THERAPEUTIC ADVANCES in
Medical Oncology

Review

Belzutifan for the treatment of renal cell carcinoma

Ther Adv Med Oncol

2025, Vol. 17: 1–14

DOI: 10.1177/17588359251317846

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***Abstract*:** Belzutifan received its first FDA approval in 2021 for treating clinical manifestations of von Hippel-Lindau (VHL) disease including renal cell carcinoma (RCC) followed by approval in 2023 for treating advanced sporadic RCC that has progressed through multiple lines of treatment. It is the first FDA-approved drug to target hypoxia-inducible factor 2 alpha (HIF-2α). By inhibiting the HIF-2α transcription factor, belzutifan prevents HIF-2α from dimerizing with HIF-1β, thereby preventing the transcription of downstream oncogenes. Most clear cell renal cell carcinoma (ccRCC) tumors are associated with VHL deletion or inactivation resulting in HIF-2α overexpression that represents a key contributor to tumorigenesis, thereby making belzutifan a uniquely optimal drug for targeting ccRCC. Belzutifan has demonstrated activity in clinical trials as a front- and later-line therapy, and in combination with tyrosine kinase inhibitors. It has been largely well tolerated, although anemia represents a common on-target side effect and, along with hypoxia, requires monitoring during treatment. Ongoing phase III trials are investigating belzutifan in combination regimens in the relapsed/refractory, front-line, and adjuvant settings. Future studies will focus on identifying predictive biomarkers and resistance pathways.

Keywords: belzutifan, hypoxia-inducible factor, renal cell carcinoma, systemic treatment, VHL

Received: 30 October 2024; revised manuscript accepted: 17 January 2025.

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Introduction

Renal cell carcinoma (RCC) accounts for 134,000 deaths worldwide and 14,000 deaths yearly in the United States.[1] Approximately 75% of RCCs have clear cell histology, the common subtype associated with most of the current treatment evidence.[1] The von Hippel-Lindau (VHL) tumor suppressor gene located on the short arm of chromosome 3 is the most altered gene in clear cell renal cell carcinoma (ccRCC) via mutations, deletions, and/or epigenetic silencing.[1] VHL plays a key role in regulating the cellular response to hypoxia, including the production of growth factors, glycolytic enzymes, and glucose transporters.[1] As the substrate-recognition component of an E3 ligase complex, VHL is responsible for ubiquitinating hypoxia-inducible factor 2 alpha (HIF-2α) and HIF-1α for proteasomal degradation.[1] Under hypoxic conditions, HIF-2α and HIF-1α are protected from VHL ubiquitination and translocate to the nucleus where they dimerize with HIF-1β/aryl hydrocarbon receptor nuclear translocator[2,3] (Figure 1). The HIF-α/HIF-1β complexes bind to hypoxia response elements to activate the transcription of HIF target genes such as vascular endothelial growth factor (VEGF) and erythropoietin that results in uncontrolled tumor-promoting functions, including angiogenesis, glycolysis, cancer proliferation, cell survival, and metastatic spread[1,2] (Figure 1). Some research suggests that the activation of HIF-2α may play a greater role in promoting tumorigenesis over HIF-1α.[2] With loss of VHL, HIF-2α and HIF target genes are constitutively activated independent of oxygen conditions, resulting in a state of pseudohypoxia. VHL loss and HIF dysregulation serve as the key initiating genetic events leading to ccRCC.[4]

While most ccRCC are associated with acquired somatic loss or mutations of VHL, some ccRCC arise in association with hereditary germline *VHL*

