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HIF Inhibition and Emerging Therapeutic Targets in Clear Cell Renal Cell Carcinoma

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Abstract

Clear cell renal cell carcinoma (ccRCC) is characterized by inactivation of the von Hippel-Lindau (VHL) pathway, resulting in stabilization of hypoxia-inducible factors (HIFs) and activation of transcriptional programs involved in angiogenesis, metabolism, and tumour survival. This biology established HIF-2α as a rational therapeutic target and led to the development of belzutifan, the first HIF-2 inhibitor to demonstrate randomized clinical benefit in ccRCC. In this review, we summarize the biologic rationale for HIF inhibition in ccRCC, review the key data supporting belzutifan with a focus on the LITESPARK-005, LITESPARK-011, and LITESPARK-022 studies, discuss next-generation HIF-2 inhibitors, including casdatifan, and briefly highlight other emerging therapeutic targets in ccRCC.

Introduction

Clear cell renal cell carcinoma (ccRCC) is characterized by dysregulation of the von Hippel-Lindau (VHL)/hypoxia-inducible factor (HIF) axis, resulting in stabilization of HIF-α subunits and activation of transcriptional programs involved in angiogenesis, proliferation, erythropoiesis, and metabolic adaptation.[1,2] This biology provided the foundation for vascular endothelial growth factor (VEGF)-directed therapy, but also identified HIF-2α as a more proximal and disease-specific therapeutic target. Belzutifan, the first HIF-2 inhibitor to demonstrate clinical benefit in ccRCC, has expanded the treatment landscape beyond VEGF receptor tyrosine kinase inhibitors (TKI) and immune checkpoint inhibitors (ICI).[3]

This review summarizes the biological rationale for HIF-2 inhibition in ccRCC and reviews the key clinical data supporting belzutifan, with emphasis on the LITESPARK-005, LITESPARK-011, and LITESPARK-022 clinical trials. It also briefly discusses next-generation HIF-2 inhibitors, particularly casdatifan, and outlines other emerging non-HIF therapeutic targets under investigation in ccRCC.

Biologic Rationale for HIF-2 Inhibition

Loss of VHL function is a defining molecular event in most ccRCCs. Under normal oxygen conditions, VHL targets HIF-α subunits for ubiquitin-mediated degradation. When VHL is inactivated, HIF accumulates and drives expression of genes involved in tumour growth and survival, including *VEGF*, *GLUT1*, *CXCR4*, and cyclin D1 (*CCND1*).[1] Although both HIF-1α and HIF-2α contribute to hypoxia signalling, preclinical and translational data support HIF-2α as the more relevant therapeutic target in many ccRCC tumours.[2] HIF-2 inhibition is therefore distinct from conventional antiangiogenic therapy, as it targets a proximal transcriptional driver upstream of multiple downstream programs.

This biology also provides a rationale for combination strategies and for evaluation in earlier disease settings. Combining HIF-2 inhibition with VEGF-directed therapy may enhance pathway suppression by targeting both the upstream driver and downstream angiogenic signalling. There is also interest in moving HIF-2 inhibition to earlier lines of treatment, when tumours may remain more dependent on VHL/HIF biology and before the emergence of resistance mechanisms associated with prior systemic therapy.

Belzutifan: A First-in-class HIF Inhibitor

Early proof-of-concept for belzutifan came from germline/VHL disease-associated ccRCC, in which it showed durable activity and manageable toxicity, demonstrating that HIF-2 could be safely inhibited.[2] The key question, however, was whether this biology would translate to sporadic ccRCC.

In the LITESPARK-005 phase III trial, 746 patients with sporadic mRCC who had previously received both ICI and antiangiogenic therapy were randomized to belzutifan or everolimus.[3] Median progression-free survival (PFS) was 5.6 months in both arms, but the curves separated over time, with a 24-month PFS of 17.5% for the belzutifan arm versus 4.1% for the everolimus arm. The objective response rate was 21.9% versus 3.5%, and median overall survival (OS) was 21.4 versus 18.1 months, respectively; the difference in OS was not statistically significant.[3] The improved landmark PFS suggests that there is a subset of tumours that remain dependent on HIF activity and may experience durable disease control. These data established belzutifan as a clinically relevant option in patients with ICI/anti-VEGF-refractory sporadic metastatic RCC (mRCC). Importantly, patient-reported outcomes from the LITESPARK-005 trial also favoured belzutifan, with better disease-related symptom control and global quality of life relative to everolimus.[4]

