic reactions due to receptor agonism or antagonism. Several molecules have been described in the literature and some of them have been approved for antineoplastic effect. Moreover, various combined

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therapies have been assessed to improve the treatment outcome in clinical studies.

Targeted therapies can be classified according to the mechanism of action. Enzyme inhibitors reduce catalytic activity of these enzymes. The kind of the enzyme-linked antagonist complexes are used in their classification.

Kinase Inhibitors

The protein kinase enzyme catalyzes the transfer of the γ-phosphate group from ATP to protein residues containing hydroxyl groups. They have a major effect on cell growth, proliferation, and differentiation. Kinase inhibitors can be classified into six types based on their acting mechanisms according to Roskoski's classification system (2). Instead of this pharmacological classification, protein kinases were classified such as receptor or non-receptor tyrosine kinases, serine/ threonine kinases, and tyrosine kinase-like enzymes in our review.

Receptor Tyrosine Kinase Inhibitors (TKIs)

ALK Inhibitors

Anaplastic lymphoma kinase (ALK) gene is a transmembrane tyrosine kinase of the insulin receptor family (3). ALK can stimulate several downstream signaling pathways in the cell (4). Activation of the ALK gene by mutations has been identified in different cancers. ALK inhibitors are effective against multiple tyrosine kinases, including ALK, cellular mesenchymal-epithelial transition factor (c-Met), and proto-oncogene tyrosine-protein kinase reactive oxygen species (ROS), and IGF1R/epidermal growth factor receptor (EGFR)/ FMS-like tyrosine kinase 3 (FLT3) pathway. ALK inhibitors such crizotinib, ceritinib, alectinib, brigatinib, and Lorlatinib.

c-Met Inhibitors [Hepatocyte Growth Factor Receptor (HGFR)]

The c-Met, is encoded by the MET proto-oncogene located on chromosome 7q21-31.41,42. It has a crucial role in different cellular pathways and activates HGF/c-Met, PI3K/AKT, MAPK, signal transducer and activator of transcription (STAT), and NF-κB signaling pathways. Therefore, it regulates angiogenesis, proliferation, survival, invasion, motility, and epidermal mesenchymal transition (5). c-Met overexpression has been reported to be related to poor prognosis and resistance to targeted therapies (6). These mutations are common in advanced cancers with metastases such as renal cell carcinoma (RCC) (7). c-Met inhibitors have been classified as multi-kinase inhibitors (crizotinib, cabozantinib) and selective inhibitors (capmatinib, tepotinib). As a member of this family, Cabozantinib-S-Malate inhibits vascular endothelial growth factor receptor (VEGFR) 1/2/3/ TROY3/ ROS/ TIE2/ c-MET/HGFR c-KIT/TRK2/c-RET pathways and has been approved for treating advanced RCC.

EGFR Inhibitors

EGFR is a transmembrane protein that affects some intracellular pathways. ERBB2/3/4 [human epidermal growth factor receptor (HER2/3/4)] are members of this family (8,9). EGFR TKIs clinically available such as gefitinib, erlotinib, icotinib, lapatinib, afatinib, osimertinib, neratinib, dacomitinib, almonertinib, tucatinib.

FLT3 Inhibitors

FLT3 is a transmembrane protein encoded by the proto-oncogene FLT3. It is a member of the type III receptor tyrosine kinase (RTKs) family, which also includes platelet-derived growth factor receptor (PDGFR), FMS, and KIT. After the autophosphorylation of FLT3, it activates cellular signaling pathways such as PI3K/AKT/ mammalian target of rapamycin (mTOR), RAS/RAF/MAPK, and JAK/STAT pathways (10). These pathways are related to several cellular functions such as proliferation, differentiation, survival, and apoptosis. FLT3 inhibitors have been classified as multi-kinase inhibitors (sorafenib, sunitinib, midostaurin, tandutinib, lestaurtinib) or specific inhibitors (gilteritinib, quizartinib, pexidartinib) (11). Multi-kinase inhibitors are not specific for FLT3 receptor and can inhibit various receptor tyrosine kinases such as PDGFR, KIT, VEGFR, RAF, or JAK2.

VEGFR/FGFR/PDGFR Inhibitors

Angiogenesis is a complex function and is regulated by various endogenous proangiogenic and antiangiogenic factors. By secreting pro-angiogenic factors, tumors trigger the generation of new blood vessels from the preexisting vessels in the tumor microenvironment (12). Antiangiogenic therapy inhibits this process, which is crucial to the development, growth, and metastases of cancer leading to the death of cancer cells due to starvation (13).

Angiogenesis-related genes, transcription factors, and signaling pathways are effective in this process. VEGF, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), insulin-like growth factor, epidermal growth factor (EGF), and angiopoietin are members of the angiogenic family. Bevacizumab is the oldest biological inhibitor for angiogenesis due to its anti-VEGF effect and has been licensed for treating advanced RCC. In the context of these growth factors, antiangiogenic treatments have inhibited the activities of their receptors such as VEGF receptors (VEGFR-1-3), FGF receptors (FGFR1-4), PDGF receptors (PDGFR α/β), and TGF-β receptors (TGF-βR I/II/III). Many anti-angiogenic TKIs have been licensed by the authorities such as sorafenib, sunitinib, pazopanib, vandetanib, axitinib, cabozantinib, regorafenib, afatinib, lenvatinib, tivozanib, fruquintinib, nintedanib, anlotinib, erdafitinib, pemigatinib, avapritinib, and ripretinib. Most of them are members of the multi-kinase inhibitors family.

A member of this family, Sorafenib can inhibit several receptor tyrosine kinases (RTKs) including VEGFR-1/2/3, c-Kit, FLT3, RET, PDGFRβ, RAF1, BRA, especially on the RAS (RAF/MEK/ ERK) signaling pathway. It has been approved as the first anti-angiogenic inhibitor (anti-VEGFR 2/3) for treating advanced RCC (14). Other approved anti-angiogenic inhibitors for the first- or second-line treatment of advanced RCC are sunitinib, pazopanib, axitinib, cabozantinib, and tivozanib. The adverse reactions to sorafenib include hand-foot syndrome, diarrhea, hypertension, decreased appetite, and fatigue. Another anti-angiogenesis-related common side effect is hypothyroidism.