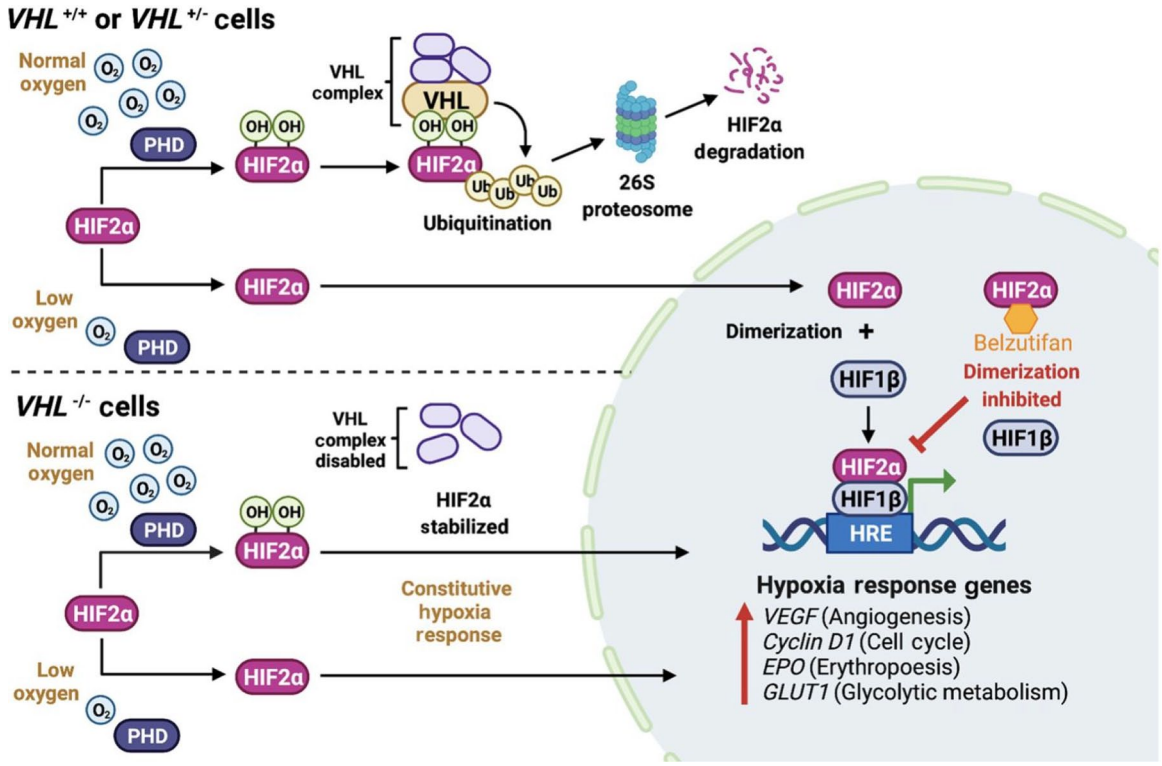

Figure 1. Overview of hypoxia pathway and its inhibition by belzutifan.
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mutations. VHL syndrome is a rare condition arising from the inheritance of a germline mutation in one VHL allele and, as per the Knudson two-hit hypothesis, a later sporadic loss of the second allele in affected tissues. Patients with this disease present with an elevated risk of acquiring multiple benign and malignant tumors including ccRCCs, pheochromocytomas, retinal and central nervous system (CNS) hemangioblastomas, endolymphatic sac tumors, and pancreatic neuroendocrine tumors. By age 60, 70% of VHL syndrome patients develop ccRCC, and this is the leading cause of mortality in this group of patients.[5]

Management of ccRCC differs by staging. Surgical resection achieves high cure rates for those with early-stage disease.[1] Patients at high risk for recurrence post-nephrectomy are advised to receive adjuvant pembrolizumab, which has shown a survival benefit in the KEYNOTE-564 trial (an National Comprehensive Cancer Network (NCCN) category 1 recommendation).[6,7] In the metastatic setting, doublet combinations of immune checkpoint inhibitors (ICIs) or an ICI in combination with VEGF pathway inhibitors have become the standard of care.[8–11] In the first-line setting, objective response rates (ORRs) range between 42% and 71%, progression-free survival (PFS) ranges between 11 and 23 months, and overall survival (OS) ranges from 46 to 56 months.[8–11] Unfortunately, most patients ultimately develop resistant disease and optimizing therapy following disease progression is less well-defined. Among NCCN-recommended regimens for patients failing front-line therapy, ORRs range from 17% to 43%, PFS ranges from 4.6 to 14.6 months, and OS ranges from 20.1 to 25.8 months.[12–18]

Belzutifan (previously known as PT2977 or MK-6482) was developed as a small-molecule antagonist of HIF-2α that prevents HIF-2α/HIF-1β dimer formation.[19] It was shown to have more consistent and higher drug exposure than the first-in-class HIF-2α inhibitor PT2385.[19] In a phase I trial of belzutifan for advanced solid tumors, belzutifan showed clinical activity in a heavily pretreated population and was well tolerated.[20] In 2021, the FDA-approved belzutifan for RCC or other manifestations of VHL disease in patients who do not require immediate surgery

based on outcomes observed in a phase II study.[21] The FDA approved belzutifan in 2023 for patients with advanced sporadic RCC who have received a prior PD(L)1 inhibitor and a VEGF tyrosine kinase inhibitor (TKI). Approval was based on data from the phase III LITESPARK-005 study, which showed superior efficacy of belzutifan versus everolimus in patients with locally advanced or metastatic ccRCC after 1–3 prior systemic therapies.[22] In this review, we summarize the pharmacology, clinical efficacy, and safety/side effect profile of belzutifan, and provide insights on future directions for the clinical development of this agent.

