Editorial
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Drugs Approved for Renal Cancer

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Editorial

Kidney cancer is among the ten most common cancers in both men and women, representing 3.7% of all new cancer cases [1]. Renal cell carcinoma (RCC) is the most common form of kidney cancer and is responsible for up to 85% of cases; it is more frequent in men than in women (ratio, 1.7:1), and most people are older, with an average age of 64 years [2,3]. Over the last decade, improved understanding of pathways implicated in the unique biology of renal cell carcinoma (RCC) has fueled the development of several new approaches to treatment for this malignancy. It led to the development of tyrosine kinase inhibitors; mammalian target of rapamycin inhibitors; and, more recently, targeted immunotherapies such as checkpoint inhibitors. In this article, we discuss the mechanism of action of various US FDA approved therapies for treatment of RCC (Table 1).

Kinase Inhibitors

Various approved kinase inhibitors include Everolimus, Temsirolimus, Axitinib, Sorafenib, Pazopanib, Sunitinib and Cabozantinib.

Everolimus and Temsirolimus are inhibitors of mTOR (mammalian target of rapamycin), a serine-threonine kinase, downstream of the PI3K/AKT pathway (Figure 1). The mTOR pathway is dysregulated in several human cancers. Everolimus and Temsirolimus bind to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation and inhibition of mTOR kinase activity. It results in reduced activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP), downstream effectors of mTOR, involved in protein synthesis. In addition, both compounds inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by both the compounds has been shown to reduce cell proliferation, angiogenesis, and glucose uptake *in vitro* and/or *in vivo* studies.

Axitinib has been shown to inhibit receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3). These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression (Figure 2 and 3). Sorafenib is a multikinase inhibitor and was shown to interact with multiple intracellular (CRAF, BRAF and mutant

Table 1: Drugs approved for treatment of renal cell carcinoma.

S. No.	Drug (Brand Name)	Year of FDA Approval	Line of Therapy
1	Aldesleukin (Proleukin)[a]	1992	First
2	Sorafenib Tosylate (Nexavar)	2005	Second
3	Sunitinib Malate (Sutent)	2006	First
4	Temsirolimus (Torisel)	2007	First
5	Everolimus (Afinitor)	2009	Second
6	Bevacizumab[a]	2009	First
7	Pazopanib HCl (Votrient)	2009	First/second
8	Axitinib (Inlyta)	2012	Second
9	Nivolumab[a]	2015	Second
10	Cabozantinib (Cabometyx)	2016	Second
11	Lenvatinib	2016	Second

[a]: Biologic therapy.

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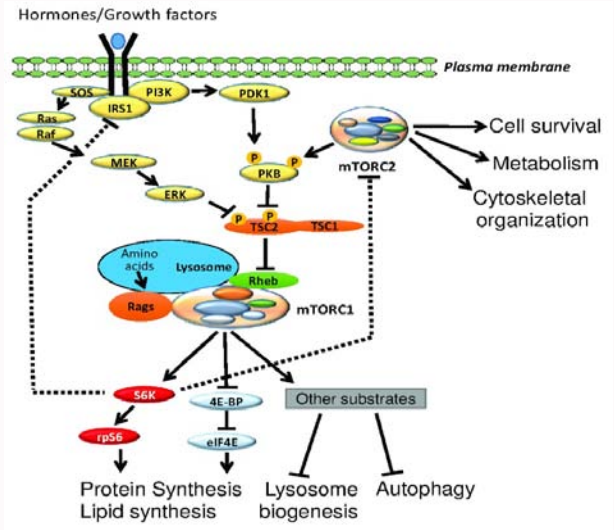

Figure 1: Schematic representation of signaling pathways involving mTOR complexes and various kinases. Typically, hormones and growth factors activate mTOR complex 1 (mTORC1) through the SOS/Ras/Raf-MEK-ERK (MAPK) or the IRS1/PI3K-PDK1-PKB pathways or both. mTORC2 also contributes to the activation of PKB through the direct phosphorylation of its turn motif as well as its hydrophobic motif. These pathways impinge on the tuberous sclerosis complex (TSC), which serves as a GTPase activator protein for the small G-protein Rheb. Upon inhibitory phosphorylation evoked by upstream kinases such as PKB, the activity of TSC is suppressed, promoting the accumulation of GTP-bound Rheb, which in turn activates mTORC1 on the surface of lysosomes. Amino acids also activate mTORC1 by bringing the latter onto lysosomes via the Rag GTPases. S6K-rpS6 and 4EBP1-eIF4E are the best-characterized mTORC1 downstream targets and are responsible for controlling a variety of anabolic effects driven by mTORC1. Dashed lines indicate feedback mechanisms. mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase [6].

