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Current Perspective

The road to systemic therapy in von Hippel-Lindau (VHL) disease: Are we there yet?

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Abstract Pathogenic germline mutations in *VHL* gene cause von Hippel-Lindau (VHL) disease, an autosomal dominant hereditary cancer syndrome associated with high penetrance of benign and malignant neoplasms, including clear cell renal cell carcinoma (ccRCC), central nervous system haemangioblastomas (CNS-HB), retinal angiomas, phaeochromocytomas and pancreatic neuroendocrine tumours (pNET). Management of VHL disease involves lifelong radiological and biochemical surveillance, often leading to repeat surgical intervention causing significant morbidity and mortality. Systemic therapy that prevents or reduces the need for surgical intervention could improve clinical outcomes and quality of life for affected individuals. Belzutifan is a second-generation small molecule hypoxia-inducible factor 2α (HIF-2α) inhibitor recently approved by US and UK regulators for the treatment of VHL (disease)-associated ccRCC, CNS-HB and pNET. While this is a welcome step forward, it is vital that we consider in what circumstances these drugs are recommended and how they fit into the overall management of VHL disease. In this *personal view* article, we reflect on the history of the use of systemic therapy in localised VHL disease and consider open questions relating to the use of HIF-2α inhibitors, including the need to involve medical oncologists in the multidisciplinary team moving forward. Indeed, VHL disease is the perfect paradigm for similar settings in the future.

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1. Von Hippel-lindau (VHL) disease: clinical syndrome and molecular pathogenesis

von Hippel-Lindau (VHL) disease is an autosomal dominant hereditary cancer syndrome caused by pathogenic germline variants in the *VHL* tumour suppressor gene [1]. It has an estimated population prevalence of 1 in 47,000 individuals and affects 1 in 27,000 live births [2,3]. Affected individuals are at risk of developing multiple benign and malignant neoplasms (Fig. 1A) including clear cell renal cell carcinomas (ccRCC), retinal and central nervous system haemangioblastomas (CNS-HB), pancreatic neuroendocrine tumours (pNET), phaeochromocytoma/paraganglioma (PPGL) and kidney and pancreatic cysts [3,4]. Rare manifestations include epididymal or broad ligament cysts and endolymphatic sac tumours.

VHL disease is characterised by high penetrance with lifetime risk of developing ccRCC and/or CNS-HB 69% and 84%, respectively [3,4]. Affected and at-risk individuals are subject to active surveillance protocols for early detection and monitoring of disease. CNS-HB are typically monitored until neurological symptoms develop at which point a surgical approach is favoured although