The characteristic toxicities of belzutifan largely reflect on-target biology. Anemia is a

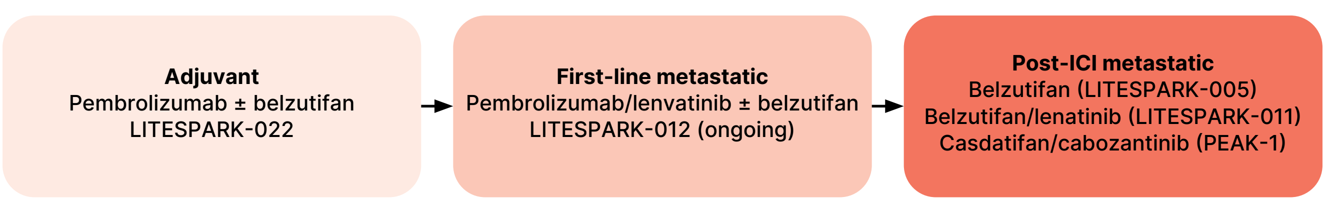

Figure 1. Positioning HIF-2 inhibition across the ccRCC disease continuum, including belzutifan in first-line development (LITESPARK-012), post-PD-(L)1 therapy (LITESPARK-005 and -011), and the adjuvant setting (LITESPARK-022); *courtesy of Bharath Gangadharaiah, MD, and Jeffrey Graham, MD, MPH.*

Abbreviations: ccRCC: clear cell renal cell carcinoma; **HIF-2:** hypoxia-inducible factor 2; **ICI:** immune checkpoint inhibitors; **PD-1:** programmed cell death protein 1; **PD-L1:** programmed cell death ligand 1 common adverse event (AE), as HIF signalling regulates erythropoietin homeostasis. Hypoxia is another common AE and is thought to reflect the drug's impact on oxygen sensing and ventilatory adaptation. In the LITESPARK-005 study, grade ≥3 AEs occurred at similar rates in both arms, but discontinuation due to AEs was lower with belzutifan (5.9%) than with everolimus (14.7%).[3] In practice, anemia and hypoxia require close monitoring, but the safety profile is generally manageable with drug holds and dose reductions. Notably, anemia in the belzutifan arm was managed with an erythropoiesis-stimulating agent alone in 16.7% of participants, blood transfusion alone in 18.5%, and both in 11.3%, supporting the feasibility of continued treatment with appropriate supportive care. Hypoxia occurred in 14.5% of participants receiving belzutifan, with grade ≥3 events in 10.5%, and oxygen therapy was required in 14.5% of participants receiving belzutifan, with grade ≥3 in 5%, and oxygen therapy was required in 10.2%, underscoring the need for vigilance while confirming that these toxicities are usually managed with appropriate intervention.

Belzutifan Combinations and Earlier-line Development: The LITESPARK-011, LITESPARK-022, and LITESPARK-012 Trials

Two phase III trials have reported efficacy data for belzutifan-based combinations in ccRCC: the LITESPARK-011 trial provided evidence for use in previously treated advanced disease, while the LITESPARK-022 study assessed use in the adjuvant setting.

In LITESPARK-011, patients with advanced RCC progressing after anti-PD-(L)1 therapy were randomized to belzutifan plus lenvatinib or cabozantinib.[5] At a median follow-up of 29.0 months, belzutifan plus lenvatinib improved PFS compared with cabozantinib (hazard ratio [HR]: 0.70), with median PFS of 14.8 versus 10.7 months. The objective response rate was also higher with the combination (52.6% vs. 40.2%), as was the duration of response (23 months vs. 12.3 months). Interim OS analysis numerically favoured belzutifan plus lenvatinib (HR: 0.85), but