Axitinib acts on the receptors as VEGFR 1/2/3, PDGFRβ, and c-KIT (15). Tivozanib hydrochloride inhibits PDGFRα, VEGFR 1/2/3, FGFR 1/2/3/4, c-KIT/RET (16). Similarly, pazopanib inhibits PDGFRβ, VEGFR 1/2/3, FGFR 1/3/ c-KIT/ Itk/Lck/ c-GSK.

Sunitinib is a member of the multi-kinase RTK inhibitor and acts on the receptors as VEGFR-1/2/3, PDGFRα/β, c-Kit, CSF1R, RET, and FLT3 (17). Sunitinib is the second approved antiangiogenic TKI for treating advanced RCC. Adverse reactions to sunitinib include nausea, vomiting, weakness, and fatigue.

Selpercatinib and pralsetinib have been certified as specific RET inhibitors. Several selective FGFR (erdafitinib, pemigatinib) or PDGFR (avapritinib, ripretinib) inhibitors have also been accepted for therapeutic use.

Erdafitinib is the initial FGFR-selective inhibitor (FGFR 1/2/3/4) that has been used for the second-line treatment of locally advanced or metastatic urothelial carcinoma (18).

Lenvatinib mesylate inhibits VEGFR1/2/3, FGFR 1/2/3/4, PDGFRα, c-KIT/ RET and has been approved for advanced RCC (19). Adverse reactions to lenvatinib include hypertension, diarrhea, loss of appetite, and weight loss.

Additionally, targeting TGF-β signaling by galunisertib, vactosertib is also an alternative for anti-angiogenic therapy.

Antiangiogenic therapy not only inhibits neovascularity but also regulates the immune microenvironment, allowing the combination of antiangiogenic agents with immunotherapy. The combination of axitinib with the PD1 antibody pembrolizumab has been used for treating advanced RCC (20).

TRK Inhibitors

The tropomyosin receptor kinase (TRK) family includes three members, TRKA, TRKB, and TRKC, which are encoded by the neurotrophic tyrosine receptor kinase (NTRK) genes (21). After binding to TRK receptors, neurotrophins (TRK ligands) stimulate autophosphorylation of TRK proteins, thereby activating downstream signaling pathways such as RAS/MAPK/ERK, PI3K/AKT, and PLCγ. Aberrant activation of TRKs and generated fusion proteins have been identified as oncogenic factors in various cancers. Therefore, TRKs are important targets for the treatment of cancer patient. Currently, TRK inhibitors have been approved for the treatment of cancer patients such larotrectinib and entrectinib. Cabozantinib has been licensed as an antiangiogenic inhibitor for treating advanced RCC and has efficacy against NTRK fusions.

Non-receptor TKIs

Breakpoint Cluster Region (BCR)-ABL-1 Inhibitors

c-Abl [Abelson murine leukemia 1 (ABL1)] gene is located on chromosome (9). The ABL family is a member of the non-receptor tyrosine kinase group. It is effective in the modulation of cell differentiation, cell cycle, and survival. The BCR-ABL fusion gene is on chromosome 22 (Philadelphia). After autophosphorylation, it activates the downstream pathway (22). Imatinib is the first approved BCR-ABL1 inhibitor and the first licensed TKI. Second-generation BCR-ABL1 inhibitors include dasatinib, nilotinib, bosutinib, and radotinib. The other is ponatinib, a third-generation BCR-ABL1 inhibitor.

Bruton's Agammaglobulinemia Tyrosine Kinase (BTK) Inhibitors

BTK is a crucial component in the BCR pathway and belongs to the non-receptor tyrosine kinase of the *TEC* gene family. *TEC* kinase is expressed in hematopoietic, liver, and kidney cells and plays a major role in T-helper cell function. The B-cell receptor (BCR) function plays a key role in the progression of B-cell malignancies (23). Ibrutinib, Acalabrutinib, and Zanubrutinib are members of this family.

Janus Kinases (JAK) Inhibitors

JAKs are members of non-receptor tyrosine kinases and are classified as JAK1, JAK2, JAK3, and TYK2 (24). JAKs regulates to the DNA transcription and protein expression. The JAK system is activated when inflammatory cytokines such as interleukin (IL) and interferon bind to their receptors. Then JAKs catalyze the phosphorylation of receptor tyrosine and phosphorylate the downstream STAT proteins. The activation of the STAT protein promotes their translocation to the nucleus and regulation of target-gene transcription and expression. The JAK/STAT cascade activates more than 50 cytokines and growth factors and is the central communication point for the immune system. For this reason, JAKs are potential targets for the treatment of cancer patients, and their inhibitors include ruxolitinib, lestaurtinib, fedratinib, and tofacitinib.

Serine/Threonine Kinase Inhibitors

BRAF/MEK/ERK Inhibitors

RAS-RAF-MAPK-ERK signaling pathway includes the small GTPase Ras, the serine/threonine kinase RAF, and the protein kinases MEK1/2 and ERK1/2. RAF system contains ARAF, *BRAF*, and CRAF and is effective on the downstream of RAS, which serves as a transducer of receptor stimuli (25). Moreover, *Src* is a human proto-oncogene and belongs to the non-receptor tyrosine kinases family. *Src* plays a major role in the field of molecular genetics of cancer and is involved in many signal transduction pathways such as the RAS/MEK/ERK pathway, STAT/c-myc pathway, and PI3K/AKT pathway. Sorafenib is a pan-RAF inhibitor and has multi-kinase inhibitor properties. Another novel MEK1/2 inhibitor is selumetinib. Currently, no ERK inhibitor has been approved for clinical use. New combinations of this targeted therapy drugs with ERK inhibitors, CDK4/6 inhibitors, or inhibitors of the PI3K/AKT/mTOR pathway have been under evaluation for more efficacy and low resistance rates. Vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib, binimetinib, selumetinib are members of this family.

Cyclin-dependent Kinase (CDK) Inhibitors

Uncontrolled proliferation due to cell cycle defects is one of the member pivotal factors in the development of cancer. CDKs regulates to the cell cycle progression and many CDKs/cyclin proteins activate to downstream phosphorylation in humans (26). Among them, CDK4 and CDK6 play a key role in regulating growth signaling and driving the transition of the cell cycle from G1 to the S phase. Non-selective pan-CDK inhibitors (flavopiridol, seliciclib, UCN-01) have been discontinued due

to their low efficacy and serious side effects. Today, clinically available three CDK inhibitors are palbociclib, ribociclib, and abemaciclib. They are orally selective reversible inhibitors that specifically target CDK4/6. Hematological toxicities such as neutropenia and gastrointestinal toxicities, particularly diarrhea, are side effects of CDK inhibitors.

