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Tumor Discovery

REVIEW ARTICLE

Hypoxia-inducible factor-1α inhibition in renal cell carcinoma

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Abstract

The tumorigenesis of clear cell renal cell carcinoma (ccRCC), an aggressive variant of renal cell carcinoma (RCC), is primarily attributable to the mutational inactivation of the Von Hippel–Lindau (VHL) gene. This mutation causes VHL syndrome, which is associated with tumor growth in various body parts, including the brain, spinal cord, eyes, adrenal glands, pancreas, kidney, and reproductive tract. RCC is the leading cause of death in patients with VHL syndrome. The VHL gene acts as a tumor suppressor that prevents the proliferation of various oncogenes by controlling the hypoxia-inducible factor (HIF). The HIF pathway is directly linked to the control of metabolic adaptation, cell proliferation, migration, angiogenesis, and apoptosis, which, in turn, is linked to ccRCC tumorigenesis. Consequently, many treatments have been developed to directly or indirectly inhibit HIF1α. Direct inhibition of HIF-1α was briefly explored but has not yet resulted in any treatment strategy approved by the Food and Drug Administration. Most prevalent are the indirect inhibitors targeting vascular endothelial growth factor receptors (VEGFR), the mammalian target of rapamycin (mTOR), and heat shock protein 90 (Hsp90). The VEGFR inhibitor category has the most FDA-approved drugs as they have been proven to be the most efficacious and safe early on. Thus, VEGFR inhibitors, along with mTOR inhibitors, have become the mainstay in RCC treatment. Most recently, therapies targeting HIF-2α inhibition have gained traction with FDA approval, whereas emerging therapies targeting direct inhibition of hsp90 have shown promise.

Keywords: Renal cell carcinoma; HIF-1α; HIF-2α; HIF-1α inhibitor; HIF-2α inhibitor; VEGF inhibitor; mTOR inhibitor

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1. Introduction

Renal cell carcinoma (RCC) originates from the kidney epithelium and constitutes approximately 2% of all cancers worldwide. Common risk factors include smoking, obesity, and hypertension (HTN), with approximately 2% being hereditary. The classic triad of RCC symptoms includes hematuria, abdominal pain, and a palpable mass, but most cases remain asymptomatic until advanced stages. Over 50% of RCCs are discovered incidentally, and 20 – 30% are metastatic at diagnosis. Metastases commonly occur in the lungs, bones, liver, and brain. Primary treatment is surgical resection, followed by medical therapy for locally advanced or metastatic disease as recurrence can

occur in 2 – 5% of patients without adjuvant treatment. Treatment can be challenging due to the poor response to chemotherapy and frequent recurrence.[1-3]

There are five types of RCCs: clear cell, chromophilic (papillary), chromophobic, oncocytic, and collecting duct. Clear cell RCC (ccRCC) is the most common, accounting for 75 – 85% of all RCCs.[3,4] Defects in the Von Hippel–Lindau (VHL) gene account for 60% of sporadic ccRCC cases. VHL is a tumor suppressor gene that regulates hypoxia-inducible genes (vascular endothelial growth factor [VEGF], transforming growth factor-alpha, and GLUT1) by controlling hypoxia-inducible factor (HIF).[2] HIF is a heterodimer that comprises alpha and beta subunits. HIF- is constitutively expressed, and unlike the alpha subunit, its expression is not influenced by oxygen levels in the cellular environment. In normoxic conditions, HIF-α is hydroxylated and acetylated for recognition by VHL. Once bound to VHL, HIF-α is ubiquitinated and targeted for proteasomal degradation, thus preventing the transcription of hypoxia-inducible genes. Under hypoxic conditions, the oxygen-dependent degradation domain senses the oxygen levels and interacts with the NH2-terminal transactivation domain to stabilize HIF-α; this prevents its recognition by VHL and subsequent degradation. Stabilized HIF-α translocates to the nucleus, dimerizes with HIF-β, and initiates gene transcription. The COOH-terminal transactivation domain binds co-activators to modulate HIF-α gene transcription. The HIF pathway regulates metabolic adaptation, cell proliferation, migration, angiogenesis, and apoptosis.[5,6] Loss of VHL results in the constitutive expression of HIF-α, which then leads to the overexpression of hypoxia-inducible genes and proliferation of epithelial cells.[2] HIF-α is encoded by three genes: HIF1-α, HIF2-α, and HIF3-α. HIF1-α and HIF2-α both respond to hypoxia and contribute to tumorigenesis when the HIF pathway is uncontrolled. The role of HIF3-α is less understood.[7]