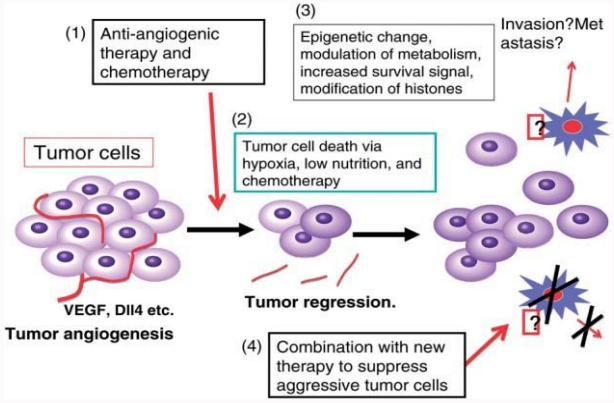

Figure 2: A hypothetical model of tumour responses to anti-angiogenic therapy. The VEGF-VEGFR system plays crucial roles in tumour angiogenesis. Therefore, anti-angiogenic therapy targeting VEGF signals efficiently suppresses cancer progression. However, during therapy, tumour cells may be subjected to hypoxia and/or low nutrient stresses for extended periods, and some of the cells may acquire epigenetic modifications and resistance to these stresses, resulting in a higher cell migration as well as an increased survival signal [7].

BRAF) and cell surface kinases (KIT, FLT- 3, VEGFR- 2, VEGFR- 3 and PDGFR- ß). Pazopanib is a multi- tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and β, fibroblast growth factor receptor (FGFR) -1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane

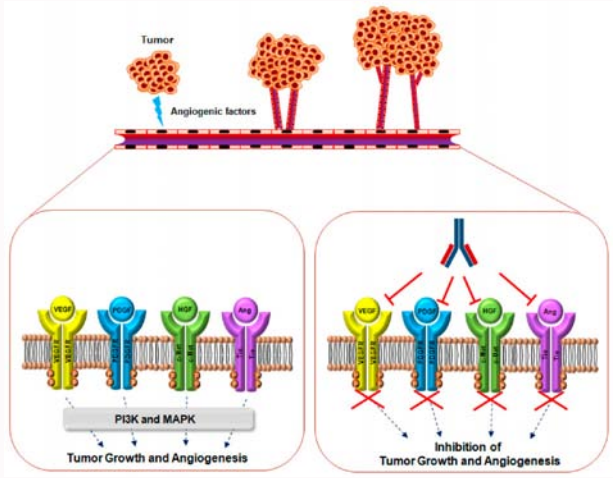

Figure 3: Mechanisms of action of monoclonal antibodies targeting VEGF, PDGF, HGF, Ang, and their receptors for suppressing tumor growth and angiogenesis. Under pathological conditions, including hypoxia, most tumor cells and/or adjacent cells up regulate the expression of many angiogenic factors, including VEGF, PDGF, HGF, and Ang, and secrete them within the tumor micro environment. When these molecules bind their cognate receptors, receptor dimerization and auto phosphorylation stimulate downstream signaling molecules including phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K)/v-Akt murine thymoma viral oncogene (Akt) and MAPK (dash lines) for the promotion of tumor growth and angiogenesis. Currently, most antibody therapeutics is being developed to block the interaction between agonists and their receptors (T arrows) [8].

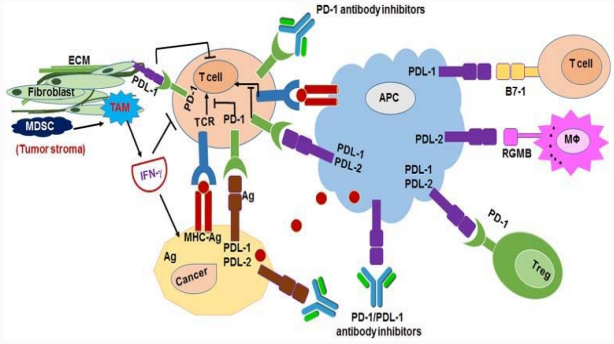

Figure 4: Mechanism of anti-programmed death 1 (PD-1) receptor and anti-programmed death ligand 1 (PD-L1)/L2 inhibitors mediated cancer immunotherapy. Antigen-presenting cells (APCs) bind to antigen (Ag) that released from tumor cells and T cells to activate T-cell receptor (TCR) and MHC binding. PD-L1 of tumor stroma interacts with PD-1 of T cells to suppress the T-cell mediated tumor cytotoxicity. Tumor associated macrophage (TAM), myeloid derived suppressor cells (MDSC) has crucial role in PD-1/PD-L1 mediated tumor immunosuppression [9].

glycoprotein receptor tyrosine kinase (c-Fms). Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Cabozantinib inhibits the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2.

Checkpoint Inhibitor

Nivolumab is the first approved PD-1 checkpoint inhibitor. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal

antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occur in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

Immune Modulator

Aldesleukin (recombinant IL-2; rIL-2) is a non-glycosylated interleukin-2 (IL-2) product. It is made via recombinant DNA technology that uses an *E. coli* strain containing an analog of the human IL-2 gene. The biological activity of aldesleukin is similar to that of endogenous IL-2. IL-2 is a type I cytokine belonging to a subfamily of cytokines that uses the common γ-chain receptor. Physiologically, IL-2 is produced in secondary lymphoid organs, primarily by CD4 cells, following activation by antigen. Once bound to the IL-2 receptor, IL-2 can activate multiple signaling pathways, including the JAK-STAT, PI3K-AKT, and MAPK pathways [4,5].

Monoclonal Antibody

Bevacizumab is a monoclonal antibody that binds to VEGF-A and prevents its interaction with VEGFRs, halting angiogenesis.

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