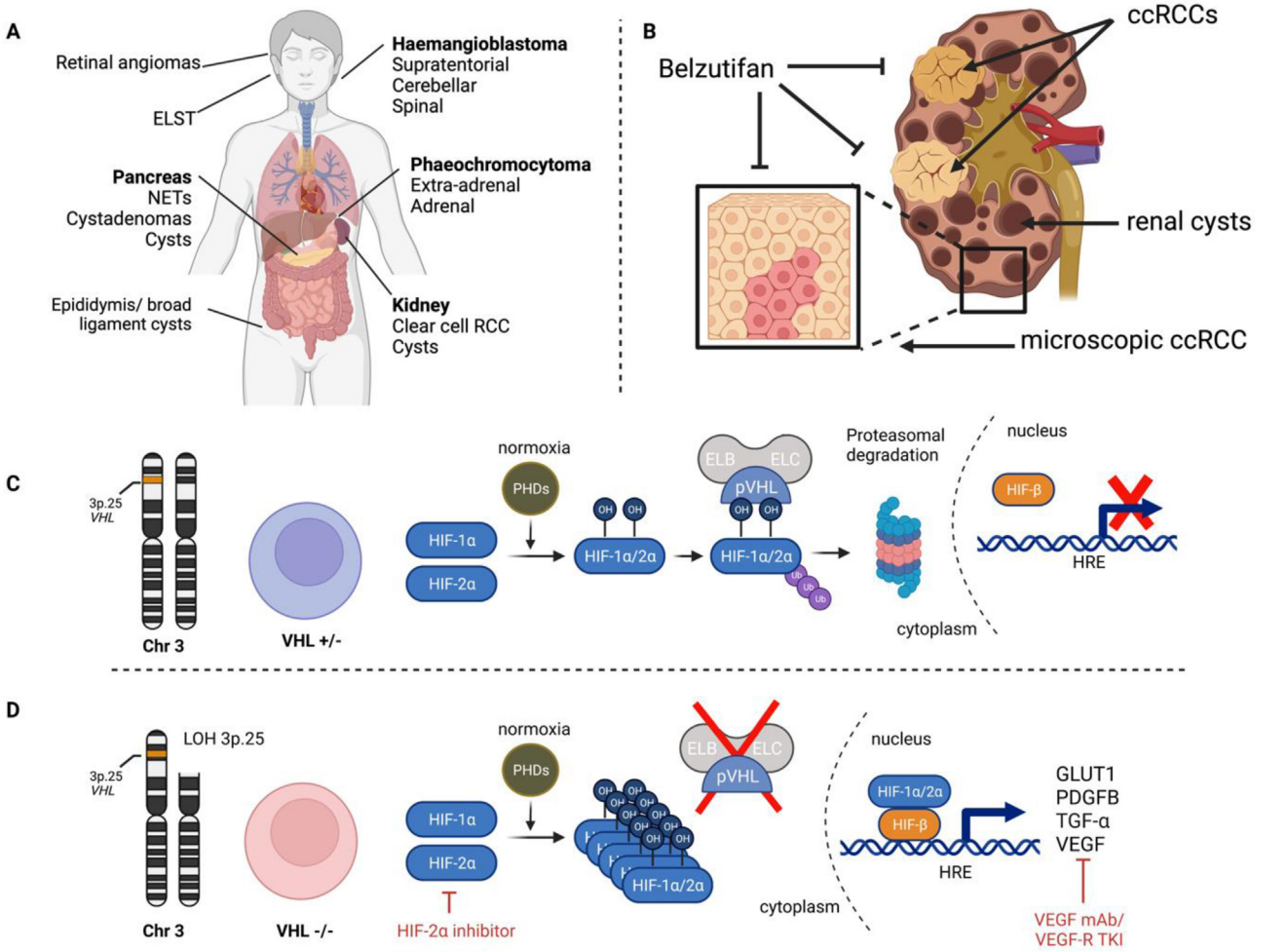

Fig. 1. VHL-HIF axis in VHL disease. **(A)** Clinical phenotype of VHL disease. **(B)** HIF2α antagonist belzutifan inhibits impact of constitutive activation of VHL-HIF axis in clinically significant and microscopic manifestations of VHL disease **(C)** under normoxic conditions hypoxia-inducible factor-1α (HIF1α) and HIF2α are hydroxylated on conserved proline residues by prolyl-hydroxylase enzymes (PHDs) and are recognised by pVHL which acts as the substrate recognition component of a E3 ubiquitin ligase complex with Elongin B and C (collectively VCB complex). HIF1α/2α is then targeted for ubiquitylation and proteosomal degradation **(D)** following loss of the wild-type copy of VHL, typically through loss of heterozygosity of chromosome 3p, HIF1α/2α accumulates and forms heterodimers with HIF1β which translocate to the nucleus, bind to hypoxia response elements (HREs) leading to activation of HIF-mediated transcription and a pro-tumorigenic cellular phenotype. The dysregulated VHL-HIF axis may be targeted either at the proximal node through small molecule inhibitors of HIF2α or distally by targeting HIF-mediated transcription products such as VEGF. Chr, chromosome; ELB, elongin-b; ELC, elongin-c; ELST, endolymphatic sac tumour; GLUT1, Glucose transporter 1; HIF, hypoxia-inducible factor; HRE, hypoxia response element; LOH, loss of heterozygosity; mAB, monoclonal antibody; OH, hydroxylated proline residue; PDGFB, platelet derived growth factor b; PHD, prolyl-hydroxylase; TGF-α, Transforming growth factor alpha; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; pVHL, VHL gene product; VEGF-R, vascular endothelial growth factor receptor

intervention with stereotactic radiosurgery may also provide disease control [5,6]. In the kidney, tumours are frequently bilateral and multifocal with innumerable tumour foci visible microscopically [7,8]. Where possible, nephron sparing surgery is most commonly performed when the dominant lesion reaches 3 cm diameter as the risk of metastasis is minimal below this threshold although consideration may be given to removal of a rapidly growing lesion measuring <3 cm. Dozens of tumours may be removed in a single surgery [9], and repeat surgeries are common at intervals of 3–5 years [10,11].