PI3K/AKT/mTOR Inhibitors

The phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/V-AKT murine thymoma viral oncogene homolog (AKT)/mTOR signaling pathway has a major role in cell growth, proliferation, survival, apoptosis, and motility (27). This pathway is activated by phosphatase and tensin homolog (PTEN) loss due to be deleted from chromosome 10 for oncogenesis and progression. Moreover, inhibition of the tumor suppressor PTEN gene negatively regulates the PI3K pathway by dephosphorylating PIP3 to PIP2. *PIK3CA* gene is frequently overexpressed in many cancers by mutation and amplification. Activation of the PI3K/AKT/mTOR pathway is common in metastatic castration-resistance prostate cancer (mCRPC) and is associated with a poor prognosis. PI3K/AKT/mTOR pathways reciprocally crosstalk with the androgen receptor (AR) signaling so that inhibition of one leads to the upregulation of the other. However, activated PI3K/AKT/mTOR signaling is related to cancer cell growth and drug resistances. The PI3K/AKT/mTOR cascade interacts with many other signaling pathways such as Wnt and MAPK signaling. Therefore, this pathway has become an attractive target for developing antineoplastic drugs. AKT inhibitors bind to all three isoforms of AKT, which is a key component of the PI3K/AKT/mTOR pathway. Several small-molecule inhibitors of PI3K, AKT, and mTOR have been under evaluation. Ipatasertib is an oral, specific AKT inhibitor that shows a clinically significant activity when combined with abiraterone acetate and prednisone/prednisolone for (mCRPC) in patients with loss of the tumor suppressor protein PTEN (on immunohistochemistry) within the tumor (28,29). The adverse events are rash and diarrhea.

mTOR inhibitors have been divided into the two categories as rapamycin analogs (rapalogs) and ATP-competitive inhibitors. Sirolimus (rapamycin), temsirolimus, and everolimus have been licensed for treating various cancers such as advanced RCC. Moreover, these agents have serious immune-suppressive properties.

Another, perifosine is a member of PI3K inhibitors. Other inhibitors belonging to this pathway are idelalisib, copanlisib, duvelisib, and alpelisib.

Small molecule agents are summarized in Table 1 and Figure 1.

Epigenetic Inhibitors

Epigenetics is an important part of genetics that studies the changes in gene expression without changing the nucleotide sequence of genes. A better understanding of the mechanisms and differences of epigenetic alterations in different cancers may contribute to further development of new therapies. When we explain epigenome better, we can more sensitize chemotherapy, targeted therapy, and immunotherapy.

Epigenomic factors act on the genetic code with DNA Methylation, Histone Methylation, and Histone Acetylation. It is regulated by modifying enzymes and recognition proteins, which are named writers, erasers, and readers (30). The writers are some types of enzymes that transfer chemical groups to DNA or histones, which include DNA (DNA methyltransferases),

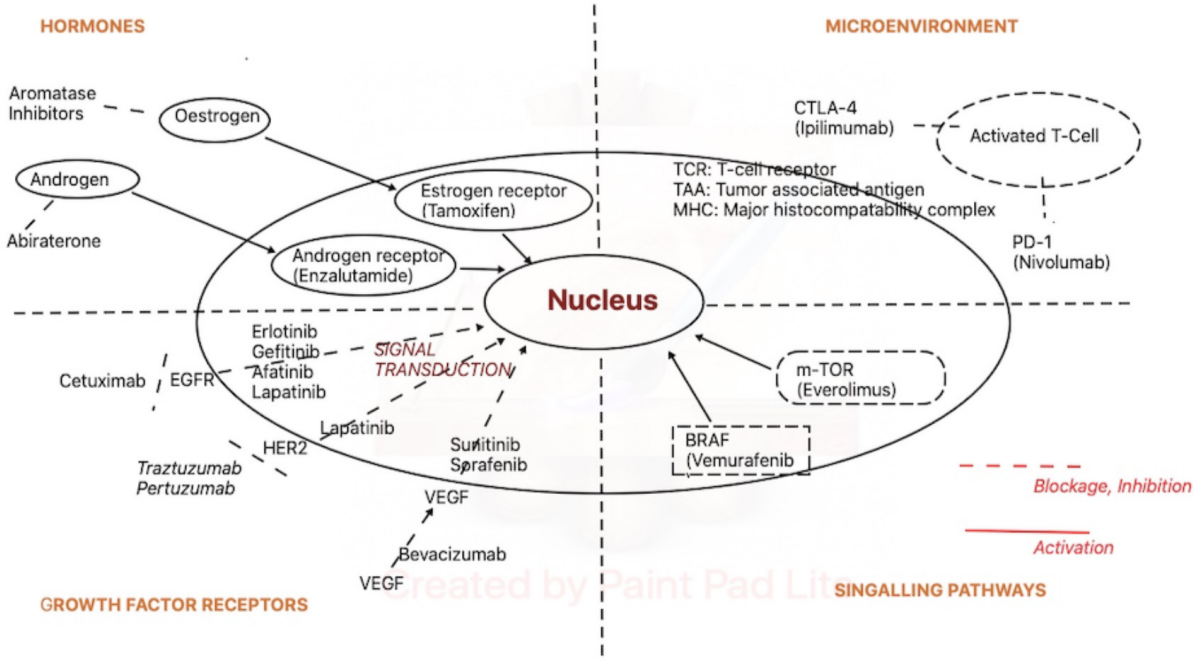

Figure 1. Illustration of the targeted therapies for cancer treatment

CTLA-4: Cytotoxic T lymphocytes-4, EGFR: Epidermal growth factor receptor, HER2: Human epidermal growth factor receptor 2, VEGF: Vascular endothelial growth factor, mTOR: Mammalian target of rapamycin

histone acetyltransferases, and histone lysine methyltransferases. The erasers remove post-translational modifications and include histone deacetylases (HDACs) and histone lysine demethylases (KDMs). The readers can recognize the modified histones or DNA, such as methyl-binding domain proteins and bromodomain and extra-terminal family proteins. The abnormal epigenetic regulation is related to various diseases, including tumors, immune diseases. Many epigenetic regulatory proteins have been identified as potential disease targets, but few epigenetic drugs are approved for clinical usage such as azacitidine, decitabine, vorinostat, and romidepsin, belinostat, panobinostat, chidamide.

