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Belzutifan: A Breakthrough in Targeted Therapy for ccRCC

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Abstract. Belzutifan, a novel orally bioavailable small-molecule inhibitor of hypoxia-inducible factor 2α (HIF-2α), represents a mechanistically distinct and clinically promising therapy for clear cell renal cell carcinoma (ccRCC), particularly in patients with von Hippel–Lindau (VHL) disease. By selectively disrupting the VHL–HIF–2α signaling axis, Belzutifan effectively inhibits hypoxia-driven transcriptional programs that promote tumor progression. Unlike traditional therapies such as VEGF inhibitors and immune checkpoint blockade, Belzutifan directly targets a core oncogenic pathway unique to VHL-deficient tumors. Clinical trials have demonstrated encouraging response rates and manageable safety profiles, both as monotherapy and in combination with agents like cabozantinib. However, emerging resistance, limited efficacy in pre-treated populations, and concerns about long-term toxicity highlight areas that require further investigation. This article reviews the underlying molecular mechanism, clinical trial data, therapeutic advantages, and key limitations of Belzutifan, while also exploring its future potential in broader contexts of renal cell carcinoma and in rational combination strategies.

Keywords: Belzutifan, HIF-2α inhibition, clear cell renal cell carcinoma, VHL disease, targeted therapy

1. Introduction

Clear cell renal cell carcinoma (ccRCC) is the most common subtype of renal cancer, accounting for approximately 75%-80% of all cases [1].RCC is the sixth most common form of renal cancer in men and the ninth most common form in women, with an increasing global incidence, partly due to advances in imaging techniques and increased rates of incidental detection. However, despite early diagnosis, a significant proportion of patients are diagnosed with advanced or metastatic disease, with poor prognosis and limited treatment options.

In recent years, the emergence of immune checkpoint inhibitors and tyrosine kinase inhibitors (TKIs) targeting the VEGF and mTOR pathways has changed the treatment landscape for clear cell renal carcinoma (ccRCC) [2]. Although these therapies have significantly improved survival outcomes, many patients ultimately experience disease progression or treatment intolerance. Furthermore, these therapies do not directly address the inactivation of the von Hippel-Lindau (VHL) oncogene, the underlying genetic driver of ccRCC.

VHL gene deletion leads to the stabilization and accumulation of hypoxia-inducible factors (HIF), particularly HIF-2α, which in turn activates transcriptional programs that promote

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angiogenesis, cell proliferation, metabolic reprogramming, and tumor progression [3]. This dysregulated hypoxic response is now recognized as a central feature of ccRCC pathogenesis, making the VHL-HIF pathway an attractive and rational therapeutic target.

Belzutifan (MK-6482) is the first selective HIF-2α small molecule inhibitor with a mechanism of action that is distinct from existing VEGF and mTOR inhibitors. The drug is designed to directly disrupt the dimerization of HIF-2α with ARNT (aryl hydrocarbon receptor nuclear transport protein), thereby blocking the transcriptional activity of HIF-2α [4]. In August 2021, Belzutifan became the first HIF-2α inhibitor to receive FDA approval for the treatment of tumors associated with von Hippel-Lindau (VHL) disease [5]. marking an important milestone in the field of hypoxia-targeted cancer therapy. In this article, we discuss the mechanism of action, clinical performance, and future potential of Belzutifan in the treatment of ccRCC.

2. Mechanism of action

Belzutifan is a first-in-class, orally bioavailable small molecule inhibitor that selectively targets the hypoxia-inducible factor HIF-2α, a key transcription factor in clear cell renal cell carcinoma (ccRCC). Under normoxic conditions, VHL proteins promote the degradation of HIF-α subunits, including HIF-2α. However, the von Hippel-Lindau (VHL) tumor suppressor gene is inactivated in most ccRCC cases. When VHL is lost or mutated, HIF-2α is no longer degraded but accumulates intracellularly. Subsequently, it dimerizes with its chaperone ARNT (aryl hydrocarbon receptor nuclear transport protein) to form a transcriptional complex that activates genes involved in angiogenesis (e.g., VEGF), erythropoiesis, metabolic reprogramming, and tumor progression [3].

At the molecular level, Belzutifan binds to a specific hydrophobic pocket within the PAS-B structural domain of HIF-2α. This interaction prevents HIF-2α from forming a heterodimer with ARNT, which is essential for activating gene transcription. Structural studies, including X-ray crystallographic analysis at 2.75 Å resolution, showed that Belzutifan induces metastructural changes in the vicinity of the key residue, methionine 252 (M252), thereby destabilizing the HIF-2α/ARNT dimer interface [6].

The potency of Belzutifan was further confirmed by biochemical analyses.TR-FRET analysis by Chen et al. showed that it blocked HIF-2α/ARNT binding with a dissociation constant (Ki) of approximately 23 nM. Similarly, in their luciferase reporter gene assay, Belzutifan inhibited HIF-2α-driven transcriptional activity with an IC50 of approximately 17 nM. Thus, in ccRCC cell lines, Belzutifan treatment leads to dose-dependent inhibition of downstream target genes (e.g., VEGFA, NDRG1, and GLUT1) [6].