By consequence, the risk of renal metastasis with modern surveillance is low [2]; however, lifelong surveillance and repeat surgical intervention are associated with considerable physical morbidity, including renal insufficiency or neurological sequale, and psychological morbidity [2,12,13]. Moreover, while such measures have improved survival [2,14,15], recent population studies indicate persistent excess mortality with most deaths attributable to complications of CNS-HB. Systemic therapies that control VHL disease-related neoplasms could significantly benefit patients by minimising surgical intervention, preserving organ function and improving overall survival.

The *VHL* gene is located on the short arm of chromosome 3 (3p25) and encodes pVHL protein that orchestrates the cellular response to hypoxia [1,4] (Fig. 1C). Under normoxic conditions, pVHL targets hypoxia inducible factor alpha (HIF-α) for proteasomal degradation. In the presence of hypoxia, HIF-α accumulates leading to transcriptional activation of genes involved in metabolism, angiogenesis, proliferation and cellular survival [4]. In patients with VHL disease, one copy of *VHL* is mutated in the germline, and the second allele can be lost somatically (usually through loss of chromosome 3p). Subsequent loss of pVHL leads HIF-α to accumulate in the absence of hypoxia (referred to as 'pseudohypoxia') resulting in constitutive activation of the downstream HIF targets-and tumorigenesis in the affected tissues [4,16]. Loss of *VHL* is also observed in the majority of sporadic ccRCC, although the order of events is reversed, with 3p loss occurring first and *VHL* mutation second [17].

Belzutifan is a second-generation small molecule hypoxia-inducible factor 2α (HIF-2α) inhibitor recently approved by US and UK regulators for the treatment of non-metastatic VHL-disease-associated ccRCC, pNET and CNS-HB not requiring immediate surgery [18–21]. This is the first instance of approval of a systemic therapy in the setting of VHL disease, and it is vital that we consider the principles of application of potentially lifelong drug therapy. We outline the potential challenges firstly by reviewing the experience to date with systemic therapy in localised VHL disease; we define the open questions on the use of HIF-2α inhibitors in this setting, and finally, we suggest a model for integration of medical oncology into existing multi-disciplinary networks and a framework for future trials and to support research in this area.

2. The role of VEGF inhibition in VHL disease

The role of HIF signalling in sporadic ccRCC led to the clinical development of therapies targeting downstream HIF effectors, in particular VEGF (Fig. 1D) [22–24]. Small molecule inhibitors of VEGF revolutionised treatment of metastatic sporadic ccRCC, a chemotherapy-refractory cancer. In this setting, objective response rates are seen in a third of patients, median duration of therapy is 8 months (usually discontinued for disease progression) and the treatment is associated with a clear overall survival benefit [22,25].

Two prospective studies (Table 1) of VEGF inhibitors sunitinib [26] and pazopanib [27] have been performed in patients with localised VHL disease. Reported objective responses were reported in 6/18 (33%) and 31/59 (49%) of ccRCCs, respectively. Complete tumour regression was rare and following discontinuation of treatment, renal tumours typically grew back to their pre-treatment dimensions over a 6-month period [27]. Critically, there was limited efficacy in CNS-HBs (overall response rate [ORR] 0–4%), and results for pancreatic tumours were mixed (ORR 0–53%) [26–28].

VEGF-targeted therapy in the setting of localised VHL disease was associated with significant toxicity. Although the toxicity was comparable to that seen in patients with metastatic ccRCC, dose reduction and/or early therapy discontinuation was required in around two thirds of patients (Table 1) in contrast to less than one quarter in patients with advanced sporadic ccRCC. Notably, two patients with CNS-HB had intracranial bleeding while receiving or immediately after discontinuation of pazopanib, raising concern that VEGF-targeted therapy can exacerbate vascular friability and increase risk of haemorrhage [27].