VHL syndrome is an autosomal dominant familial cancer syndrome that is caused by mutations in the VHL gene on chromosome 3p.[3] This disorder occurs in 1/36,000 – 45,000 live births. Common manifestations of the disease include retinal and central nervous system (CNS) hemangiomas, ccRCC, pheochromocytomas, pancreatic neuroendocrine tumors, and endolymphatic sac tumors. Further, this syndrome can be diagnosed using one of the following three criteria: (1) the presence of at least two CNS/retinal hemangioblastomas; (2) the presence of at least one CNS/retinal hemangioblastoma and one other manifestation; or (3) at least one manifestation and a pathogenic mutation in the VHL gene or a first-degree relative with VHL syndrome. DNA sequencing and Southern blotting techniques can be used on peripheral leukocytes to detect VHL gene mutations. The disease usually manifests in patients in their 20s, with 95% of patients presenting with symptoms by the age of 34. The most common initial symptom is cerebellar hemangioblastomas, occurring in 35% of cases. RCC is rarely the first symptom, with only 7% of cases presenting RCC initially.[8] Genotype-phenotype correlations in VHL syndrome create subtypes based on the type of mutation in the VHL gene and disease features. Types 1A and 2B are associated with a higher incidence of RCC than the other types. In these cases, somatic inactivation of the VHL gene is the second requirement before progressing to malignancy.[9] RCC and renal cysts develop bilaterally and typically appear in patients in their 30s and 40s. By the age of 60, 70% of patients with VHL syndrome develop RCC. Hemangiomas and RCC are the leading causes of death in patients with VHL syndrome.[8]

RCC is highly vascularized tumors, tumors, primarily due to VHL mutations that activate the HIF pathway, leading to hyperactive angiogenesis.[10] These tumors exhibit elevated levels of HIF1-α. ccRCC shows the highest nuclear accumulation of HIF1-α among RCC types.[11] VHL gene mutations on chromosome 3p are present in over 80% of ccRCC cases, and more than 90% of all RCCs have a mutated or inactivated VHL gene. ccRCC is the most aggressive RCC subtype, and elevated HIF1-αα levels are linked to a poorer prognosis.[4,12] A study examining the correlation between HIF1-α levels and disease severity found that higher HIF1-α levels are linked to renal pelvis invasion, renal capsule rupture, and renal hilar invasion, along with increased nodal involvement. Patients with these characteristics had a worse prognosis and were more challenging to treat.[10] Another study investigated the survival of patients with RCC based on their HIF1-α expression levels. It was found that the median survival of those with high HIF1-α expression (>35%) was 13.5 months compared to 24.4 months for those with low HIF1-α expression (<35%).[11] In a study by Xu *et al*., downregulation of HIF1-α *in vitro* inhibited RCC cell growth, migration, and invasion, and induced caspase-dependent apoptosis. *In vivo* animal studies with downregulated HIF1-α RCC cell lines showed significant suppression of RCC cell proliferation, migration, and invasion under both normoxic and hypoxic conditions.[13] Overexpression of HIF1-α is associated with more aggressive biological behavior and reduced overall survival (OS).[14]

There are various treatments for RCC due to its poor response to traditional chemotherapy and its tendency to develop resistance. Inhibiting the HIF pathway has

garnered significant attention for its promising results in treating RCC and other cancers. The primary focus of these studies is on inhibiting the accumulation of HIF1-α or its downstream products. Direct HIF1-α inhibitors target the expression or function of HIF molecules by inhibiting mRNA expression, HIF protein synthesis, dimerization of the alpha and beta subunits, DNA binding with HIF, and HIF's transcriptional activities. Indirect HIF1-α inhibitors regulate molecules in the upstream or downstream pathways affecting HIF.[15] HIF2-α is another therapeutic target for RCC. Overexpression of HIF2-α promotes angiogenesis and tumor invasion, similar to HIF1-α, but complete loss of HIF2-α can also contribute to oncogenesis. Therefore, direct inhibitors of HIF2-α, which reduce its cellular concentration, are an appealing treatment for RCC. At present, HIF2-α inhibitors are used only in patients with VHL syndrome but show promise as an effective treatment for sporadic RCC.[7]

2. Methods

The initial search for articles was conducted through Google Scholar and PubMed using the keywords "Renal Cell Carcinoma," "RCC," "ccRCC," "HIF1-α," "HIF1-α inhibitor," "hypoxia-inducible factor," "VEGF inhibitor," and "VHL gene." Studies on drugs that inhibited HIF1-α and HIF2-α directly or indirectly and those on RCC were included in the study. The selected studies were further narrowed down to include studies on the treatment of locally advanced or metastatic RCC. Studies on HIF1-α inhibitors not targeting RCC, those conducted >2 years before FDA approval, and those not in English were excluded from the study.