Preclinical development

The first HIF-2α inhibitor to enter clinical testing was the compound PT2385. It was shown in preclinical models to bind to a lipophilic cavity on HIF-2α and disrupt HIF-2α/HIF-1β dimer formation.[23] In vitro data showed that PT2385 selectively inhibited HIF2α-dependent gene expression, and in patient-derived xenograft models, PT2385 showed greater antitumor activity compared with the VEGF-receptor targeting TKI sunitinib with a better safety side effect profile.[23] Belzutifan (then known as PT2977) emerged as a superior HIF-2α inhibitor candidate with improved potency and reduced interindividual pharmacokinetic variability when compared with PT2385.[19]

Pharmacology

Mechanism of action

Belzutifan functions by inhibiting HIF-2α, a transcription factor crucial for cellular adaptation to hypoxia. By attaching to a binding pocket on HIF-2α, belzutifan prevents HIF-2α from interacting with HIF-1β, disrupting subsequent activation of genes associated with cell proliferation and angiogenesis, thereby inhibiting tumor growth (Figure 1).[3]

Pharmacokinetics

No clinically significant differences in pharmacokinetics were observed based on age, sex, ethnicity, race, body weight, or mild-to-moderate renal or hepatic impairment; therefore, no dose adjustments are needed.[24] However, the pharmacokinetic behavior in the setting of severe renal and moderate-to-severe hepatic impairments has not been studied. The excretion profile of belzutifan shows that approximately 49.6% of the dose is excreted in urine and 51.7% in feces, primarily as inactive metabolites.[25] Belzutifan's plasma pharmacokinetics are characterized by a linear two-compartment model with first-order absorption and elimination. The half-life of belzutifan is 14 h with a median T_{max} at 1 to 2 h after administration. A high-fat, high-calorie meal delays T_{max} by approximately 2 h but does not significantly affect C_{max} or the area under the curve (AUC). In patients with VHL disease-associated RCC, belzutifan achieves steady state after about 3 days.[25]

Belzutifan is primarily metabolized by UGT2B17 and CYP2C19 and to a lesser extent by CYP3A4. The FDA data sheet and a pharmacokinetic study reported that dual poor metabolizers of UGT2B17 and CYP2C19 have higher belzutifan AUC and recommended closer monitoring for adverse reactions.[24,25] Notably, such dual poor metabolizers are estimated to make up ~0.5% of the US population.[24] The LITESPARK-013 trial revealed no significant differences in efficacy or toxicity between 120- and 200-mg doses.[26] Overall, no intrinsic patient clinical factors or phenotype status of any metabolic enzymes require belzutifan dose adjustments, while dual poor metabolizers of UGT2B17 and CYP2C19 may require closer monitoring.

Clinical efficacy

VHL disease

The first FDA approval for belzutifan treatment of RCC was granted in 2021 based on results from a phase II, open-label, single-arm trial that studied belzutifan in patients with ccRCC associated with VHL disease.[21] Patients were eligible if they had a germline *VHL* alteration, no RCC tumor larger than 3 cm that necessitated immediate surgical intervention and no evidence for metastatic disease. Of 61 enrolled patients, belzutifan treatment achieved an ORR in RCC tumors of 49% and 92% of patients had a reduction in their RCC target lesions. The median time to response was 8.2 months and with 21.8 months of follow-up, the median duration of response (DOR) was not reached. The 2-year rate of PFS was 96%. Responses were also confirmed in 77% of pancreatic lesions, 30% of CNS hemangioblastomas, and 100% of retinal hemangioblastomas. At time of data cutoff, only one patient had required surgical management for

RCC (a partial nephrectomy) after start of belzutifan. This compared with 97% of enrolled patients who had completed at least one prior tumor-reduction surgery before initiation of belzutifan. In summary, with nearly 2 years of follow-up, belzutifan showed ongoing activity against RCC and non-RCC manifestations of VHL disease and has potential to significantly reduce the need for invasive interventions in this population.

Sporadic ccRCC

Monotherapy. The first signal of clinical activity for an HIF-2α inhibitor came from a phase I dose-escalation trial of PT2385.[27] In a heavily pretreated population of patients with advanced ccRCC (median of four prior systemic treatments), PT2385 showed an ORR of 14%, a disease control rate (DCR) of 66%, and 25% of patients had PFS greater than 14 months.[27] 100% of patients had received a prior VEGF TKI, 61% had received a prior mammalian target of rapamycin (mTOR) inhibitor, and 22% had received a prior ICI. Further study was then transitioned to the more potent and pharmacologically favorable drug, belzutifan. In a phase I, open label, single-arm, first-in-human trial of belzutifan (LITESPARK-001), 55 patients were enrolled in the ccRCC cohort.[20] In this heavily pretreated population (62% had received ⩾3 prior systemic treatments and 91% had progressed on prior anti-VEGF therapies), the ORR was 25%, DCR was 80%, and median DOR was not reached with 41 months of follow-up. The median PFS was 14.5 months.[20,28] Given that the maximum tolerated dose was not reached in LITESPARK-001, a phase II study (LITESPARK-013) compared belzutifan at 120 or 200 mg daily in advanced ccRCC patients.[26] This study found comparable ORR of 23.7% versus 23.1% and PFS of 7.3 versus 9.1 months, (p = not significant) between 120 and 200 mg.[26]

