HIF-inhibitors in Renal Cell Carcinomas: A Review of Current Trials

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ABSTRACT

Hypoxia is common in solid tumors, due to poorly functional tumor vasculature and rapidly proliferating malignant cells outgrowing their blood supply.[1] Hypoxia-inducible factor 1 (HIF-1) and hypoxia-inducible factor 2 (HIF-2) inhibitors are a new experimental therapy in treating clear cell renal cell carcinomas (RCC)s. There are many clinical trials that have evaluated the inhibition of HIF-1/2α in human tumors.[2-11] Non-selective drugs targeting both HIF-1/2α have shown modest-to-disappointing results to date, but drugs selectively targeting HIF-2α have shown more promise in both preclinical and early human trials. This paper discusses the mechanisms of HIF-1/2α inhibitors as well as the current clinical trials studying both direct and indirect targeting/inhibition.

KEYWORDS: **Kidney cancer • Renal Cell Carcinoma • Hypoxia inducible factor • HIF-inhibitors • targeted therapy •**

INTRODUCTION

Hypoxia is common in all types of solid tumors, due to poorly functional tumor vasculature and rapidly proliferating malignant cells that outgrow their tenuous blood supply. But, the roles that hypoxia-inducible factor 1 (HIF-1) and hypoxia-inducible factor 2 (HIF-2) play in driving the development of clear cell renal cell carcinomas (RCC) are distinct, and have led to the creation of a new class of experimental targeted therapeutics aimed at inhibiting HIF. These new drugs are currently under investigation in several trials. If they gain regulatory authority approval as expected, they are likely to represent a new wave of targeted therapies for RCC.

HIF-inhibitors are HIF-1/2 are heterodimeric proteins that transactivate genes involved in many cancer processes including cell de-differentiation, genetic instability, pH regulation, invasion/metastasis, glucose metabolism, and resistance to chemotherapy[2, 3]. They are composed of oxygen sensitive α and β subunits, which are activated by hypoxia. They are often overexpressed in cancers due to intratumoral hypoxia as well as genetic mutations in oncogenes and loss-of-function in tumor-suppressor genes. Increased HIF-1α and HIF-2α levels are generally associated with treatment failure and increased mortality in cancer patients. Drugs that inhibit HIF create anti-tumor effects by stopping metastasis and resistance to antineoplastic therapies. Clinical trials are now underway to establish how these drugs can affect those with many various cancers, especially renal cell carcinoma.

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Molecular Basis

HIF-1α and HIF-2α each have two transactivation domains (TAD) on the NH2-terminal (N-TAD) and COOH-terminal (C-TAD). C-TAD interacts with the p300/CREB-binding protein (CBP) co-activators under hypoxic conditions, and N-TAD stabilizes HIF-α. HIF-1/2α is degraded through the von Hippel-Lindau protein (pVHL) pathway. Under normal conditions, HIFα is rapidly hydroxylated by prolyl hydroxylase (PHD), which mediates the binding by pVHL, and promotes degradation. Under hypoxia, PHD loses its activity, thus preventing VHL binding and HIF-1/2α can accumulate.

HIF-α Inhibitors for Cancer Therapy

Since the discovery of the HIF and its mechanisms, researchers have been utilizing downstream VEGF and mTOR pathways to directly and indirectly, target cancer. Targeted therapies that influence multiple mechanisms such as modulating expression, protein synthesis, protein accumulation and degradation, dimerization, and/or DNA binding and transcription by targeting the PI3K/AKT/mTOR pathways or the VEGF pathway