3. Results

3.1. Direct HIF1-α inhibitors

Direct inhibition of HIF1-α impacts the expression or function of HIF molecules and is a less common therapeutic approach due to the numerous pathways controlled by HIF. At present, these therapies are not FDA-approved for RCC treatment, but several studies have investigated these drugs in combination with other approved treatments. These studies have shown promising results and could potentially be highly effective against RCC.[15,16]

3.2. VEGF inhibitors

The most commonly targeted molecules for treatment are the upstream and downstream components of the HIF pathway that can indirectly inhibit HIF1-α.[15] VEGF and VEGF receptor inhibitors are commonly used as targets for RCC treatment due to its the highly vascularized nature of these tumors. At present, there are eight FDA-approved RCC treatments in this category. The first drug in this category to receive FDA approval was sorafenib in 2005. Sorafenib is a tyrosine kinase inhibitor (TKI) of the VEGF receptor (VEGFR) that has been shown to delay progression and help preserve the patient's quality of life. In a trial study, sorafenib resulted in an OS that was 3.4 months longer than the placebo and an overall response that was 8% higher in patients with advanced RCC. Adverse events (AE) occurred in 13% of the patients, necessitating dose reduction. Some common AEs and toxicities of sorafenib include diarrhea (43%), rash (40%), hand-foot syndrome (30%), and HTN (17%).[17-19] The next drug to receive FDA approval was sunitinib in 2006, another VEGFR inhibitor similar to sorafenib, that replaced interferon-alpha (IFN-α) as the standard of care for RCC treatment. Compared with IFN-α, which has an average progression-free survival (PFS) of 5 months, sunitinib has an average PFS of 11 months. In patients with advanced RCC, sunitinib had an overall response rate that was 25% higher than IFN-α.[20-22] Patients receiving this therapy commonly presented with thrombocytopenia, leukopenia, neutropenia, fatigue, diarrhea, vomiting, and HTN. Considering the AEs and toxicities, 32% of the patients receiving sunitinib required dose reduction, and 38% needed a break in treatment.[23] Bevacizumab, an anti-VEGF antibody that targets and inhibits VEGFRs, was approved by the FDA in 2009. Compared with IFN-α alone, bevacizumab in combination with IFN-α had a longer PFS (10.2 vs. 5.4 months) and higher objective tumor response rates (31% vs. 13%).[17,24] Common Grade 3 or 4 AEs for bevacizumab include fatigue (35%), anorexia (17%), proteinuria (13%), and HTN (9%).[25] In 2009, pazopanib, a VEGFR inhibitor, was approved by the FDA for the treatment of metastatic RCC.[26] Compared with sunitinib, pazopanib had a longer PFS (9.8 vs. 4.3 months) and OS (14.4 vs. 8.9 months) but had a higher rate of treatment discontinuation due to toxicities (3% vs. 1%). Common side effects include aspartate transaminase (AST)/alanine transaminase (ALT) elevation, HTN, fatigue, anorexia, nausea, stomatitis, and diarrhea. The most common Grade 3 or 4 AEs are leukopenia, neutropenia, and ALT elevation.[27] Axitinib is a second-generation VEGFR inhibitor that was approved by the FDA in 2012 for the treatment of advanced RCC after one prior systemic therapy failure.[21,28] When used for the treatment of advanced ccRCC, axitinib in combination with avelumab, an anti-programmed death-ligand 1 antibody, showed antitumor activity and a longer PFS of 13.8 months compared with 8.4 months for sunitinib.[20] The most common Grade 3 or 4 AEs for patients receiving axitinib with avelumab were HTN (24.4%), diarrhea (5.1%), and fatigue (3%). Patients receiving axitinib combined with avelumab had similar