The first comparison trial of belzutifan versus an established therapy for RCC was LITESPARK-005.[22] This was an open-label, randomized phase III study that compared belzutifan to everolimus in advanced ccRCC patients who had received 1–3 prior systemic regimens that included an anti-PD(L)1 antibody and VEGF TKI.[22] Despite an equivalent median PFS for belzutifan and everolimus (5.6 vs 5.6 months), at an 18-month landmark analysis, the co-primary endpoint of PFS was met with 22% of patients in the belzutifan arm remaining progression free compared with 9% in the everolimus arm (hazard ratio of 0.74 (0.63–0.88)). Belzutifan also demonstrated an improved ORR of 21.9% vs 3.5% ($p < 0.00001$) and median DOR of 19.5 versus 13.7 months (p = not reported). Notably, the Kaplan–Meier PFS curve for belzutifan declined sharply in the first 6 months and 34% of patients had progressive disease as their best response, suggesting that clinical benefit was limited to only a fraction of treated patients.

Combination therapies. An open-label, single-arm phase II study (LITESPARK-003) evaluated the efficacy of belzutifan plus cabozantinib in patients with advanced ccRCC who had not received previous systemic therapy for advanced disease (cohort 1) or who had received prior immunotherapy for advanced disease and maximum of two previous regimens (cohort 2).[29] At a median follow-up of 39.8 months, of 52 patients enrolled in cohort 2, the ORR was 31%, DCR was 92% and median DOR was 31.5 months. The median PFS was 13.8 months, and median OS was 26.7 months. Response rates were similar across subgroups that differed by the International Metastatic RCC Database Consortium (IMDC) risk group and prior treatment history (ICI or ICI and VEGF TKI).[29,30] At a median follow-up of 24.3 months, of 50 patients with advanced ccRCC with no prior systemic treatment (cohort 1), ORR was 70%, DCR was 98% and median DOR was 28.6 months. The median PFS was 30.3 months, and median OS was not reached.[30]

Arm B5 of the KEYMAKER-U03B study examined belzutifan plus lenvatinib in patients with advanced ccRCC who had received a prior PD(L)1 inhibitor and VEGF-TKI therapy.[31] Preliminary results at median follow-up of 6.9 months showed an ORR of 50%, the median DOR was not reached, and the median PFS was 11.2 months.[31]

Ongoing phase III trials of combination therapy with practice changing potential. LITESPARK-011 (NCT04586231) is a randomized phase III study investigating the combination of belzutifan plus lenvatinib versus cabozantinib as standard of care in patients with advanced ccRCC who have progressed on or after PD(L1)-1 inhibitor therapy.[32] While belzutifan suppresses HIF-2α-induced oncogene upregulation including VEGF at the transcriptional level, lenvatinib disrupts the downstream activity of growth factors including VEGF and fibroblast growth factors by inhibiting

their receptors.[33] Lenvatinib was previously FDA approved in 2016 for treatment of relapsed/refractory RCC in combination with everolimus. In a randomized phase II trial, lenvatinib plus everolimus demonstrated superior efficacy to everolimus monotherapy in patients who had progressed on prior VEGF TKI with improved median PFS (14.6 months vs 5.5 months, $p = 0.0005$), ORR (43% vs 6%, $p < 0.0001$), and median OS (25.5 months vs 15.4 months, $p = 0.024$).[33] In addition to direct comparison to cabozantinib, the benchmark data with lenvatinib plus everolimus will provide additional context to judge efficacy and tolerability outcomes for the belzutifan plus lenvatinib regimen.

In the front-line setting, LITESPARK-012 (NCT04736706) is a randomized, three-arm, phase III study evaluating the efficacy of adding belzutifan (or the CTLA-4 inhibitor quavonlimab (MK-1308A)) to a backbone of pembrolizumab plus lenvatinib as a first-line treatment for advanced ccRCC.[34] Pembrolizumab plus lenvatinib was FDA approved as front-line treatment for advanced RCC in 2021 based on outcomes from the phase III CLEAR study that showed superior ORR (71% vs 36.1%, relative risk 1.97 with 95% CI 1.69–2.29), median PFS (23.9 vs 9.2 months, $p < 0.001$) and median OS (HR 0.66, 95% CI 0.49–0.88) compared to sunitinib.[10] The addition of belzutifan to the lenvatinib and pembrolizumab standard of care doublet will be evaluated for improvements in efficacy as well as tolerability.