Table 1. Small molecules and target pathways (2)

Small molecules	Target pathways
Afatinib	EGFR, ErBb 2/4
Axitinib	VEGFR 1/2/3, PDGFRβ, Kit
Bosunitib	BCR-Abl, Src, Lyn, Hck
Caozantinib	RET, c-Met, VEGFR1/2/3, Kit, Trkβ, Flt3, Axl, Tie2
Ceritinib	ALK, IGF-1R, InsR, ROS1
Crizotinib	ALK, c-MET (HGFR), ROS1, MST1R
Dafrafenib	B-Raf
Dasatinib	BCR-Abl, Src, Lck, Lyn, Yes, Fyn, Kit, EphA2, PDGFRβ
Erlotinib	EGFR
Everolimus	FKBP12/mTOR
Gefitinib	EGFR, PDGFR
Ibrutinib	BTK
Imatinib	BCR-Abl, Kit, PGFR
Lapatinib	EGFR, Erb2
Lenvatinib	VEGFR1/2/3, FGFR1/2/3/4, PDGFRα, Kit, RET
Nilotinib	BCR-Abl, PDGFR, DDR1
Nintedanib	FGFR1/2/3, Flt3, Lck, PDGFRα/β, VEGFR1/2/3
Palbociclib	CDK4/6
Pazopanib	VEGFR1/2/3, PDGFRα/β, FGFR1/3, Kit, Lck, Fms, ltk
Ponatinib	BCR-Abl, BCR-Abl T3151, VEGFR, PDGFR, FGFR, EphR, Src, Kit, RET, Tie2, Flt3
Regorafenib	VEGFR1/2/3, BCR-Abl, B-Raf, B-Raf (V600E), Kit, PDGFRα/β, RET, FGFR1/2, Tie2, Eph2A
Ruxolitinib	JAK1/2
Sirolimus	FKBP12/mTOR
Sorafenib	B-Raf, CDK8, Kit, Flt3, RET, VEGFR1/2/3, PDGFR
Sunitinib	PDGFRα/β, VEGFR1/2/3, Kit, Flt3, CSF-1R, RET
Temsirolimus	FKBP12/mTOR
Tofacitinib	JAK3
Trametinib	MEK1/2
Vandetanib	EGFR, VEGFR, RET, Tie2, Brk, EphR
Vemurafenib	A/B/C-Raf, B-Raf (V600E)

EGFR: Epidermal growth factor receptor, VEGFR: Vascular endothelial growth factor receptor, BCR: Breakpoint cluster region, PDGFR: Platelet-derived growth factor receptor, mTOR: Mammalian target of rapamycin

EZH2 Inhibitors

Enhancer of zeste homolog 2 (EZH2) is a member of histone methyltransferase and acts on DNA with methylation. EZH2 is frequently mutated and overexpressed in various cancers such as prostate cancer (31). This enzymatic change can be crucial for oncogenesis so the inhibition of EZH2 has been thought of as an alternative for the treatment of cancer patients. DZNep is a non-specific EZH2 inhibitor. Although treatment with DZNep showed significant antitumor activity in various preclinical studies, drug resistance is a major problem often due to EZH2. Tazemetostat and lirametostat are members of this family.

HDAC Inhibitors

HDACs are major epigenetic regulators that remove the acetyl groups from the N-acetylated lysine residues of histones. These alterations can act to the transcription of oncogenes and tumor suppressor genes, which are associated with proliferation, apoptosis, differentiation, migration, and cancer angiogenesis (32). HDAC inhibitors have been suggested to be effective for the treatment of cancer patients. Recently, a few HDAC inhibitors have been approved or are undergoing clinical trials. Vorinostat, romidepsin, belinostat, tucidinostat, and panobinostat are members of this family.

IDH1/2 Inhibitors

Isocitrate dehydrogenases (IDH1, IDH2, and IDH3) are important enzymes that catalyze the conversion of isocitrate to α-ketoglutarate using nicotinamide adenine dinucleotide phosphate ($NADP^+$) or NAD^+ as a cofactor in the tricarboxylic acid cycle (33). Enasidenib and ivosidenib are the members of this group.

BCL-2 Inhibitors

The B-cell lymphoma 2 (BCL-2) family of proteins consists of more than 20 members and includes three subfamilies (antiapoptotic proteins, proapoptotic proteins, and cell death mediators) (34). BCL-2 family proteins regulate the apoptosis and survival. Abnormality of the apoptosis is common in cancer. BCL-2 was first discovered as an inhibitor of apoptosis, after that BCL-2 inhibitors were tried for cancer treatment (35). These agents inhibit the anti-apoptotic effect of BCL-2 and promote apoptosis. Drug resistance is the main problem with this treatment. Mutations of the BCL-2 family members or pro-apoptotic proteins BAX and BAK can be effective in resistance development (36). Today, combination therapy with conventional chemotherapy is the main strategy to overcome resistance. Venetoclax, obatoclax, navitoclax, and gossypol are members of this family.

Hedgehog (Hh) Pathway Inhibitors

The Hh signaling pathway plays a key role in embryonic development and tissue regeneration. The Hh pathway contains both canonical and non-canonical parts (37). Hh ligand upregulation and transmembrane receptor Patched-1 or transmembrane transducer protein smoothened (SMO) mutations can activate the Hh signaling pathway. Abnormal activation of the Hh pathway is related to the oncogenesis

and progression due to activation of the glioma-associated oncogene transcription factors. SMO inhibitors have shown significant antineoplastic activity. This pathway may be a more attractive target for cancer therapy. Nowadays, three Hh pathway inhibitors have been approved for clinical usage such as glasdegib, vismodegib and sonidegib. High-dose itraconazole was effective in the treatment of prostate cancer due to Hh signaling inhibition rather than an anti-androgen effect (38).