rates of Grade 3 and 4 AEs as those receiving sunitinib.[29] Cabozantinib was approved by the FDA in 2017 as the first-line treatment for advanced RCC.[30] In a trial that compared cabozantinib to sunitinib in patients with metastatic ccRCC, cabozantinib had a longer PFS (8.2 months vs. 5.6 months) and a significantly higher overall response rate (33% vs. 12%). The incidence of Grade 3 or 4 AEs was similar between the two groups. Among patients receiving cabozantinib, the most common Grade 3 or 4 AEs were HTN (28%), diarrhea (10%), palmar-plantar erythrodysesthesia (8%), and fatigue (6%).[31] Tivozanib was approved for advanced RCC after two or more prior systemic therapies.[32] Compared with sorafenib, tivozanib demonstrated improved PFS (11.9 vs. 9.1 months) and comparable OS (29.3 vs. 28.8 months) and ORR (33.1% vs. 23.3%) but lower rates of Grade 3 and 4 AEs (61% vs. 70%). Further, 4% of the patients on tivozanib had to discontinue treatment due to toxicities compared with 5% of those on sorafenib. The most common side effects of tivozanib are HTN, diarrhea, dysphonia, and palmar-plantar erythrodysesthesia. HTN (27%) and fatigue (5%) were the most common Grade 3 or 4 toxicities reported in patients on tivozanib.[33] Lenvatinib plus pembrolizumab, an immunotherapy, was approved by the FDA as the first-line therapy for advanced RCC in 2021.[34] Compared with sunitinib, the combination therapy of lenvatinib and pembrolizumab had greater PFS (23.9 vs. 9.2 months) and ORR (71% vs. 36%) but a higher rate of Grade 3 and 4 toxicities (82.4% vs. 71.8%). The most common AEs associated with lenvatinib and pembrolizumab were diarrhea, HTN, hypothyroidism, decreased appetite, and fatigue. The most common Grade 3 or 4 toxicities for the combination therapy were diarrhea, HTN, elevated lipase, and hypertriglyceridemia.[35] A comparison of FDA-approved treatments for RCC is outlined in Table 1. VEGF inhibitors provide many options for first-line treatment of RCC and initially have great results but patients commonly develop resistance and must switch to a different type of therapy.[21]

3.3. mTOR inhibitors

Indirect inhibitors of HIF1-α may also target upstream molecules to reduce its expression. Normally, VHL controls HIF1-α expression, but in cases of mutated VHL, as in RCC, this regulation fails.[36] mTOR activation increases HIF1-α expression and regulates cellular metabolism, growth, proliferation, and angiogenesis.[37,38] mTOR complex 1and mTOR complex 2 control HIF1-α expression; thus, inhibiting these complexes limit HIF1-α accumulation and block the G1-S cell cycle transition.[38,39] Besides promoting HIF1-α expression, mTOR stabilizes HIF1-α, allowing its nuclear translocation and accumulation. Rapamycin, an mTOR inhibitor, decreases HIF1-α stabilization and transcriptional activity in hypoxic cancer cells.[40] Temsirolimus, a single-agent mTOR inhibitor, has been FDA-approved since 2007 for first-line treatment of advanced RCC with poor prognosis. It has demonstrated improved PFS (3.8 vs. 1.9 months), OS (10.9 vs. 7.3 months), and ORR (8.6% vs. 4.8%) compared to IFN-α treatment. In addition, it resulted in fewer Grade 3 or 4 toxicities compared to IFN-α (67% vs. 78%).[1,36,41] Common AE with temsirolimus includes asthenia, rash, anemia, nausea, dyspnea, diarrhea, peripheral edema, hyperlipidemia, and hyperglycemia.[42] Everolimus, another mTOR inhibitor, was FDA-approved 2 years after temsirolimus for RCC treatment following VEGF-targeted therapy failure.[1,21,41] In a study of patients with metastatic RCC progression on VEGFR TKI, everolimus prolonged PFS (14.6 vs. 5.5 months) and OS (25.5 vs. 17.5 months) compared to placebo. The study also showed improved ORR (43% vs. 6%) in the everolimus arm. Despite prolonged survival, patients on everolimus had more AE/toxicities than the placebo arm (71% vs. 50%).[36] Motzer *et al.* found that anemia (12%), dyspnea (8%), hypertriglyceridemia (8%), and hyperglycemia (10%) are the most common Grade 3 or 4 AE in patients on everolimus.[43]

3.4. Hsp90 inhibitors

The accumulation of stabilized HIF1-α in the nucleus activates HIF signaling. Heat shock protein 90 (Hsp90), a chaperone molecule, ensures correct folding and protects HIF1-α from degradation.[40,44] Disruption of this association leads to ubiquitination and proteasomal degradation of HIF1-α.[45,46] Studies have shown that Hsp90 inhibitors lower HIF1-α protein levels regardless of the VHL status of the cells. Further, investigation of these drugs could lead to more effective treatments against RCC.[44,45]