LITESPARK-022 (NCT05239728) is a randomized phase III study examining the efficacy of adding belzutifan to pembrolizumab versus placebo plus pembrolizumab as adjuvant therapy in patients with high-risk ccRCC post-nephrectomy.[35] One year of adjuvant pembrolizumab for high-risk, completely-resected RCC was FDA approved in 2021 based on outcomes from the phase III KEYNOTE-564 trial. Adjuvant pembrolizumab improved disease-free survival (DFS) over placebo (hazard ratio 0.68, 95% confidence interval 0.53–0.87)[36] and more recently has shown improved OS.[6]

Taken together, belzutifan monotherapy has demonstrated meaningful clinical activity in the later-line setting. Early phase testing has established adequate safety and tolerability for belzutifan in combination with VEGF TKIs in both front- and later-line regimens. Ongoing phase III combination studies incorporating belzutifan will have the potential for practice changing results for systemic therapy in the relapsed/refractory, front-line, and adjuvant setting (Table 3).

Adverse events

Anemia

Anemia was the most common adverse reaction to belzutifan. The proposed mechanism for belzutifan-related anemia is due to the role of HIF-2α to upregulate erythropoietin production and erythropoiesis to counteract hypoxia. Thus, when belzutifan inhibits HIF-2α, it also hinders erythropoietin production.[21,37] In the LITESPARK-001, -003, and -004 trials, anemia of all grades occurred in 76%–90% of study participants, while 12%–24% of treated patients developed grade 3 anemia. In a pooled analysis of 576 belzutifan-treated patients from four trials (LITESPARK-001, LITESPARK-005, LITESPARK-013, and LITESPARK-004), all-grade anemia occurred in 84.2% of patients and grade 3 or 4 occurred in 28.8% of patients.[38] LITESPARK-013 demonstrated that increasing the belzutifan dose from 120 to 200 mg only slightly increased anemia incidence from 81.6% to 83.3%.[26]

FDA guidance for belzutifan-associated anemia recommends withholding belzutifan for a hemoglobin <9 g/dl or in cases of life-threatening anemia. Providers should resume belzutifan at a lower dose once hemoglobin has recovered to >9 g/dl or discontinue belzutifan altogether. Transfusion is advised as clinically indicated.[25] However, in practice we find a subset of patients can tolerate a hemoglobin <9 g/dl with minimal symptoms encouraging customization of treatment holds, dose reductions and transfusion support. Given belzutifan's exposure-dependent reduction in plasma erythropoietin (EPO) levels, erythropoiesis-stimulating agents (ESA's) (epoetin alfa and darbepoetin alfa) would seem to offer a physiologic replacement strategy to an on-target belzutifan toxicity. Although ESAs are not recommended by the FDA due to their known risk of worsening malignancy,[25] ESA use was not excluded in early belzutifan clinical trials and among 485 patients with anemia in a pooled analysis, 22.9% were treated with ESAs.[38] Our approach has been to consider ESA support in metastatic patients counseled regarding the theoretical risk for worsening outcomes. Interestingly,

a LITESPARK-004 post hoc analysis suggested that those who received ESAs had a higher ORR than those who did not.[39] While the etiology behind this is unclear, patients requiring ESA support had a higher rate of belzutifan dose reduction and may represent a group of patients who are exquisitely sensitive to HIF inhibition.[39] Furthermore, patients receiving ESAs had a higher duration of belzutifan exposure.[39]

Hypoxia

Hypoxia is a significant and common adverse effect of belzutifan. Although the mechanism is not well understood, it is suggested that the inhibition of HIF-2α impairs the vasoconstriction response within the pulmonary arterial vasculature to ventilation/perfusion mismatch. Most reported cases of belzutifan-related hypoxia were in the context of acute triggering events, such as pneumonia or pleural effusions.[20] In the LITESPARK-001, -003, and -004 trials, hypoxia occurred in 4%–33% of participants, with 1.6%–22% developing grade 3 hypoxia. In a pooled analysis, 16.3% of patients developed hypoxia and 9.9% developed grade 3 or 4 hypoxia.[38] LITESPARK-013 revealed that increasing the belzutifan dose from 120 to 200 mg only slightly increased hypoxia incidence from 23.7% to 26.9%.