Renal Cell Carcinoma and HIF1/2-α

Renal cell carcinoma (RCC) is the most common kidney cancer in

Table 1 | Selected Current Trials of HIF-inhibitors in RCC Patients

TRIAL NAME	CLINICAL TRIAL ID	PHASE	INTERVENTION	PATIENT POPULATION	# OF SUBJECTS EXPECTED	RANDOMIZED	ASSIGNMENT	STATUS	EST COMPLETION	COUNTRIES	SPONSOR
A Phase 1b Adaptive Dose-Finding Study of ARO-HIF2 in Pts with Adv Clear Cell Renal Cell Carcinoma	NCT04169711	1	ARO-HIF2	Adv ccRCC	18	No	Sequential	Recruiting	Mar 30, 2022	USA	Arrowhead Pharma
A Phase 1, Multiple-Dose, Dose-Escalation Trial of PT2385 Tablets, a HIF-2a Inhibitor, in Pts with Adv Clear Cell Renal Cell Carcinoma	NCT02293980	1	PART 1: PT2385 PART 2: PT2385 in combination with nivolumab PART 3: PT2385 in combination with cabozantinib	Adv ccRCC	110	No	Single Group	Active, not recruiting	Nov 30, 2021	USA	Peloton Therapeutics
A Trial of PT2977 in Combination with Cabozantinib in Pts with Clear Cell Renal Cell Carcinoma	NCT03634540	2	Cohort 1: PT2977 in combination with cabozantinib in pts who have not received prior systemic therapy for ccRCC Cohort 2: PT2977 in combination with cabozantinib in pts who have not received prior immunotherapy & no more than 2 prior treatments	Adv ccRCC	118	No	Parallel	Recruiting	Aug 14, 2023	USA	Peloton Therapeutics
An Open Label Phase 2 Study to Evaluate PT2385 for the Treatment of Von Hippel-Lindau Disease-Associated Clear Cell Renal Cell Carcinoma	NCT03108066	2	PT2385	VHL associated ccRCC	25	No	Single Group	Active, not recruiting	Jun 15, 2021	USA	Peloton Therapeutics
A Phase 1, Multiple-Dose, Dose-Escalation and Expansion Trial of PT2977, a HIF-2α Inhibitor, in Pts With Adv Solid Tumors	NCT02974738	1	Part 1A: PT2977 for adv solid tumors Part 1B: PT2977 for adv ccRCC Part 2A: PT2977 for other specified solid tumors Part 2B: PT2977 for recurrent GBM who have been previously treated with radiation therapy and temozolomide	Adv ccRCC, Adv solid tumors, glioblastoma	125	No	Single Group	Active, not recruiting	Apr 14, 2023	No Locations Provided	Peloton Therapeutics
Proof of Concept for Lenvatinib and Everolimus Prior to Nephrectomy in Eligible Pts with Local and Metastatic Renal Cell Carcinoma (RCC)	NCT03324373	1	Lenvatinib & Everolimus prior to cytoreductive nephrectomy	Local and metastatic RCC	15	No	Single Group	Recruiting	Apr 30, 2021	USA	University of Iowa Hospitals and Clinic, Eisai Inc
Phase 2 Study of MK-6482 in Participants with Adv Renal Cell Carcinoma	NCT04489771	2	Dose A: Standard dose of MK-6482 Dose B: Higher dose of MK-6482	Adv RCC with clear cell component	150	Yes	Parallel	Recruiting	Oct 4, 2025	USA, Israel	Merck
An Open-label, Randomized Phase 3 Study of MK-6482 Versus Everolimus in Participants with Adv Renal Cell Carcinoma That has Progressed After Prior PD-1/L1 and VEGF-Targeted Therapies	NCT04195750	3	Experimental: 120 mg of MK-6482 orally once daily Active Comparator: 10 mg Everolimus orally once daily	Adv RCC	736	Yes	Parallel	Recruiting	Sep 17, 2025	USA and others*	Merck

adults and accounts for 3% of all malignancy, with more men than women being affected. Surgical resection, when feasible, is recommended as a potentially curable option, but many patients with advanced and metastatic RCC have unresectable disease. Also, approximately one third of patient who undergo potentially curative resection of RCC develop a recurrence. In these cases, systemic therapy with immunotherapy, targeted therapies, or combinations of these has become standard of care to delay disease progression and improve survival time.

Clear cell RCC can develop sporadically when the VHL protein is inactivated. Most sporadic ccRCCs having somatic inactivation of both VHL alleles leading to loss of function of the VHL tumor suppressor protein (pVHL). About 60–80% of ccRCC have either loss-of-function mutations in the VHL gene, chromosomal abnormalities on chromosome 3p25 at the VHL locus, or hypermethylation of the VHL promoter.