In addition, preclinical studies demonstrated that in a xenograft model, Belzutifan (PT2977) exhibited better tumor growth inhibition and more complete target binding compared to the first-generation HIF-2α inhibitor PT2385 [4]. Taken together, these data establish Belzutifan as a potent, highly selective, and mechanistically unique therapeutic agent. It acts upstream of the hypoxia signaling cascade, rather than just downstream effector molecules, by blocking transcriptional activation, thus providing a precision therapeutic strategy against VHL-deficient tumors.

3. Clinical evidence

Several clinical trials have demonstrated the antitumor activity and safety of Belzutifan in both hereditary and sporadic clear cell renal cell carcinoma (ccRCC). Its therapeutic role was initially established in patients with von Hippel-Lindau (VHL)-associated ccRCC.

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In a pivotal phase 2 trial involving 61 patients with VHL-associated ccRCC, Belzutifan monotherapy achieved an objective remission rate (ORR) of 49% and 92% of patients experienced tumor shrinkage [7]. Although complete remission (CR) was not observed, i.e., the rate of complete remission was low (<1%), the therapy was well tolerated, and the main adverse events were low-grade adverse events such as anemia (90%) and fatigue (66%). Simultaneously, it is these results that have prompted the drug to be approved by the FDA for the treatment of VHL-related tumors in 2021.

Additionally, Belzutifan's clinical application is now expanding to sporadic and advanced renal cell carcinoma (ccRCC). In the Phase 2 pilot study of LITESPARK-003, investigators evaluated the effectiveness of Belzutifan in combination with Cabozantinib as first-line treatment for advanced renal cell carcinoma (ccRCC). The trial was set up with two cohorts: cohort 1 contained patients who had not received prior treatment (n=50) and cohort 2 contained patients who had received immunotherapy (n=52).

In Cohort 1, the combination regimen achieved an objective remission rate (ORR) of up to 70%, a complete remission rate (CR) of 8%, and an acceptable toxicity response [8]. In contrast, the objective remission rate (ORR) of cohort 2 was only 31% [8], suggesting the need for further research on population selection for combination therapy with HIF-2α inhibitors and multi-target tyrosine kinase inhibitors.

In another phase 1b/2 trial, Belzutifan is being used in combination with Lenfatinib for the treatment of advanced renal cell carcinoma (ccRCC). Preliminary results presented at an oncology conference have demonstrated promising antitumor activity, but complete data from this study have not yet been published in a peer-reviewed journal [9]. Therefore, the efficacy and safety of this combination therapy remain to be further confirmed by future reports.

To crystallize these results, Table 1 [7,8,10,11] compares Belzutifan (alone and in combination) with other standard therapies such as VEGF-TKI and immune checkpoint inhibitors (ICIs):

Table 1. Comparative efficacy and toxicity of ccRCC therapies

Treatment	ORR	CR	Toxicity Burden
Belzutifan (monotherapy)	49%	0%	Low to moderate
Belzutifan + Cabozantinib (cohort 1)	70%	8%	Acceptable
Belzutifan + Cabozantinib (cohort 2)	31%	2%	Acceptable
VEGF-TKIs (e.g., sunitinib)	25–35%	<5%	Moderate to high
ICIs (e.g., nivolumab + ipilimumab)	~40%	12%	Immune-related

4. The advantages and limitations of Belzutifan

4.1. Advantages

Belzutifan opens a new therapeutic paradigm in renal oncology by acting not only on tumor symptoms (e.g., angiogenesis or immune escape), but also by targeting the underlying molecular weakness - hypoxia signaling through HIF-2α. This specificity makes it fundamentally different from conventional VEGF-TKIs or immunotherapies, which act downstream and typically have broader biological effects. Rather than inhibiting HIF activation products (e.g., VEGF), Belzutifan inhibits the HIF-2α transcription factor itself, directly blocking its interactions with ARNT and thereby preventing expression of pro-oncogenes [4].

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This mechanism has two major clinical advantages. First, it reduces the risk of systemic off-target effects by limiting the therapeutic effect to HIF-2α-dependent tumors (especially VHL-deficient tumors). Second, this centralized mechanism allows for better integration into combination regimens, as it avoids overlapping toxicity with other drugs acting on different pathways.

Belzutifan's tolerability is another noteworthy advantage. Compared to immune checkpoint inhibitors (ICIs), which carry a risk of severe autoimmune toxicity, or vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKIs), which are associated with dose-limiting hypertension and gastrointestinal problems, the major adverse events (i.e., anemia and fatigue) of Belzutifan are generally not life-threatening and are easily manageable [7]. However, its hematologic toxicity, particularly grade ≥3 anemia, is of concern and may be a dose-limiting factor in some patients, especially those with pre-existing myelosuppression or poor physical status. Therefore, its tolerability is best characterized as relatively good rather than absolutely good, and clinical intervention may be required.