The FDA recommends monitoring oxygen saturation before and during treatment. For decreased oxygen saturation (<88% oxygen saturation) with exercise or at rest, belzutifan should be withheld until saturation improves and then resumed at the same or a reduced dose.[25] Life-threatening or recurrent symptomatic hypoxia necessitates permanent discontinuation.[25]

Embryo-Fetal toxicity

Belzutifan has shown potential risks during pregnancy, with animal studies showing embryo-fetal lethality and malformations. Although there are no adequate human data on the use of belzutifan in pregnant women, these animal studies suggest a high risk of severe adverse developmental outcomes. Therefore, belzutifan is not recommended for use during pregnancy. Women of reproductive potential should use effective contraception during treatment and for 1 week after the final dose. Males with female partners of reproductive potential should also use effective contraception during treatment and for 1 week after the final dose due to potential male-mediated teratogenicity.[25] Although no studies have directly explored interactions between belzutifan and oral contraceptives, its partial metabolism by CYP3A4, which also metabolizes contraceptives containing ethinyl estradiol, raises the potential for drug–drug interactions.[25,40–42]

Other adverse effects

In the largest clinical trial experience with belzutifan monotherapy, the LITESPARK-005 trial reported the following common adverse reactions (⩾25%): anemia (82.8%) and fatigue (31.5%). Less common adverse reactions observed in ⩾10% of patients included nausea (18.0%), constipation (16.7%), peripheral edema (16.1%), dyspnea (15.1%), back pain (14.8%), arthralgia (14.5%), asthenia (14.5%), decreased appetite (14.5%), hypoxia (14.5%), vomiting (12.9%), dizziness (12.4%), increased alanine aminotransferase level (12.1%), headache (12.1%), diarrhea (11.8%), and increased aspartate aminotransferase level (11.6%).[22]

Belzutifan had lower rates of treatment interruptions and discontinuations when compared with everolimus (Tables 1 and 2). Participant-reported outcomes also favored belzutifan with longer median time to confirmed worsening of disease-related symptoms and deterioration in quality of life as measured by the Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – Disease Related Symptoms (FKSI-DRS) and the European Organization for Research and Treatment of Cancer Core quality of life questionnaire (EORTC QLQ-C30) scores.[22]

Future directions

Optimizing patient selection

Optimizing responses to belzutifan will benefit from further insights into mechanisms of resistance and developing biomarkers to identify likely responders. In LITESPARK-005, about one-third of patients had progressive disease as their best response, and the Kaplan–Meier PFS curves for belzutifan and everolimus had a similar trajectory for the first 6 months, at which point the curves separated in favor of belzutifan. The suspicion of discretely different sensitive and resistant tumor phenotypes encourages a search for specific biological or molecular markers that predict for response or resistance to belzutifan.

In an imaging and biomarker companion study involving a subset of patients enrolled in the phase

Table 1. Efficacy data for belzutifan in ccRCC.

Trial	Treatment	Population	Treated (*N*)	ORR, % (95% CI)	DCR, % (95% CI)	Median DOR, months (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)
Monotherapy								
NCT03401788 LITESPARK-004[21]	Belzutifan	Germline *VHL* alteration, no metastatic disease	61	49 (36–62)	98 (—)	NR (2.8–22.3)	2-year PFS: 96% (87%–99%)	—
NCT02974738 LITESPARK-001[20,28]	Belzutifan	Previously treated advanced ccRCC	55	25 (—)	80 (—)	NR (3.1–38)	14.5 (7.3–22.1)	—
NCT04489771 LITESPARK-013[26]	Belzutifan 120 mg daily vs 200 mg daily	Advanced ccRCC, treat with previous anti-PD(L)1	76 vs 78	23.7 vs 23.1 ($p = 0.5$)	NR	NR vs 16.1 (p = NS)	7.3 vs 9.1 (p = NS)	NR vs NR (p = NS)
NCT04195750 LITESPARK-005[22,43]	Belzutifan vs everolimus	Advanced ccRCC, treated with previous anti-PD(L)1	374 vs 372	21.9 vs 3.5 ($p < 0.00001$)	61 vs 69.4 (p = (—))	19.5 vs 13.7 (p = (—))	5.6 vs 5.6 ($p < 0.001$)	21.4 vs 18.1 ($p = 0.1$)
Combination therapy								
NCT03634540 LITESPARK-003[30] Cohort 1	Belzutifan + Cabozantinib	Advanced ccRCC, no prior systemic therapy	50	70 (55–82)	98 (—)	28.6 (—)	30.3 (16–NR)	NR (NR–NR)
Cohort 2	Belzutifan + Cabozantinib	Advanced ccRCC, treated with previous immunotherapy	52	31 (19–45)	92 (—)	31.5 (—)	13.8 (9.2–19.4)	26.7 (20.0–41.1)
NCT04626518 KEYMAKER-U03B[31]	Belzutifan + Lenvatinib	Advanced ccRCC, treated with previous anti-PD(L)1 and VEGF inhibitor	32	50 (29–71)	—	NR (1.4+ to 14.0+)	11.2 (4–NR)	—

ccRCC, clear cell renal cell carcinoma; DCR, disease control rate; DOR, duration of response; NR, not reached; NS, no significant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Table 2. Treatment-related adverse events for belzutifan in ccRCC.