In summary, VEGF-targeted therapy showed modest clinical activity with significant toxicity leading to early therapy discontinuation in most patients with VHL disease. It is important to consider the context of treatment; most VHL patients are asymptomatic of their disease and do not have an immediate risk of shortened survival, so the incentive to continue experimental therapy in the face of uncertain benefit and significant reduction in quality of life is less than in patients with metastatic disease.

3. Targeting HIF-2α in VHL disease

Although VEGF inhibitors transformed the treatment of sporadic RCC, emergence of resistance was inevitable, and efforts began to target the HIF-α pathway more proximally. The two isoforms of HIF α, HIF-1α and HIF-2α, play distinct roles in the hypoxia response [4,16], with HIF-2α implicated as the main driver of tumorigenesis [29,30]. The discovery of a druggable cavity within the PAS-B domain of HIF-2α [31] led to the development of selective, potent HIF-2α antagonists

Table 1
Prospective evaluation of systemic therapy in localised VHL disease-related neoplasms. Reporting of response rates variable between studies; symbols in table indicate if response reported as sum of all target lesions or reported as response in individual lesions.

Design	Drug	Duration of Rx	Targets	n patient	ORR, n (%)			Early cessation Rx, n (%)
					RCC	Pancreatic	CNS-HB	
Sunitinib [26]	Phase II, open label	24 weeks only	VEGFR, PDGF-R, c-KIT, RET	15	6/18[b] (33)	0/5[b] (0)	0/21[b] (0)	6/15 (40)
Dovitinib [28]	Phase II, open label	24 weeks only	VEGFR, FGFR, PDGFR	6	NR	NR	0/9[b] (0)	6/6 (100)
Pazopanib [27]	Phase II, open-label	24 weeks, option to continue	VEGFR, PDGFR, c-KIT	31	31/59[b] (53)	9/17[b] (53)	2/49[b] (4)	25/31 (81)
Belzutifan [21]	Phase II, open-label	Until PD or toxicity	HIF-2a	61	30/61[a] (49)	47/61[a] (77)	15/50[a] (30)	7/61 (11)

CNS-HB, central nervous system haemangioblastoma; FGFR, fibroblast growth factor; HIF, hypoxia inducible factor; N, number; NR, not reported; ORR, overall response rate; PD, progressive disease; PDGFR, platelet derived growth factor; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; Rx, treatment; VEGFR, vascular endothelial growth factor.
[a] Patient level (i.e. sum of all target lesion diameters) or individual lesion.
[b] Lesion level (i.e response in individual target lesions). Responses in pancreatic neoplasms included both pancreatic cystadenomas and pancreatic neuroendocrine tumours in these studies.

(Fig. 1C) [32]. Belzutifan (MK-6482, previously PT2977) is a first-in-class small-molecule HIF-2α antagonist that first demonstrated clinical activity (ORR 25%) in the setting of advanced ccRCC refractory to VEGF-targeted therapy [18]. Belzutifan is currently evaluated in multiple randomised phase three studies in combination with other agents, both in adjuvant and metastatic setting. In a single-arm study when combined with cabozantanib (a multikinase inhibitor), bezultifan is associated with an ORR 57% and median progression free survival of 30 months in the first line treatment of metastatic ccRCC [33].

In the context of localised VHL disease, belzutifan was evaluated in a single-arm phase II study (NCT03401788, inclusion criteria in Box 1) where the primary end-point was ORR in renal neoplasms, and secondary end-points were safety and ORR in extra-renal tumours. Of the 61 patients enrolled on the study (Table 2), all had localised ccRCCs (100%), 50/61 (82%) had CNS-HB, 20/61 (33%) had pNET and 12/61 (20%) had retinal HB that were evaluable. Patients had a median of 2.0 (range, 1.0 to 5.0) ccRCC target lesions, 1.0 (range, 1.0 to 3.0) pancreatic target lesions and 1.5 (range, 1.0 to 5.0) CNS-HB target lesions, none of which required immediate surgery.

At median 21.8 months of follow-up, ccRCC objective responses were evident in 30/61 (49%) patients, and a reduction in the sum of target renal lesions was observed in56/61 (91%) patients. Considering extra-renal tumours, 47/61 (77%) of patients had response in pancreatic lesions (including 20/22 (91%) in pNETs), 15/50 (30%) in HBs and all retinal-HB were graded as showing improvement. Patients under study underwent 64 surgical interventions in the 2.5 years prior to commencing belzutifan, and only three were required during 22 months of the study.