In addition, Belzutifan is expected to redefine the order of treatment for ccRCC. Its favorable safety profile and oral dosage form make it a candidate for first-line use, especially in patients who cannot tolerate systemic VEGF-TKI or ICI. The LITESPARK-003 trial has demonstrated good efficacy in previously untreated advanced ccRCC, with an ORR of 70% in combination with Cabozantinib in cohort 1 [8]. This not only highlights the synergistic effect of Belzutifan with existing TKIs, but also raises important questions about the ideal therapeutic sequence or combination of hypoxia inhibition and angiogenesis or immunomodulation.

Thus, Belzutifan is more than just another addition to ccRCC therapeutics; it represents a conceptual shift toward upstream tumor-intrinsic targeting. Its greatest strength may lie in its ability to reshape our definition of “targetable” cancer drivers from pathway exporters to pathway modulators while providing a more refined and personalized therapeutic approach.

4.2. Limitations

Belzutifan's molecular precision is both a strength and a limitation - its effectiveness is highly dependent on HIF-2α-driven disease biology mechanisms, while its role in HIF-2α-independent tumors remains uncertain. The therapeutic benefit of Belzutifan is largely limited to von Hippel-Lindau (VHL)-deficient tumors that are highly dependent on HIF-2α activity. In sporadic ccRCC cases lacking this molecular signature, the efficacy of Belzutifan monotherapy appears to be insignificant, with objective remission rates (ORR) ranging from 25% to 30% and complete remission rates (CR) below 1%, highlighting the importance of biomarker-guided patient selection [12]. The variability in treatment response highlights the importance of biomarker-guided patient selection, as not all ccRCC tumors are equally dependent on HIF-2α signaling. In particular, those patients whose tumors lack VHL alterations or exhibit other pro-tumorigenic pathways (e.g., MET or mTOR activation) may have limited benefit from HIF-2α inhibition alone [13]. Therefore, the integration of molecular profiling (e.g., VHL mutation status, HIF-2α expression, and hypoxia-associated genetic markers) into clinical decision-making is critical to optimize therapeutic efficacy and to avoid unnecessary toxicity or delays in effective treatment.

Second, although Belzutifan is generally well tolerated, hematologic toxicities, particularly anemia, have been observed in multiple studies. In the VHL cohort, grade ≥3 anemia was seen in 8% of patients receiving monotherapy [7], and the incidence of anemia was even higher (up to 20%) in combination regimens such as Belzutifan in combination with Cabozantinib [8]. As HIF-2α plays a physiological role in erythropoietin regulation, prolonged inhibition may impair erythropoiesis, thus requiring regular hematologic monitoring and possibly dose adjustment.

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Finally, while early trials have shown favorable disease control and progression-free survival, long-term overall survival data remain limited. Belzutifan is not approved until 2021 [5] and ongoing phase III trials are needed to validate its durable efficacy, particularly in comparison to standard therapies. In addition, issues of drug accessibility and cost may limit its widespread use in resource-limited areas, especially if combination therapies become the standard regimen.

5. Future directions

Belzutifan is a mechanistically novel and clinically meaningful drug that adds a new dimension to the treatment options for clear cell renal cell carcinoma (ccRCC), particularly in patients with von Hippel-Lindau (VHL). - a key oncogenic driver of VHL-deficient tumors - thereby providing therapeutic specificity that is distinct from conventional VEGF or immunotherapy. Clinical trials have demonstrated its efficacy and tolerability both as monotherapy and in combination with multi-target tyrosine kinase inhibitors such as cabozantinib.

However, therapeutic resistance, heterogeneity of efficacy, and targeted toxicities such as anemia remain significant challenges. The increasing use of Belzutifan in sporadic and advanced renal cell carcinoma further highlights the need for more precise biomarker-driven treatment strategies, long-term safety monitoring, and rational combination regimens. As our understanding of the molecular mechanisms of hypoxia signaling continues to improve, Belzutifan holds promise for integration into personalized, biologically-based therapeutic regimens for renal and other cancers.

6. Conclusion

Belzutifan represents a significant breakthrough in the treatment of clear cell renal cell carcinoma (ccRCC), particularly for patients with von Hippel-Lindau (VHL) disease. As a first-in-class HIF-2α inhibitor, it directly targets a key oncogenic driver in VHL-deficient tumors, offering a distinct mechanism compared to VEGF inhibitors or immunotherapy. By suppressing hypoxia signaling, Belzutifan disrupts tumor growth and angiogenesis, demonstrating clinically meaningful efficacy in trials such as LITESPARK-004, both as monotherapy and in combination with agents like cabozantinib.

Despite its promise, several challenges remain. Therapeutic resistance can develop over time, likely due to adaptive tumor responses or pathway redundancy. Additionally, efficacy varies among patients, highlighting the need for predictive biomarkers to guide treatment selection. On-target toxicities, particularly anemia caused by HIF-2α's role in erythropoietin regulation, also require careful management.

As Belzutifan's use expands to sporadic and advanced ccRCC, optimizing its role will depend on biomarker-driven strategies, rational combinations, and long-term safety monitoring. Future research should explore resistance mechanisms, synergistic regimens (e.g., with mTOR or PD-1 inhibitors), and its potential in other HIF-2α-driven cancers. By addressing these challenges, Belzutifan can further solidify its place in precision oncology, offering a targeted approach for ccRCC and beyond.

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