Trial	Treatment	Population	Treated (*n*)	TRAEs (% any)[38]	Grade ⩾3 TRAEs (%)	Fatal TRAEs (%)	Dose reduction from TRAEs (%)	Interruption from TRAEs (%)	Treatment discontinuation from TRAEs (%)
NCT02974738 LITESPARK-001[20,28]	Belzutifan	Advanced ccRCC, previously treated	55	96	40	0	9	24	4
NCT03401788 LITESPARK-004[21]	Belzutifan	Germline *VHL* alteration, no metastatic disease	61	100	15	0	15	43	2
NCT04489771 LITESPARK-013[26]	Belzutifan 120 mg daily vs 200 mg daily	Advanced ccRCC, treated with previous anti-PD(L)1	76 vs 78	92.1 vs 92.3	46.1 vs 46.2	0 vs 0	23.7 vs 28.2	13.2 vs 20.5	2.6 vs 9.0
NCT04195750 LITESPARK-005[22]	Belzutifan vs everolimus	Advanced ccRCC, treated with previous anti-PD(L)1	374 vs 372	89.0 vs 89.4	38.7 vs 39.4	0.3 vs 0.6	14.0 vs 14.7	43.5 vs 48.1	2.7 vs 10.6

ccRCC, clear cell renal cell carcinoma; TRAEs, treatment-related adverse events.

I dose-escalation trial of PT2385, EPO levels were inversely correlated with PT2385 levels.[44] One patient whose EPO levels failed to decrease had the lowest PT2385 trough levels and had rapid disease progression. This suggests that EPO might be used as a pharmacodynamic marker for the titration of belzutifan dosing. In another study that utilized the HIF-2α inhibitor PT2399 to treat RCC tumor xenografts, it was observed that sensitive tumors had higher HIF-2α expression (83% in sensitive tumors vs 23% in resistant tumors) and demonstrated a unique gene expression signature.[45] Successful interrogation of tumor HIF expression via tumor biopsy or novel technologies such as positron emission tomography tracers that are selective for HIF expression represents intriguing directions to identify patients more likely to respond to HIF-2α inhibition.[46,47]

Overcoming mechanisms of resistance

Primary or acquired tumor resistance is the final common endpoint for most belzutifan treated patients. Studies have identified G323E substitution in HIF-2α and F446L substitution in HIF-1β as possible gatekeeper mutations that prevent HIF-2/ HIF-1β dissociation by HIF-2α targeting drugs PT2385 and PT2399.[44,45] Structural analyses revealed that the G323E mutation induced changes to the HIF-2α binding site that prevented inhibitor binding.[48,49] Molecular analysis showed that the F446L mutation was positioned at the HIF-2α/HIF-1β dimer interface and enhanced HIF-1β affinity for HIF-2α.[50] Of interest, preliminary results from an in vitro analysis showed that the addition of an inhibitor against Hsp70 (chaperone protein that stabilizes HIF-2α) was able to overcome G323E-mediated belzutifan resistance.[51]

Another potential mechanism of resistance was recognized by analyses showing elevation of phosphoglycerate dehydrogenase (PHGDH) in HIF-2α negative ccRCC cells.[52] In The Cancer Genome Atlas (TCGA) data, PHGDH amplification was associated with inferior DFS and OS. Consequently, targeting PHGDH with inhibitors showed tumor suppression in HIF-2α knock-out cells grown in vitro or as murine xenografts.[52]

The FK506 binding protein 10 (FKB10) also promotes RCC proliferation and metastasis, and is negatively regulated by HIF-2α.[53] HIF-2α inhibition results in increased FKB10 expression, and as a result, the addition of FKBP10 inhibition can enhance the antitumor effect of HIF-2α in a murine xenograft model.[53]

Taken together, these preclinical studies identify pathways associated with resistance to sustained HIF-2α blockade as well as potential targets for rationale drug development that could enhance the antitumor properties of HIF-2α inhibitors for metastatic ccRCC.

Early phase combination clinical trials

Multiple ongoing early phase clinical trials seek to explore novel combination regimens incorporating belzutifan (Table 3).