As briefly discussed earlier, VHL also works to decrease HIF-1/2α during normoxia. When VHL is lost, there is increased activation of HIF-1/2α even under normoxic conditions. This can be the result of hereditary mutations as seen in Von Hippel Lindau Syndrome, due to exposure to toxins, or as is often the case through sporadic mutations. A few studies have investigated the polymorphisms in the HIF-1/2α gene and found that an increase in many haplotypes activated by HIF-α in those with RCC.[5, 6] There are also multiple studies that confirm a direct increase in HIF-1/2-α expression in those with RC.[5, 6] Clear cell RCC was found to have the highest expression levels of HIF-1/2α.[5]

A clinical trial entitled "Imaging Correlates of Renal Cell Carcinoma Biological Features" is currently analyzing RCC tumors in patients with >3cm mass. These patients will undergo contrast-enhanced magnetic resonance-Fluorodeoxyglucose-positron emission tomography (MR-FDG-PET) scans. The tumors will also be tested and undergo biomarker assessment for HIF-1/2α. The primary outcome is to evaluate HIF activation by examining both imaging and tumor tissue.

HIF1/2- α Inhibitors and Renal Cell Carcinoma Clinical Trials

There are many clinical trials that have evaluated the inhibition of HIF-1/2α in human tumors.[7-16] Given the driving mechanism of HIF-1/2α and the development of ccRCC, there has been much work in recent towards the development on HIF inhibitor therapy in the clinical setting. Non-selective drugs targeting both HIF-1/2α have demonstrated modest-to-disappointing results to date, but drugs selectively targeting HIF-2α have shown more promise in both preclinical and early human trials.

One of the first major positive human studies of these agents was presented at the 2020 Genitourinary Cancers Symposium. The phase I/II study of HIF-2α inhibitor MK-6482 enrolled 55 patients in the dose expansion cohort. All patients had previously received at least one line of systemic therapy for advanced RCC. The study found an overall response rate of 24% with 13 confirmed partial responses. Thirty-one patients (56%) had SD, for a disease control rate (CR+PR+SD) of 80%. The drug was found to have an acceptable toxicity profile.[17]

Selected Ongoing HIF-inhibitor Clinical Trials in RCC

Several ongoing clinical trials are examining HIF-inhibitors in ccRCC. The study, *"ARO-HIF2 in Patients With Advanced Clear Cell Renal Cell Carcinoma" is evaluating the safety and efficacy of* ARO-HIF2, which is a HIF-2α inhibitor, as well as determining the recommended Phase 2 dose in the treatment of patients with advanced ccRCC. The study is recruiting participants with histologically confirmed locally advanced or metastatic ccRCC that have progressed during or after two prior therapeutic regimens which must include VEGF-targeted therapy and an immune checkpoint inhibitor therapy. The participants must have an ECOG performance status 0 or 1, estimated life expectancy of longer than 3 months, and adequate organ function at screening.[18]

Another institution is also evaluating another HIF-2α inhibitor, PT2385, to define the maximum tolerated dose (MTD) and the recommended phase 2 dose in patients with advanced ccRCC, as well as the MTD in combination with nivolumab or cabozantinib. This study is entitled, *"A Phase 1, Dose-Escalation Trial of PT2385 Tablets In Patients With Advanced Clear Cell Renal Cell Carcinoma*." Inclusion criteria in their trial include participants who have locally advanced or metastatic ccRCC and progressed during treatment with at least one and no more than three prior systemic treatment regimens, and must have received at least one but not more than two prior anti-angiogenic therapy regimens, and must have received at least one VEGFR targeting tyrosine kinase inhibitor. The study is active and enrolling patients at the time of this writing.[19]

An additional phase II clinical

trial called "*A Trial of Belzutifan (PT2977, MK-6482) in Combination With Cabozantinib in Patients With Clear Cell Renal Cell Carcinoma (ccRCC)*" is evaluating another HIF-2α inhibitor, PT2977/MK-6482 also known as belzutifan in combination with cabozantinib, with a primary outcome of ORR in patients with advanced ccRCC. Secondary outcomes include PFS, duration of response (DOR), time to response (TTR), and OS. Participants must have locally advanced or metastatic RCC with predominantly clear cell subtype, at least one measurable lesion as defined by RECIST version 1.1, ECOG 0-1, adequate organ function, and cohort 1 must have not received prior systemic therapy for advanced or metastatic ccRCC while cohort 2 must have received prior immunotherapy and no more than two prior treatments. The study is currently recruiting participants. [20]