Trial	Setting	Intervention / comparator	Key efficacy signal	Development status
LITESPARK-005	Post-ICI and antiangiogenic therapy	Belzutifan vs. everolimus	18-mo PFS: 24.0% vs. 8.3%; ORR: 21.9% vs. 3.5%; median OS: 21.4 vs. 18.1 mo	Phase III positive for PFS
LITESPARK-011	After anti-PD-(L)1 therapy	Belzutifan + lenvatinib vs. cabozantinib	Median PFS: 14.8 vs. 10.7 mo; HR: 0.70; ORR: 52.6% vs. 40.2%	Phase III positive; OS immature
LITESPARK-022	Adjuvant intermediate-high risk / high risk / M1 NED	Pembrolizumab + belzutifan vs. pembrolizumab + placebo	24-mo DFS: 80.7% vs. 73.7%; HR: 0.72	Phase III positive; OS immature
LITESPARK-012	First-line metastatic	Pembrolizumab + lenvatinib vs. pembrolizumab + lenvatinib + belzutifan vs. pembrolizumab + quavonlimab + lenvatinib	Primary endpoints: PFS and OS	Ongoing phase III
PEAK-1	After prior PD-(L)1 therapy	Casdatifan + cabozantinib vs. placebo + cabozantinib	Registrational study of next-generation HIF-2 inhibitor	Ongoing phase III

Table 1. Key HIF-2–directed trials in ccRCC; *courtesy of Bharath Gangadharaiah, MD, and Jeffrey Graham, MD, MPH.*

Abbreviations: ccRCC: clear cell renal cell carcinoma; **DFS:** disease-free survival; **HIF-2:** hypoxia-inducible factor 2; **HR:** hazard ratio; **ICI:** immune checkpoint inhibitors; **M1 NED:** metastatic with no evidence of disease; **mo:** months; **ORR:** objective response rate; **OS:** overall survival; **PD-1:** programmed cell death protein 1; **PD-L1:** programmed cell death ligand 1; **PFS:** progression-free survival.

these data remain immature.[5] Grade ≥3 treatment-related AEs occurred in 71.6% of patients receiving belzutifan plus lenvatinib and were comparable to those associated with cabozantinib (65.8%).[5] These findings support further development of belzutifan-based combinations in previously treated ccRCC, although longer follow-up, particularly for OS, will be important. The higher ORR and longer duration of response suggest a subgroup of patients can achieve prolonged disease control, making this combination an attractive option post-ICI, pending regulatory approval.

LITESPARK-022 was a randomized phase III trial in patients with resected intermediate-high-risk, high-risk, or stage M1 with no evidence of disease (NED; defined as metachronous solitary metastasis completely resected within 2 years of primary nephrectomy) ccRCC, comparing adjuvant pembrolizumab plus belzutifan with pembrolizumab plus placebo.[6] This study builds on KEYNOTE-564, which established pembrolizumab as the current standard of treatment in the adjuvant setting. At a median follow-up of 28.4 months, disease-free survival favoured the belzutifan arm (HR: 0.72), and 24-month disease-free survival was 80.7% in the belzutifan arm versus 73.7% for the placebo arm. Median disease-free survival was not reached in either arm, and OS data remain immature.[6] Grade ≥3 treatment-related AEs were more frequent with pembrolizumab plus belzutifan than with pembrolizumab alone (52.1% vs. 30.2%), with anemia and hypoxia contributing to this difference.[6] These results are encouraging, but longer follow-up will be needed to determine whether the disease-free survival benefit is maintained and if this translates into improved OS. Given the added toxicity and potential for overtreatment in the adjuvant setting, demonstrating an OS benefit will be important for defining the risk-benefit profile of this combination.

LITESPARK-012 is an ongoing phase III first-line study evaluating pembrolizumab plus lenvatinib with the addition of belzutifan or quavonlimab in treatment-naïve mRCC.[7] Although efficacy data are not yet available, the first-line setting is an important space to test belzutifan. Tumours may be more dependent on VHL/HIF-driven biology before exposure to prior systemic therapy and the emergence of treatment-related resistance. In addition, incorporating belzutifan into a pembrolizumab/lenvatinib backbone may provide a mechanistically distinct strategy to improve depth and durability of response.[7]

Platform / target	Example	Stage	Current role in ccRCC
PD-1/VEGF bispecific	Ivonescimab (IVORY)	Phase II	Conceptually attractive; RCC efficacy not yet established
ENPP3 × CD3 bispecific	XmAb819	Phase I	Early dose-escalation/expansion in relapsed or refractory ccRCC
CD70-directed cellular therapy	CTX130	Phase I	Proof of concept shown; durability and scalability remain open questions
Individualized neoantigen vaccine	V940 + pembrolizumab (INTerpath-004)	Phase II	Adjuvant strategy under active evaluation
Other oral immune modulators	HPK1 / PTPN2 programs	Early phase	Interesting biology but no definitive RCC efficacy signal yet

Table 2. Selected emerging non-HIF targets in ccRCC; *courtesy of Bharath Gangadharaiah, MD, and Jeffrey Graham, MD, MPH.*

Abbreviations: ccRCC: clear cell renal cell carcinoma; **ENPP3:** Ectonucleotide pyrophosphatase / phosphodiesterase 3; **HIF:** hypoxia-inducible factor; **VEGF:** vascular endothelial growth factor.