3.5. HIF2-α inhibitors

HIF2-α is a major point of focus in research on RCC treatment and has emerged as a promising therapeutic target, including upstream proteins that regulate the concentration of HIF2-α. At present, there is one FDA-approved HIF2-α inhibitor. Belzutifan was approved for use in 2021 and has been used to treat tumors associated with VHL syndrome, including RCC, as an alternative to surgery for solid tumors.[47] This drug has demonstrated effectiveness in treating RCC in patients with VHL syndrome with an ORR of 49% and a 96% PFS at 24 months. The most common AEs for belzutifan include anemia, fatigue, headache, and dizziness. Although not yet approved for sporadic RCC, studies are underway to determine its efficacy for tumors other than those associated with VHL syndrome.[48]

Table 1. Comparison of HIF pathway inhibitors

Experimental arm	Therapy target	Approved use	PFS (months)	OS (months)	ORR	CRR	PRR	FDA Approval	AE	References
Sorafenib versus placebo	VEGF inhibitor	Advanced RCC	5.5 versus 2.8	19.3 versus 15.9	10% versus 2%	<1% versus 0%	10% versus 2%	2005	10% discontinued treatment; 13% required dose reduction	17-19
Sunitinib versus IFN-α	VEGFR inhibitor	Advanced RCC	11 versus 5	–	31% versus 6%	0% versus 0%	31% versus 6%	2006	38% required dose interruption; 32% required dose reduction	22,23
Bevacizumab +IFN-α versus single- agent IFN-α	anti-VEGF antibody	mRCC	10.2 versus 5.4	–	31% versus 13%	–	–	2009	Grade 3 or 4 – 79% versus 61%	21,24,25
Pazopanib versus sunitinib	VEGFR inhibitor	mRCC	9.8 versus 4.3	14.4 versus 8.9	36% versus 23%	0% versus 0%	36% versus 23%	2009	3% versus 1% discontinued treatment due to toxicities	26,27
Axitinib+ Avelumab (anti-PD-L1 antibody) versus sunitinib	VEGFR inhibitor	Advanced ccRCC after failure of one prior systemic therapy	13.8 versus 8.4	11.6 versus 10.7	55.2% versus 25.5%	4.4% versus 2.1%	50.7% versus 23.4%	2012	Grade 3 or 4 – 71.2% versus 71.5%	20,28,29
Cabozantinib versus sunitinib	VEGFR inhibitor	Advanced RCC	8.2 versus 5.6	30.3 versus 21.8	33% versus 12%	1.3% versus 0%	31.6% versus 12%	2017	Grade 3 or 4 – 67% versus 68%	30,31
Tivozanib versus sorafenib	VEGFR inhibitor	Advanced RCC following two or more prior systemic therapies	11.9 versus 9.1	29.3 versus 28.8	33.1% versus 23.3%	–	–	2021	Grade 3 or 4 – 61% versus 70%	32,33
Lenvatinib+ Pembrolizumab (immunotherapy) versus sunitinib	VEGFR inhibitor	Advanced RCC	23.9 versus 9.2	–	71% versus 36%	16.1% versus 4.2%	54.9% versus 331.9%	2021	Grade 3 or 4 – 82.4% versus 71.8%	34,35
Temsirolimus versus IFN-α	mTOR inhibitor	mRCC	3.8 versus 1.9	10.9 versus 7.3	8.6% versus 4.8%	–	–	2007	Grade 3 or 4 – 67% versus 78%	42
Everolimus+ Lenvatinib (VEGFR TKI) versus single-agent everolimus	mTOR inhibitor	RCC following prior TKI failure	14.6 versus 5.5	25.5 versus 17.5	43% versus 6%	2% versus 0%	41% versus 6%	2009	Grade 3 or 4 – 71% versus 50%	21,43
Belzutifan	HIF2-α inhibitor	VHL- syndrome associated solid tumors	96% at 24 months	–	49%	0%	49%	2021	Grade 3 or 4 – 15%	47,48

Abbreviations: CRR: complete response rate; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PRR: partial response rate; IFN-α: Interferon-alpha, VEGFR: Vascular endothelial growth factor receptor; TKI: Tyrosine kinase inhibitor; HIF: Hypoxia-inducible factor; RCC: Renal cell carcinoma; ccRCC: Clear cell renal cell carcinoma, mTOR: Mammalian target of rapamycin, VHL: Von Hippel–Lindau, AE: Adverse events.