HC-7366 is a novel activator of the general control nonderepressible 2 (GCN2) kinase that is part of the integrated stress response, a key metabolic stress sensor in cells. Overactivation of GCN2 by HC-7366 has been shown to have antitumor activity in preclinical models of colorectal, head and neck, sarcoma, and prostate cancer patients, and clinical activity in patients with AML.[54,55] Transcriptomic analyses have identified that a compelling target for HC-7366 is reduced activity of HIF transcription factors.[54] These data support the investigation of HC-7366 in combination with belzutifan. NCT06234605 is a phase I trial examining the safety and efficacy of HC-7366 plus belzutifan in patients with advanced ccRCC.

Preclinical studies have shown synthetic lethality when inactivation of VHL is combined with loss of the cell cycle regulatory gene, CDK4/6. This synthetic lethal relationship was not dependent on HIF-2α expression, and synergistic antitumor activity was seen with the combination of CDK4/6 inhibition and HIF-2α inhibition in human-derived ccRCC cells and mouse xenograft models.[56] These observations served as the rationale for LITESPARK-024—a phase II study of belzutifan plus palbociclib (CDK4/6 inhibitor) versus belzutifan in patients with relapsed/refractory advanced ccRCC.[57]

Finally, novel agents targeting T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) have shown clinical activity in various advanced solid tumors including NSCLC.[58,59] Preclinical studies have shown that blocking TIGIT inhibits RCC proliferation, migration, and invasion.[60] A current phase Ib/II study (NCT04626479) is investigating the

Table 3. Select ongoing trials of belzutifan in ccRCC.

Trial	Population	Treatment	Select primary endpoints
Phase I			
NCT04626479	Advanced, untreated ccRCC	Vibostolimab/pembrolizumab coformulation + belzutifan	DLT, AE, ORR
NCT06234605	Advanced ccRCC	Cohort 1: HC-7366 Cohort 2–4: HC7366 + Belzutifan dose escalation Cohort 5–6: HC7366 + Belzutifan dose expansion	MTD, RP2D, DLT, AE
Phase II			
NCT05468697 LITESPARK-024	Advanced ccRCC with previous anti-PD(L)1 and VEGF TKI	Belzutifan + palbociclib vs belzutifan	DLT, AE, ORR
Phase III			
NCT04586231 LITESPARK-011	Advanced ccRCC with prior anti-PD(L)1, ⩽2 prior systemic regimens	Belzutifan + Lenvatinib vs cabozantinib	PFS, OS
NCT04736706 LITESPARK-012	No prior systemic therapy for advanced ccRCC	Pembrolizumab (P) + belzutifan (B) + Lenvatinib (L) or P + L + Quavonlimab vs P + L	PFS, OS
NCT05239728 LITESPARK-022	ccRCC with intermediate-high or high risk for recurrence or M1 NED. Undergone resection of primary tumor and metastatic lesion in M1 NED.	Belzutifan + pembrolizumab vs placebo + pembrolizumab	DFS

AE, adverse events; ccRCC, clear cell renal cell carcinoma; DFS, disease-free survival.; DLT, dose limiting toxicity; MTD, maximally tolerated dose; NED, no evidence of disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RP2D, recommended phase II dose.

combination of vibostolimab (TIGIT inhibitor)/pembrolizumab coformulation plus belzutifan in patients with untreated, advanced ccRCC.

Conclusion

Belzutifan has emerged as a novel and effective treatment for ccRCC, targeting HIF-2α to inhibit dimerization with HIF-1β and prevent subsequent tumorigenesis. Belzutifan has gained FDA approval as monotherapy in the later-line setting for sporadic advanced disease, and as a first-line treatment in localized ccRCC associated with VHL disease. Important treatment-related adverse events include anemia and hypoxia, which require close monitoring during treatment. Ongoing phase III clinical trials are positioned to have practice-changing results, exploring novel combinations with belzutifan in the relapsed/refractory, front-line, and adjuvant setting. Further development of predictive biomarkers and insights into resistance pathways may lead to better patient selection and novel drug targets to enhance the clinical impact of HIF-2α targeting.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Author contributions

Xiancheng Wu: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

David Lazris: Investigation; Methodology; Writing – original draft; Writing – review & editing.

Risa Wong: Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing.

Scott S. Tykodi: Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing.

Acknowledgements
None.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
S.S.T. has received research funding (Institutional) from Merck, Xencor, AVEO Oncology, Bristol-Myers Squibb, Exelixis, Pfizer, Nektar Therapeutics, Iovance Biotherapeutics and HiberCell; Consulting fees from FirstWord, Bristol-Myers Squibb, AVEO Oncology, and Exelixis; Honoraria from OncLive/MJH Life Sciences, Targeted Oncology, CancerNetwork and Topline Bio; Support for attending meetings and/or travel from DAVA Oncology. X.W., D.L., and R.W. declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials
Not applicable.

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