All patients had at least one treatment-related adverse effect (AE), mostly grade 1 or 2, including anaemia, fatigue, headache and dizziness. All patients experienced a decrease in haemoglobin, due to expected on-target inhibition of erythropoietin (EPO) and 9/61 (15%) patients had grade 3 AEs including symptomatic anaemia, 4/61 (7%) patients required blood transfusion and 12/61 (20%) received erythropoietin stimulating agents. Dose reductions due to AEs occurred in 9/61 (15%) patients, treatment interruption in 26/61 (43%) and one patient (2%) discontinued treatment due to treatment related AEs (grade 1 dizziness). There were no grade 4 or 5 treatment related AEs.

Updated efficacy and safety data [34] at median 37.8 months follow-up indicate durable responses in renal and extra-renal lesions with the median duration of response not reached (Table 2). In addition, the number of patients with objective responses in renal, pancreatic and CNS tumours increased with additional follow-up (ORR 64% ccRCC; 90% pNET; 44% CNS-Hb), and

Box 1. Clinical trial design and end-points of LITESPARK-004 (NCT03401788)

Study design	Open-label, single-arm, phase 2 study
Eligibility criteria	Diagnosis of VHL disease, based on presence of germline mutation >1 measurable RCC tumour No prior systemic anticancer therapy No metastatic disease ECOG PS 0 or 1
Intervention	Belzutifan 120 mg orally once daily
Primary end points	ORR in VHL disease-associated RCC per RECIST v1.1 by IRC
Secondary end points	ORR in non-RCC neoplasms DOR in RCC and non-RCC neoplasms Safety

ORR, overall response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumours; VHL, von Hippel-Lindau.

Table 2
Longitudinal follow-up data from LITESPARK-004 study.

Report	LITESPARK-004 (NCT03401788)		
	Jonasch *et al.* [21]	Srinivasan *et al.* [34]	Srinivasan *et al.* [46]
Months of follow-up, n	21.8	29.3	37.8
ccRCC, n = 61 patients			
ORR, n (%)	30 (49)	36 (59)	39 (64)
CR, n (%)	0 (0)	2 (3)	4 (7)
pNET,n = 20 patients			
ORR, n (%)	18 (90)	18 (90)	18 (90)
CR, n (%)	3 (15)	3 (15)	4 (20)
CNS-HB, n = 50 patients			
ORR, n (%)	15 (30)	19 (38)	22 (44)
CR, n (%)	3 (6)	3 (6)	4 (8)
Retinal-HB, n = 16			
Improvement, n (%)	16 (100)	16 (100)	16 (100)
VHL disease related surgeries			
Number of patients[a], n (%)	3 (6)	3 (6)	10 (16)
Treatment discontinuation, n (%)	7 (11)	11 (18)	23 (38)
Reason for discontinuation, n (%)			
Progressive disease in RCC	0 (0)	4 (7)	6 (10)
Patient decision	4 (7)	4 (7)	11 (18)
Adverse events	1 (2)	2 (3)	NR
Patient death	1 (2)	1 (2)	NR

CNS, central nervous system; CR, complete response; HB, haemangioblastoma; N, number; NR, not reported; ORR, overall response rate; RC, renal cell carcinoma.
[a] Some patients required surgery on multiple organ systems at a single time point and/or multiple surgeries over different time points.

no new safety signals were seen. More patients required surgical intervention (10/61 patients, 16%) with some requiring multiple surgeries at different time points. At median of 37.8 months follow-up, 38/61 (62%) patients remained on therapy; reasons for therapy discontinuation included progressive disease in renal neoplasms (6/61, 10%) and patient decision to withdraw (11/61, 18%).

In summary, belzutifan has demonstrated durable responses in renal and extra-renal VHL disease-related tumours with a manageable toxicity profile. Following 3 years of therapy, majority of patients remained on treatment with a significant reduction in the need for surgical intervention.

4. HIF-2α antagonists in VHL disease: a new treatment paradigm?

Belzutifan has received US and UK marketing authorisation for the treatment of VHL-associated RCC, pNET and CNS-HB not requiring immediate local procedures [19,20]. European Medicines Agency approval is awaited, and UK National Health Service (NHS) reimbursement remains the subject of ongoing review [35,36]. Notably, neither marketing licence includes treatment of PPGL which are subject of an ongoing clinical trial (NCT04924075). While these approvals mark an important milestone in management of VHL disease, important considerations remain.