This company is also evaluating ORR in VHL disease-associated ccRCC in VHL patients treated with the oral HIF-2α inhibitor PT2385 through the trial, "*PT2385 for the Treatment of Von Hippel-Lindau Disease-Associated Clear Cell Renal Cell Carcinoma*." Participants must have at least 1 measurable ccRCC lesion and no solid ccRCC tumors greater than 3.0 cm, based on radiologic diagnosis. Patients may have VHL disease-associated lesions in other organ systems and had a diagnosis of VHL based on germline VHL alteration. The study is active and but currently recruiting. [21]

Furthermore, they are conducting an additional trial, "*A Trial of Belzutifan (PT2977, MK-6482) Tablets In Patients With Advanced Solid Tumors*." PT2977 assess' the MTD and the recommended phase 2 dose in patients with advanced solid tumors and once determined, expanded to patients with advanced ccRCC, other specified solid tumors, up to 3 different tumor types, including glioblastoma multiforme (GBM). Participants must have a diagnosis of locally advanced or metastatic solid tumor, with a life expectancy of 6 months or more, with adequate organ function. The study is active.[22]

Another institution is evaluating different doses of belzutifan (PT2977/MK-6482) in a randomized phase II study of RCC patients: "*A Study of Belzutifan (MK- 6482) in Participants With Advanced Renal Cell Carcinoma (MK-6482-013)*." Patient are randomized to receive a higher doses or the standard dose with a primary outcome of ORR. Secondary outcomes include PFS, DOR, and clinical benefit rate (CBR). Inclusion criteria includes participants who have a histologically confirmed diagnosis of locally advanced/metastatic RCC with clear cell component, measurable disease per RECIST 1.1 as assessed by BICR, have progressed on or after having received first-line systemic treatment for locally advanced or metastatic RCC with prior anti-PDL 1 therapy plus anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) combination OR anti-PD-1/L1 plus a VEGF tyrosine kinase inhibitor combination, and have received no more than 3 prior systemic regimens for a locally advanced or metastatic RCC. This study is still recruiting participants. [23]

They also studied a large (736 patients), randomized phase III study they are conducting is being done to compare belzutifan to everolimus. This is called, "*A Study of Belzutifan (MK-6482) Versus Everolimus in Participants With Advanced Renal Cell Carcinoma (MK-6482-005)*." The primary outcomes are PFS and OS in patients with advanced RCC. Secondary outcomes are ORR, DOR, number who experienced adverse events, number who discontinued study due to adverse events, time to deterioration in health-related quality-of-life, time to deterioration in physical functioning, and time to deterioration in disease symptoms. Participants must have unresectable, locally advanced or metastatic ccRCC, had disease progression on or after having received systemic treatment for locally advanced or metastatic RCC with PD-1/L1 checkpoint inhibitor and VEGF-TKI in sequence or in combination, have received no more than 3 prior systemic regimens for locally advanced or metastatic RCC, and have adequate organ function. This study is still recruiting. This trial could provide greater clarity on the utility of direct inhibition of HIF-α2 rather than indirect inhibition of HIF-1α through the mTOR pathway.[24]

Lastly, there is a large (708 subjects), randomized trial of belzutifan in combination with lenvatinib or cabozantib is expected to begin recruiting patients in November 2020. This is entitled, "*A Study of Belzutifan (MK-6482) in Combination With Lenvatinib Versus Cabozantinib for Treatment of Renal Cell Carcinoma (MK-6482-011)*." [25]

Discussion

Inactivation of the VHL gene is a hallmark of ccRCC that results in HIF overactivation and upregulations of angiogenic pathways. The last decade and a half has brought unprecedented treatment options for advanced RCC, mainly focused around anti-angiogentic targeted therapies and immunotherapies, and more recently, combinations of these. Despite great progress, most

patients with advanced RCC still develop resistance to these drugs, necessitating the development of novel therapies for these patients.

HIF-inhibitors represent an emerging class of targeted therapies that will likely be approved for the treatment of advanced RCC. By targeting the underlying molecular driver of clear cell RCC, these drugs provide a unique mechanism of action. The number of treatment options in advanced RCC continues to grow with new combinations of immunotherapies and targeted therapies dominating the treatment landscape. In which clinical scenarios and in what potential combinations HIF-inhibitors will be most useful is yet to be determined. Data from many ongoing studies are expected to emerge during the next couple of years and more studies are anticipated.

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