Proteasome Inhibitors

Proteasomes are multi-catalytic enzymes that are expressed in the cells and are responsible for protein degradation (39). The ubiquitin-proteasome system (UPS) plays a major role in cellular protein homeostasis and regulates cell survival, signal transduction, DNA repair, and antigen presentation (40). Toxic proteins are tagged by ubiquitin and destructed to peptides by the proteasome complex. Abnormality of the UPS are related to many cancers (41). For this reason, targeting UPS can be as a potential treatment strategy. Bortezomib and carfilzomib (epoxomicin) are approved proteasome inhibitors for treating cancer patient. In contrary to bortezomib, carfilzomib is an irreversible inhibitor. Proteasome inhibitors are preferable for combination therapy with other group inhibitors for drug resistance (42). Ixazomib is the other member of this group.

PARP Inhibitors

Genomic instability is one of the main features of tumor cells. Genomic integrity can be achieved with DNA repair systems that include repair of double-strand breaks (DSBs), repair of single-strand breaks (SSBs), homologous recombination and non-homologous end-joining repair, base excision repair, nucleotide excision repair, mismatch repair (MMR). Poly (ADP-ribose) polymerases (PARPs) are a group of multifunctional post-translational modification enzymes that affect DNA repair, transcription, mitosis, and cell cycle regulation (43). Inhibition of the DNA repair pathway in cancer cells may have a lethal effect. The PARP enzyme family contains different proteins such as PARP1. It has an important role in the repair of DNA SSBs. *BRCA1* and *BRCA2* are the main tumor suppressors that repair DNA double (DSBs). Therefore, PARP inhibition in *BRCA*-mutant cancers can induce synthetic mortality of cancer cells due to the blockade of both DSB and SSB repair pathways. Poly (ADP-ribose) polymerase inhibitor (PARPi) targets *BRCA* mutant cancer cells. The interaction between *BRCA* and PARP is a form of synthetic mortal effect, which means the simultaneously functional loss of two genes leads to cell death (44). Currently, four PARP inhibitors (olaparib, rucaparib, niraparib, and talazoparib) have been licensed by the authorities. The efficacy of PARP inhibitors in cancer treatment is not only used for *BRCA1/2* mutant patients. Platinum sensitivity has also been reported as a prospective indicator for predicting the response to these inhibitors (45). Olaparib and rucaparib camsylates inhibit PARP 1/2/3 and have been approved for treating prostate cancer. Adverse events in this group included anemia, nausea, decreased appetite, and fatigue. FDA approved olaparib for patients with germline or somatic homologous recombination repair gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with *BRCA1/2* alterations.

Rucaparib has been approved for patients with *BRCA1/2* mutations (germline and/or somatic) who have been treated with alternative AR-targeted agents and taxane-based chemotherapy (46).

Other Inhibitors in Targeted Therapy

HSP90 Inhibitors

HSP90 heat shock protein stabilizes various proteins required for the survival of cancer cells. HSP90 is a molecular chaperone and affects to several sets of signaling proteins critical for cell growth and survival (47). Several HSP90-inhibitor clinical trials are ongoing for treating many cancers. HSP 90 inhibitors are geldanamycin, radicicol, 17AAG, and luminespib.

Metalloproteinase Inhibitors

Matrix metalloproteinases (MMPs) belong to a family of zinc-dependent neutral endopeptidases (48). These enzymes can break down connective tissue. The expression of MMPs is increased in various pathological conditions such as cancer invasion, metastasis, and angiogenesis. In the context of this effect, many MMPs inhibitors are undergoing research for cancer treatment.

Neovastat inhibits MMPs 2/9/12, VEGFR2, and has been approved for advanced RCC treatment (49). Another a mmp, prinomastat, inhibits MMPs 2/3/9/13/14 and can be used for treating advanced RCC. Rebimastat, cipemastat, ilomastat, batimastat, periostat, tanomastat are other members of this family.

AR Pathway Targetting Agents

As we well know, we have had many drugs for treating prostate cancer since the discovery of the androgen signaling axis by Huggins. The overexpression of androgens and AR is related to prostate carcinoma. In castrate-resistance prostate cancer (CRPC), the intracellular androgen level is increased compared to androgen-sensitive cells and an over-expression of the AR has been observed, suggesting an adaptive mechanism (50). This founding has led to the development of several new compounds targeting the androgen axis. In addition to GnRH agonists (leuprolide acetate, goserelin, buserelin, nafarelin, triptoferin) or antagonists (ganirelix, degarelix, relugolix, cetrorelix), many drugs act on AR such as *bicalutamide, darolutamide, apalutamide, enzalutamide, flutamide, nilutamide* for treating prostate cancer. mCRPC, abiraterone acetate plus prednisolone and enzalutamide have been approved. In addition to androgen depletion therapy with castration, abiraterone acetate plus prednisolone, apalutamide and enzalutamide have been approved for treating metastatic hormone-sensitive PCa (mHSPC). *The abiraterone acetate* inhibits the cytochrome p450 17A1 (CYP17A1) enzyme that is hydroxylase (a combination of 17α-hydrolase and 17,20-lyase inhibition) and thereby is a key enzyme in the steroidogenic pathway that produces progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens. The abiraterone acetate decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level and inside

the cancer cells (intracrine mechanism). The abiraterone acetate must be used together with prednisone/prednisolone to prevent drug-induced hyperaldosteronism (51). Adverse events of this therapy are fluid retention, edema, and hypokalemia due to mineralocorticoids. Apalutamide, darolutamide, enzalutamide are novel non-steroidal anti-androgens with a higher affinity for the AR receptor than bicalutamide. These AR antagonists have been licensed for non-metastatic CRPC (nmCRPC) at a high risk of metastasis (52,53,54).

While previous non-steroidal anti-androgens still allow the transfer of ARs to the nucleus and would act as partial agonists, all three agents also block AR transfer and therefore suppress any possible agonist-like activity. In particular, in preclinical studies, darolutamide showed not to cross the blood-brain barrier (55,56).

However, clinical trials of new agents are ongoing on this pathway such as zopratelin doxorubicin. Zoptarelin doxorubicin is a cytotoxic hybrid molecule linking doxorubicin to an LHRH analog that selectively targets doxorubicin to cancer cells expressing LHRH-R.