4. Conclusion

The silent nature of RCC in its early stages makes early diagnosis difficult unless it is found accidentally. Consequently, many patients who are under treated for this disease have locally advanced or metastatic disease. In addition to late-stage diagnosis, the polymorphic nature of RCC and its propensity to develop drug resistance have made treatment challenging. Major advances have resulted from targeted therapies, beginning with sunitinib and, more recently, combination therapies of different types of targeted treatments. These developments have provided multiple options for first-line treatments for patients with metastatic disease. Although none of the current therapy lines are considered curative for mRCC, these drugs are promising in terms of improving patient outcomes. With the use of immunotherapies and targeted therapies such as HIF1-α inhibitors, VEGF inhibitors, and mTOR inhibitors, patients are living longer and enjoying a better quality of life than ever before.

Future research on RCC and its treatments could involve using machine learning to detect early signs of therapy failure and severe AE/toxicities, thereby personalizing treatment plans to enhance patients' quality of life during treatment. Studies of mitochondrial DNA across all RCC types may identify specific mutations linked to the diseases, leading to new potential drug targets. This review has limitations, including potential exclusions due to the keywords used in the initial search, which may have omitted studies with different terminologies. Publication bias may be present as only published studies were included in the study. In addition, restricting our search to English-language studies likely excluded an unknown percentage of published works. Focusing the review on therapies for advanced disease may have resulted in a lack of information on early-stage disease, which could have aided in understanding disease progression and early interventions.

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References

1. Bahadoram S, Davoodi M, Hassanzadeh S, Bahadoram M, Barahman M, Mafakher L. Renal cell carcinoma: An overview of the epidemiology, diagnosis, and treatment. *G Ital Nefrol*. 2022;39:2022-vol3.

2. Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med*. 2005;353(23):2477-2490.

   doi: 10.1056/NEJMra043172

3. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *N Engl J Med*. 1996;335(12):865-875.

   doi: 10.1056/NEJM199609193351207

4. Chen S, Wang Y, Xiong Y, *et al*. Wild-type IDH1 inhibits the tumor growth through degrading HIF-α in renal cell carcinoma. *Int J Biol Sci*. 2021;17(5):1250-1262.

   doi: 10.7150/ijbs.54401

5. Masoud GN, Li W. HIF-1α pathway: Role, regulation and intervention for cancer therapy. *Acta Pharma Sin B*. 2015;5(5):378-389.

   doi: 10.1016/j.apsb.2015.05.007

6. Weidemann A, Johnson RS. Biology of HIF-1alpha. *Cell Death Differ*. 2008;15(4):621-627.

   doi: 10.1038/cdd.2008.12

7. Toledo RA, Jimenez C, Armaiz-Pena G, Arenillas C, Capdevila J, Dahia PLM. Hypoxia-inducible factor 2 alpha (HIF2α) inhibitors: Targeting genetically driven tumor hypoxia. *Endocr Rev*. 2023;44(2):312-322.

   doi: 10.1210/endrev/bnac025

8. Chittiboina P, Lonser RR. Von Hippel-lindau disease. *Handb Clin Neurol*. 2015;132:139-156.

   doi: 10.1016/B978-0-444-62702-5.00010-X

9. Maher ER, Sandford RN. Von Hippel-lindau disease: An update. *Curr Genet Med Rep*. 2019;7(4):227-235.

   doi: 10.1007/s40142-019-00180-9

10. Medina Villaamil V, Aparicio Gallego G, Santamarina Caínzos I, Valladares-Ayerbes M, Antón Aparicio LM. Searching for Hif1-α interacting proteins in renal cell carcinoma. *Clin Transl Oncol*. 2012;14(9):698-708.

    doi: 10.1007/s12094-012-0857-4

11. Klatte T, Seligson DB, Riggs SB, *et al*. Hypoxia-inducible factor 1 alpha in clear cell renal cell carcinoma. *Clin Cancer Res*. 2007;13(24):7388-7393.

    doi: 10.1158/1078-0432.CCR-07-0411

12. Shen C, Beroukhim R, Schumacher SE, *et al*. Genetic and functional studies implicate HIF1α as a 14q kidney cancer suppressor gene. *Cancer Discov*. 2011;1(3):222-235.

    doi: 10.1158/2159-8290.CD-11-0098

13. Xu K, Ding Q, Fang Z, *et al*. Silencing of HIF-1α suppresses tumorigenicity of renal cell carcinoma through induction of apoptosis. *Cancer Gene Ther*. 2010;17(3):212-222.