Other HIF-2 Inhibitors: How Does Casdatifan Compare?

Belzutifan remains the only approved HIF-2 inhibitor in ccRCC and is supported by randomized phase III studies. Casdatifan is the leading next-generation HIF-2 inhibitor in development. Early studies suggest that casdatifan has clinical activity in previously treated ccRCC and may offer flexibility for combination development, but there are currently no direct comparative data with belzutifan.[8-11] At present, belzutifan remains the only HIF-2 inhibitor with mature phase III efficacy data in ccRCC.

In the phase I ARC-20 study, casdatifan monotherapy showed encouraging activity in previously treated ccRCC, and updated analyses supported 100 mg once daily as the preferred development dose.[8,9] Casdatifan plus cabozantinib has also shown promising early activity, leading to the ongoing phase III PEAK-1 trial.[12] PEAK-1 is evaluating casdatifan plus cabozantinib versus placebo plus cabozantinib in patients with advanced or metastatic ccRCC that has progressed on or after prior anti-PD-1/PD-L1 therapy, with PFS as the primary endpoint. The study design is similar to that of the LITESPARK-011 trial and may provide data for a second HIF-based combination strategy in refractory mRCC.

Data on other HIF-targeting agents remain limited. DFF332 showed modest phase I activity, and its future development in ccRCC remains uncertain.[1] NKT2152 is still in early-phase development, and currently available clinical data are too limited to place it alongside belzutifan or casdatifan.[13]

An important limitation across HIF-2 drug development is the lack of validated predictive biomarkers. At present, there are no established molecular or clinical markers that reliably identify which patients are most likely to derive durable benefit from belzutifan or other HIF-2 inhibitors.[3,9] Although translational analyses are ongoing, treatment selection remains empirical, and biomarker development should remain an important priority for future trials.

Other Emerging Non-HIF Targets in ccRCC

Although HIF-2 inhibition is the most clinically relevant novel target in ccRCC, the broader pipeline continues to expand. One example is anti-PD-1/VEGF bispecific therapy. The phase II IVORY trial is evaluating ivonescimab in patients with previously treated advanced or metastatic ccRCC who received prior ICI treatment.[14] This approach is of interest because it combines both PD-1 and VEGF pathway inhibition within a single molecule, although clinical data in RCC remain limited.

Additional immunotherapy-based strategies are also under investigation. XmAb819, an ENPP3 × CD3 bispecific antibody, is being evaluated in a phase I study in relapsed or refractory ccRCC and is supported by the relatively high ENPP3 antigen expression in this disease.[15,16] Early clinical experience remains preliminary.

CD70-directed cellular therapy is further along in development. In a phase I study, the allogeneic chimeric antigen receptor (CAR)-T cell product CTX130 demonstrated disease control in a substantial proportion of treated patients with advanced ccRCC, including a durable complete response in one patient.[17] Finally, individualized neoantigen vaccination is being studied in the adjuvant setting. INTerpath-004 is evaluating the ICI pembrolizumab with or without the mRNA-based vaccine V940 in patients with RCC at increased risk of recurrence after nephrectomy.[16] Overall, these approaches remain investigational and should be considered only in the context of clinical trials.

Conclusions

HIF-2 inhibition has evolved from a biological concept in ccRCC to a clinically relevant therapeutic strategy. Belzutifan is now supported by randomized data in advanced and adjuvant ccRCC.[3,4] Results from the LITESPARK-011 and LITESPARK-022 studies suggest that further development of HIF-2 inhibition will likely focus on combination approaches and use in earlier disease settings, although OS and longer-term outcome data remain immature.[5,6] LITESPARK-012 will be an important study in defining whether belzutifan has a role in the first-line setting.[7] Casdatifan is the leading next-generation HIF-2 inhibitor in development and is currently being evaluated in the ongoing phase III PEAK-1 trial.[8-10] At present, HIF-2 inhibition has become an important component of the therapeutic landscape in ccRCC, whereas bispecific antibodies, cellular therapies, and individualized vaccines remain in earlier stages of clinical development.

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