Mitoxantrone is an inhibitor of topoisomerase II and a combination of mitoxantrone and prednisone has been approved as a second-line treatment for metastatic hormone-refractory prostate cancer. It inhibits protein kinase C activity. The first-line treatment for this disease is a combination of docetaxel and prednisone.

PSMA-based Therapy

PSMA PET can be used as a diagnostic tracer of metastases or for therapeutic purposes (theranostics) (57). 68gallium-labeled PSMA is a diagnostic isotope. Moreover, therapeutic radiopharmaceuticals labeled with beta (lutetium-177 or yttrium-90) or an (actinium-225) emitting isotopes could be used to treat metastatic PCa. Clinical trials with these agents are ongoing.

RANK Ligand Inhibitors

Denosumab is a human monoclonal antibody against RANKL (receptor activator of nuclear factor kappa-B ligand). RANKL is a mediator of osteoclast formation, function, and survival. In M_0 CRPC, denosumab has been associated with increased bone-metastasis-free survival (58).

Monoclonal Antibody Therapies

The immune response contains different cytokines such as ILs, interferons, and chemokines. As is well known, high-dose IL-2 treatment in metastatic RCC has modest successes and serious adverse events. Currently, IL-2 treatment is not first preferable in metastatic RCC due to adverse effects. Cancer immune editing is the process is regulated by immune checkpoints and immune checkpoint inhibitors (ICIs) are now indicated in some types of cancer types. Immune checkpoints are key regulators of the immune system. Checkpoint proteins, such as B7-1/B7-2 on antigen-presenting cells and cytotoxic T lymphocytes-4 (CTLA-4) on T-cells, help keep the immune responses homeostasis. The binding of B7-1/B7-2 to CTLA-4 keeps the T-cells in an inactive state while blocking the binding of B7-1/B7-2 to CTLA-4 whilst an ICI (anti-CTLA-4 antibody) allows the T-cells to be active and to kill tumor cells. Nowadays, T-cell immune checkpoint (CTLA4, PD-1) inhibitors are used to induce an immune response against cancer cells. T-cells are currently widely recognized as the key mediators of antitumor efficacy with ICI treatment. Normally, PD-L1 binds to PD-1 and inhibits the T-cell killing of tumor cells in addition to the T-cell receptor-antigen complex, contrary to that blocking PD-L1 or PD-1 allows the T-cell killing of tumor cells.

Today, approved checkpoint inhibitors affect targets that CTLA4, programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). PD-1 is the transmembrane protein that interacts with PD-L1. Cancer-related upregulation of PD-L1 on the cell surface may inhibit T-cells. Antibodies that bind to either PD-1 or PD-L1 and therefore block the interaction, allow the T-cells to induce cell killing.

Cancer immunotherapy improves the survival and quality of life of patients. However, these therapies have some problems, such as adverse events and low efficacy. Immunotherapies are often limited by their immune-related adverse events such as autoimmunity, cytokine syndrome immune activation, and inflammatory responses against the healthy tissues. Therefore, finding the right combination of treatments to induce the optimal amount of immune activation and the tumor microenvironment remains an active area of clinical research. Tumor microenvironments have significant prognostic and predictive significance. The tumor microenvironment can affect the T-cell function and result in attenuated antitumor immune responses (59).

Targeting both cancer and T-cell metabolism can beneficially enhance immunity through metabolic checkpoints. In oncogenesis, over-dividing cancer cells require high glycolytic activity (Warburg effect) (60). This process generates high levels of lactate and metabolic wastes. The efficacy of ICIs can be affected by the metabolic pathways. Ligation of PD-L1 directly upregulates glycolysis in cancer cells by promoting glucose uptake and production of lactate, thus promoting growth and metastasis (61). However, the PI3K/AKT/mTOR pathway plays a critical role in integrating the metabolism signals of cancer and immune cells. Inhibition of this pathway with rapamycin, along with ICIs, enhances the cytotoxic effect and memory T-cell function (62). Other new targets such as amino acids (l-arginine, tryptophan, glutamine) and their metabolic pathways have become a promising strategy in cancer therapy (63). For example, indoleamine 2,3-dioxygenase-1 (IDO1)-selective enzyme inhibitor epacadostat along with pembrolizumab is under clinical trials due of its effect on tryptophan-kynurenine-aryl hydrocarbon receptor pathway (64).

Pembrolizumab and nivolumab belong to the PD-1 inhibitor family. Atezolizumab, avelumab, and durvalumab are examples of PD-L1 inhibitors, lastly, ipilimumab is a CTLA4 inhibitor (65).

PD-1 and PDL-1 Inhibitors

Pembrolizumab is an inhibitor of PD-1 proteins on the T-cells and helps the immune system kill cancer cells. It has been approved for the first-line treatment of advanced RCC in adults along with axitinib. Furthermore, it has been approved for treating locally advanced/metastatic urothelial carcinoma in adults

who have received prior platinum-containing chemotherapy as monotherapy. Another indication of pembrolizumab is the treatment of locally advanced/metastatic urothelial carcinoma in adults who are ineligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a combined positive score (CPS) ≥10 as monotherapy. The ICI pembrolizumab has been approved for all MMR-deficient cancers or in those with unstable microsatellite status (MSI-high) (66,67).

Nivolumab is another inhibitor of the PD-1 protein. It has been approved for first-line therapy for advanced RCC and second-line therapy for urothelial carcinoma (68). It is also used as a second-line treatment for RCC after anti-angiogenic treatment has failed. Nivolumab can be prescribed for locally advanced/metastatic forms of the conditions that experience disease progression during or following platinum-based chemotherapy or have progression within twelve months of neoadjuvant/adjuvant treatment with platinum-containing chemotherapy.

Atezolizumab is a PD-L1 inhibitor, a fully humanized engineered IgG1 monoclonal antibody. It can be prescribed for treating people with locally advanced/metastatic urothelial carcinoma who have disease progression during/following platinum-containing chemotherapy or have disease progression within twelve months of neoadjuvant/adjuvant treatment with platinum-containing chemotherapy. After atezolizumab failed a phase III trial for second-line bladder cancer, FDA altered the use of atezolizumab as a first-line treatment for metastatic bladder cancer in people who cannot receive cisplatin-based chemotherapy and have high levels of PD-L1 (69).