    doi: 10.1038/cgt.2009.66

14. Tassoudi A, Stefanidis I, Eleftheriadis T, Tzortzis V, Tassoudis V, Ioannou M. Study of hypoxia induced factor-1alpha (HIF-1A) and carbonic anhydrase 9 (CAIX) in Clear Cell Renal Cell Carcinoma (ccRCC). *Arch Nephrol Urol*. 2021;4(2):50-62.

    doi: 10.26502/anu.2644-2833036

15. Fallah J, Rini BI. HIF inhibitors: Status of current clinical development. *Curr Oncol Rep*. 2019;21(1):6.

    doi: 10.1007/s11912-019-0752-z

16. Greenberger LM, Horak ID, Filpula D, *et al*. A RNA antagonist of hypoxia-inducible factor-1α, EZN-2968, inhibits tumor cell growth. *Mol Cancer Ther*. 2008;7(11):3598-3608.

    doi: 10.1158/1535-7163.MCT-08-0510

17. Costa LJ, Drabkin HA. Renal cell carcinoma: New developments in molecular biology and potential for targeted therapies. *Oncologist*. 2007;12(12):1404-1415.

    doi: 10.1634/theoncologist.12-12-1404

18. Drugs.com. *Nexavar FDA Approval History*. Available from: https://www.drugs.com/history/nexavar.html#:~:text=fda%20approved%3a%20yes%20%28first%20approved%20december%2020%2c%202005%29,for%3a%20renal%20cell%20carcinoma%2c%20hepatocellular%20carcinoma%2c%20thyroid%20cancer [Last accessed on 2024 Jul 14].

19. Escudier B, Eisen T, Stadler WM, *et al*. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2007;356(2):125-134.

    doi: 10.1056/NEJMoa060655

20. Kathuria-Prakash N, Drolen C, Hannigan CA, Drakaki A. Immunotherapy and metastatic renal cell carcinoma: A review of new treatment approaches. *Life* (*Basel*). 2021;12(1):24.

    doi: 10.3390/life12010024

21. Wiechno P, Kucharz J, Sadowska M, *et al*. Contemporary treatment of metastatic renal cell carcinoma. *Med Oncol*. 2018;35(12):156.

    doi: 10.1007/s12032-018-1217-1

22. Drugs.com. *Sutent* (*Sunitinib Malate*) *FDA Approval History*. Available from: https://www.drugs.com/history/sutent.html [Last accessed on 2024 Jul 14].

23. Motzer RJ, Hutson TE, Tomczak P, *et al*. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356(2):115-124.

    doi: 10.1056/NEJMoa065044

24. Summers J, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: Bevacizumab plus interferon for advanced renal cell carcinoma. *Oncologist*. 2010;15(1):104-111.

    doi: 10.1634/theoncologist.2009-0250

25. Rini BI, Halabi S, Rosenberg JE, *et al*. Bevacizumab Plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol*. 2008;26(33):5422-5428.

    doi: 10.1200/JCO.2008.16.9847

26. Gupta S, Spiess PE. The prospects of pazopanib in advanced renal cell carcinoma. *Ther Adv Urol*. 2013;5(5):223-232.

    doi: 10.1177/1756287213495099

27. Kim JH, Park I, Lee JL. Pazopanib versus sunitinib for the treatment of metastatic renal cell carcinoma patients with poor-risk features. *Cancer Chemother Pharmacol*. 2016;78(2):325-332.

    doi: 10.1007/s00280-016-3093-8

28. Tyler T. Axitinib: Newly approved for renal cell carcinoma. *J Adv Pract Oncol*. 2012;3(5):333-335.

    doi: 10.6004/jadpro.2012.3.5.7

29. Motzer RJ, Penkov K, Haanen J, *et al*. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380(12):1103-1115.

    doi: 10.1056/NEJMoa1816047

30. Center for Drug Evaluation and Research. *FDA Grants Regular Approval to Cabometyx for First-Line Treatment of Advanced Renal Cell Carcinoma*. U.S. Food and Drug Administration, FDA. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-cabometyx-first-line-treatment-advanced-renal-cell-carcinoma#:~:text=on%20december%2019%2c%202017%2c%20the,renal%20cell%20carcinoma%20(rcc) [Last accessed on 2024 Jul 14].