Durvalumab is a known as a checkpoint inhibitor drug. It is the human IgG1 kappa monoclonal antibody (IgG1k) that blocks the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1. It has been approved for adults with locally advanced or metastatic urothelial carcinoma who either have disease progression during/following platinum-containing chemotherapy or have disease progression within twelve months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (70).

Avelumab is another PD-L1 inhibitor. It is used to treat locally advanced/metastatic urothelial carcinoma whose disease progresses during/following first-line platinum-containing chemotherapy or within twelve months of neoadjuvant/adjuvant platinum-containing chemotherapy and maintenance treatment of patients with locally advanced cancer (71). Furthermore, avelumab along with axitinib has been approved for the first-line treatment of RCC.

Another monoclonal antibody, Indium (^{111}In) Capromab pendetide is a mouse monoclonal antibody that recognizes a protein found in prostate cancer. It is a diagnostic murine IgG1 and is used to imagine the extent of prostate cancer (72).

The other monoclonal antibodies are: *Rituximab* targets CD20 found on B cells and activates cell death. Trastuzumab binds to the HER2/neu (ErbB2) receptor. Alemtuzumab binds to CD52, which is a protein present on the surface of mature lymphocytes. Cetuximab and panitumumab target the EGFR and bevacizumab targets the circulating VEGF ligand.

Anti-CTLA-4 Antibodies

Ipilimumab is a monoclonal anti-CTL4 antibody that works to activate the immune system by targeting CTLA-4. CTLs can recognize and destroy cancer cells. However, there is also an inhibitory mechanism (CTL4 antibody) that interrupts this destruction and anti-CTL4 antibody drugs turn off this inhibitory mechanism and allow CTLs to continue to destroy the cancer cells. Ipilimumab is undergoing clinical trials for treating advanced bladder cancer and metastatic hormone-refractory prostate cancer (73). Nivolumab along with ipilimumab is indicated for treating intermediate or poor risk, previously untreated advanced RCC (68).

Tremelimumab is a humanized monoclonal anti-CTLA-4 antibody (74). It is undergoing clinical trials for treating advanced bladder cancer with a durvalumab combination.

Treatment protocols for renal cancer, bladder cancer, prostate cancer, and testis cancer are summarized in Table 2-5.

Combination Therapies

Combination therapies are new therapy modalities for increasing the efficacy of cancer treatment with used chemotherapy, and ICIs in different regimes. Combining therapy can obtain costimulatory (agonist antibodies) and coinhibitory (antagonist antibodies) effects. Moreover, in some studies, high response rates to chemotherapy have been documented after ICIs failure (75). This additive effect can be expanded with checkpoint inhibitors, personalized cancer vaccines and novel-targeted therapies directed at the tumor microenvironment, tumor metabolism, and the host microbiome.

The first combination therapy model was used to CTLA-4 and PD-1 inhibition together. The combination use of ipilimumab and nivolumab has been approved for first-line therapy for advanced RCC. The other, durvalumab and avelumab, are anti-PD-1/PD-L1 checkpoint inhibitors that can be used in combination to treat advanced bladder cancer.

The second model is the combination of small-molecule targeted drugs with immunotherapy such as PD-1 antibody. Lenvatinib/pembrolizumab combination therapy has been approved for treating advanced or metastatic RCC. The combination of pembrolizumab with another small molecule anti-angiogenesis agent, axitinib, has been approved for the first-line treatment of advanced RCC (76,77).

The third model is the combination of ADC. Until then today, several ADC molecules have been developed. With the improvement of antibody-conjugated technology, ADC drugs such as polatuzumab vedotin-piiq, enfortumab vedotin-ejfv, fam-trastuzumab deruxtecan-nxki, sacituzumab govitecan-hziy, and belantamab mafodotin-blmf have been developed (78,79,80). Enfortumab vedotin is a new ADC agent used for locally advanced or metastatic urothelial cancer that has received a PD-1 or PD-L1 inhibitor and a platinum-containing therapy.

The other technology is PROTAC, includes uses the small molecules that recruit target proteins for ubiquitination and removal by the proteasome (81). These agents reduce the activity of target proteins by catalytic degradation. Currently, two

drugs (ARV-110 and ARV-471) designed by PROTAC technology have entered clinical trials (81). ARV-110 mediates specifically AR degradation and has been used for treating patients with metastatic CRPC (82). The other, ARV-471, is an endoplasmic reticulum protein degrading agent.

Lastly, synthetic lethality means that the inactivation of both genes simultaneously by gene mutation/deletion or pharmacological inhibition leads to cell death (83). This technology is aimed at rearranging genes by gene-editing tools. Oncogenes or tumor suppressor genes can be targeted with gains or losses. Therefore, synthetic lethality has promising potential to drive the discovery of new anti-cancer targets and subsequently the development of effective drugs or combination strategies that are still needed for treating cancers. There are the synthetic lethal interaction of combined BCL-XL and MEK inhibition in KRAS-mutant cancer models and the successful clinical application of PARP inhibitors in BRCA mutant cancer (44,84).

Tumor-Specific Vaccines

Recent studies have shown that personalized neoantigen-based tumor-specific vaccines hold considerable promise in the context of targeted therapy. Most cancer vaccines have failed for many potential reasons, including an improper selection of a target antigen. The most widely known are Oncophage and Sipuleucel-T vaccines. Oncophage is an autologous personalized cancer vaccine heat shock protein-peptide complex-9 (HSPPC-96). It has been derived from a patient's tumor by extracting heat shock protein 96. It boosts the anticancer immune response against RCC (85). The other one, Sipuleucel-T is a therapeutic vaccine as autologous cellular immunotherapy. It boosts anti-prostate cancer adaptive immune response of (86).

Toll-like Receptors (TLRs)

TLRs are receptors that recognize various pathogen-associated molecular patterns. They are key components of innate immunity which are activated in response to pathogens and non-pathogenic components of damaged tissues. TLR agonists have been developed to treat cancers by upregulating the innate immune system. In contrast, TLR antagonists may be used to treat several inflammatory conditions. TLR agonists used as single agents, especially when applied locally, can effectively eradicate tumors due to their potent stimulation of innate and adaptive immunity and their effects on the tumor microenvironment. Two TLR agonists, Bacillus Calmette-Guerin and imiquimod, have been approved for clinical use as monotherapy for cancer (87).

However, new target agents are undergoing clinical trials such as dianhydrogalacticol (VAL-083) or vintafolide. VAL-083 is a bifunctional alkylating agent that induces interstrand DNA cross-links targeting the DNA. Vintafolide is drug conjugate consisting of a small molecule targeting the folate receptor (88).

Nowadays, to deal with the major challenges of targeted anti-cancer drugs, many strategies have been applied, such as new generation anti-cancer drugs against drug resistance mutations, multitarget drugs, combination therapy, and drugs targeting CSCs (89,90). CSCs are new targets for treating cancer such as salinomycin. Moreover, some small-molecule inhibitors against miRNAs have been suggested in many types of research for cancer treatment. Furthermore, some proteins may be attractive anti-cancer targets. For example, KRAS is the most frequently mutated isoform of the RAS proto-oncogene, which has a predominant role in driving the initiation and progression of cancers (91). In addition to KRAS, novel targets can be described for anticancer therapy as myc proto-oncogene, phosphatases, and protein-protein interactions (92,93,94).

Conclusion

In summary, small-molecule targeted drugs and monoclonal antibodies will continue to be the alternative options in cancer treatment because of their advantages. With a better understanding of oncogenesis and the evolution of new drug R&D technologies (ADC, PROTAC) new targeted therapy drugs targeting new genes or mechanisms of action will be developed in the near future.

Table 2. Targeted therapies for treating RCC (95)			
First-line therapy for clear cell histology			
Risk	**Preferred regimens**	**Other regimens**	**Useful in certain circumstances**
Favorable	Axitinib + Pembrolizumab Cabozantinib + Nivolumab Lenvatinib + Pembrolizumab	Axitinib + Avelumab Cabozantinib Ipilimumab + Nivolumab Pazopanib Sunitinib	Axitinib High dose IL-2
Poor/intermediate	Axitinib + Pembrolizumab Cabozantinib + Nivolumab Lenvatinib + Pembrolizumab Cabozantinib	Axitinib + Avelumab Pazopanib Sunitinib	Axitinib High dose IL-2 Temsirolimus
Subsequent therapy for clear cell histology			
	Cabozantinib Lenvatinib + Everolimus Nivolumab	Axitinib Axitinib + Pembrolizumab Cabozantinib + Nivolumab Ipilimumab + Nivolumab Lenvatinib + Pembrolizumab Pazopanib Sunitinib Tivozanib Axitinib + Avelumab	Everolimus Bevacizumab High dose IL-2 Sorafenib Temsirolimus
Therapy for non-clear cell histology			
	Cabozantinib Sunitinib	Lenvatinib + Everolimus Nivolumab Pembrolizumab	Axitinib Bevacizumab Bevacizumab + Erlotinib Bevacizumab + Everolimus Erlotinib Everolimus Pazopanib Temsirolimus
RCC: Renal cell carcinoma			

Table 3. Targeted therapies for treating urothelial carcinoma (96)	
Adjuvant therapy	
No previous platinum-based neoadjuvant therapy (pT3, pT4a, pN+)	Other recommended regimes: After the chemotherapy regimes nivolumab
Previous platinum-based neoadjuvant therapy (ypT2-ypT4a or ypN+)	Nivolumab
First-line systemic therapy for locally advanced/metastatic disease (Stage IV)	
Cisplatin eligible	Chemotherapy followed by avelumab maintenance therapy
Cisplatin ineligible	Chemotherapy followed by avelumab maintenance therapy Atezolizumab (only for tumors express PD-L1 or who are ineligible for any platinum-containing chemotherapy regardless of PD-L1 expression) Pembrolizumab (for locally advanced or metastatic urothelial carcinoma who are ineligible for any platinum-containing chemotherapy)
Second-line systemic therapy for locally advanced/metastatic disease (Post platinum stage IV)	
Preferred regimen	Pembrolizumab
Alternative regimens	Nivolumab Avelumab Erdafitinib (or post checkpoint inhibitors) Enfortumab vedotin ejfv (or post checkpoint inhibitors)
Subsequent-line systemic therapy for locally advanced/metastatic disease (Stage IV)	
	Enfortumab vedotin ejfv Erdafitinib

Table 4. Targeted therapies for treating prostate cancer (97)	
Systemic therapy for castration naive prostate cancer	
Abiraterone Apatulamide Enzalutamide	
Systemic therapy for M0 castration resistance prostate cancer (CRPC)	
Apatulamide Enzalutamide Darolutamide	
Systemic therapy for M1 castration resistance prostate cancer (CRPC)	
No prior docetaxel/no prior novel hormone therapy	Abiraterone Enzalutamide Sipuleucel T
Prior novel hormone therapy/no prior docetaxel	Sipuleucel T Olaparib (for HRRm) Pembrolizumab (for MSI-H, dMMR, or TMB 10 mut/Mb) Rucaparib (BRCAm) Abirateron+dexamethasone Enzalutamid
Prior docetaxel/no prior novel hormone therapy	Abirateron Enzalutamide Mitoxantrone Pembrolizumab (for MSI-H, dMMR, or TMB 10 mut/Mb) Sipuleucel T
Prior docetaxel and prior novel hormone therapy	Olaparib (for HRRm) Pembrolizumab (for MSI-H, dMMR, or TMB 10 mut/Mb) Mitoxantrone Rucaparib (BRCAm) Abirateron Enzalutamide

Table 5. Targeted therapies for treating testis cancer (98)	
Third-line therapy for metastatic germ cell tumors	
Post first and second-line chemotherapy regimes	Pembrolizumab (for microsatellite instability-high (MSI-H)/double mismatch repair (dMMR) or Tumor mutational burden high (TMB-H) tumors

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Short Quiz

1- Which one is not PD-1 and PDL-1 inhibitor?

A) Pembrolizumab
B) Nivolumab
C) Bevacizumab
D) Atezolizumab
E) Avelumab

Answer: C

2- Which one is not receptor tyrosine kinase inhibitors (TKIs)?

A) c-Met inhibitors
B) BCL-2 inhibitors
C) FLT3 inhibitors
D) EGFR inhibitors
E) ALK inhibitors

Answer: B

3- Which one does not act on androgen receptors?

A) Darolutamide
B) Apalutamide
C) Enzalutamide
D) Abiraterone Acetate
E) Flutamide

Answer: D