31. Choueiri TK, Halabi S, Sanford BL, *et al*. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: The alliance A031203 CABOSUN trial. *J Clin Oncol*. 2017;35(6):591-597.

    doi: 10.1200/JCO.2016.70.7398

32. Center for Drug Evaluation and Research. *FDA D.I.S.C.O.*

Burst Edition: FDA Approval of Fotivda (Tivozanib) for Adult Patients with Relapsed or Refractory Advanced Renal Cell Carcinoma Following Two or More Prior Systemic Therapies. U.S. Food and Drug Administration, FDA. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-fotivda-tivozanib-adult-patients-relapsed-or-refractory#:~:text=on%20march%2010%2c%202021%2c%20the,or%20more%20prior%20systemic%20therapies [Last accessed on 2024 Jul 14].

33. Motzer RJ, Nosov D, Eisen T, *et al*. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: Results from a Phase III trial. *J Clin Oncol*. 2013;31(30):3791-3799.

doi: 10.1200/JCO.2012.47.4940

34. Center for Drug Evaluation and Research. *FDA Approves Lenvatinib plus Pembrolizumab for Advanced Renal Cell Car*. U.S. Food and Drug Administration, FDA. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-plus-pembrolizumab-advanced-renal-cell-carcinoma [Last accessed on 2024 Jul 14].

35. Motzer R, Alekseev B, Rha SY, *et al*. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med*. 2021;384(14):1289-1300.

doi: 10.1056/NEJMoa2035716

36. Semenza GL. Evaluation of HIF-1 inhibitors as anticancer agents. *Drug Discov Today*. 2007;12(19-20):853-859.

doi: 10.1016/j.drudis.2007.08.006

37. Motzer RJ, Escudier B, Oudard S, *et al*. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372(9637):449-456.

doi: 10.1016/S0140-6736(08)61039-9

38. Kuroshima K, Yoshino H, Okamura S, *et al*. Potential new therapy of Rapalink-1, a new generation mammalian target of rapamycin inhibitor, against sunitinib-resistant renal cell carcinoma. *Cancer Sci*. 2020;111(5):1607-1618.

doi: 10.1111/cas.14395

39. Faes S, Demartines N, Dormond O. Mechanistic target of rapamycin inhibitors in renal cell carcinoma: Potential, limitations, and perspectives. *Front Cell Dev Biol*. 2021;9:636037.

doi: 10.3389/fcell.2021.636037

40. Diaz-Gonzalez JA, Russell J, Rouzaut A, Gil-Bazo I, Montuenga L. Targeting hypoxia and angiogenesis through HIF-1alpha inhibition. *Cancer Biol Ther*. 2005;4(10):1055-1062.

doi: 10.4161/cbt.4.10.2195

41. Onnis B, Rapisarda A, Melillo G. Development of HIF-1 inhibitors for cancer therapy. *J Cell Mol Med*. 2009;13(9A):2780-2786.

doi: 10.1111/j.1582-4934.2009.00876.x

42. Hudes G, Carducci M, Tomczak P, *et al*. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007;356(22):2271-2281.

doi: 10.1056/NEJMoa066838

43. Motzer RJ, Hutson TE, Glen H, *et al*. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: A randomised, phase 2, open-label, multicentre trial. *Lancet Oncol*. 2015;16(15):1473-1482.

doi: 10.1016/S1470-2045(15)00290-9

44. Bohonowych JE, Peng S, Gopal U, *et al*. Comparative analysis of novel and conventional Hsp90 inhibitors on HIF activity and angiogenic potential in clear cell renal cell carcinoma: Implications for clinical evaluation. *BMC Cancer*. 2011;11(1):520.

doi: 10.1186/1471-2407-11-520

45. Isaacs JS, Jung YJ, Mimnaugh EG, Martinez A, Cuttitta F, Neckers LM. Hsp90 regulates a von Hippel lindau-independent hypoxia-inducible factor-1α-degradative pathway. *J Biol Chem*. 2002;277(33):29936-29944.

doi: 10.1074/jbc.M204733200

46. Albadari N, Deng S, Li W. The transcriptional factors HIF-1 and HIF-2 and their novel inhibitors in cancer therapy. *Expert Opin Drug Discov*. 2019;14(7):667-682.

doi: 10.1080/17460441.2019.1613370

47. Deeks ED. Belzutifan: First approval. *Drugs*. 2021;81(16):1921-1927.

doi: 10.1007/s40265-021-01606-x

48. Jonasch E, Donskov F, Iliopoulos O, *et al*. Belzutifan for renal cell carcinoma in von Hippel-lindau disease. *N Engl J Med*. 2021;385(22):2036-2046.

doi: 10.1056/NEJMoa2103425