First, *which* patients with VHL disease should be offered systemic therapy? Inclusion criteria for the registration study [21] (Box 1) and wording of marketing authorisations are broad, only excluding those requiring immediate surgery. In the trial, objective responses were variable and the median time to response was 8.4 months (range 2.5–22.0) for RCC, 6.8 months for pancreatic lesions and 3.2 months for CNS lesions. Therefore, belzutifan should not be considered as medical 'rescue' therapy, and symptomatic or clinically significant tumours should be managed definitively within the specialist multidisciplinary team (MDT). The goals of medical therapy should be pre-emptive, to achieve disease response and/or stabilisation to either reduce or de-risk surgical intervention and associated physical and psychological morbidity.

Second, for how long should belzutifan therapy be continued? In the context of a chronic disease where non-metastatic neoplasms are not-immediately, life-threatening balancing quality-of-life against clinical benefit is paramount. So-called 'low-grade' AEs as qualified by CTCAE can have significant detrimental impact on quality of life and any grade occurrence of anaemia (89%), fatigue (61%), dizziness (25%) and nausea (23%) were recorded. In addition, pre-clinical toxicity studies indicate that belzutifan caused foetal-embryo toxicity *in-vivo*, and so highly effective contraception is essential for all patients of childbearing age [20]. Other approaches, which would benefit from prospective evaluation, are different dosing schedules, including intermittent dosing. There is evidence in the setting of metastatic sporadic ccRCC that intermittent dosing of VEGF-targeted therapy after maximal radiological response does not lead to reduced clinical benefit [37].

Third, *how should management of treatment-related anaemia be optimised?* Anaemia and associated

symptoms are the dominant on-target toxicity of belzutifan. Repeat transfusion may not be acceptable to many patients and use of EPO-stimulating agents are usually restricted to patients receiving systemic therapy with palliative intent [38]. Optimising management of anaemia (including through treatment breaks) may improve the tolerability to the treatment and quality of life for patients.

Finally, *how do HIF-2α inhibitors alter the natural history of VHL disease and how should we manage the emergence of resistance?* In LITESPARK-004 [21], belzutifan was frequently discontinued at disease progression and therefore a role for its use beyond progression in RCCs has not been established. Although emergence of treatment resistance was infrequent, longer-term follow up is necessary to understand how belzutifan might impact lifelong management of VHL disease.

Relatedly, in morphologically normal appearing kidney from VHL patients, microscopic foci of cells expressing HIF-1α/2α are seen and expression of HIF-2α increases with the degree of dysplasia [7]. These pre-symptomatic lesions (Fig. 1B) may be vulnerable to HIF-2α inhibition, and an additional benefit of belzutifan may be in reducing the life-time burden of clinically significant tumours. This principle of utilising clinically active systemic therapy in prevention has wider relevance for the use of systemic therapy in the reversal of multisystem manifestations, such as tuberous sclerosis complex and Xeroderma pigmentosum [39–41].

5. MDT management of VHL disease: an emerging role for the medical oncologist

The VHL Alliance has advocated for a model of care prioritising multidisciplinary working through designation of comprehensive VHL clinical care centres [42] representing medical genetics, urology, neurosurgery, endocrinology, ophthalmology, interventional and diagnostic radiology, radiation oncology and clinical nurse specialists. These hubs provide coordinated care between specialities, promote timely screening and serve as a source of information for patients with VHL disease and their care givers. Globally, there is little information available on access to appropriate surveillance outside of centres with a research interest in VHL disease. In the UK, there are no centrally commissioned VHL services although majority of care is via speciality clinics coordinated through medical genetics services [43].

To realise the potential of systemic therapy in the management of the disease, it is crucial that the medical oncology community embed themselves in these MDT structures and are educated on the complexity of managing VHL disease. Conversely, the existing MDT will require education on the opportunities that systemic therapy may hold; a compelling model for delivery of belzutifan would be the establishment of tertiary referral centres drawing on medical oncology expertise in oncologic drug procurement, governance for safe prescribing, oncologic toxicity management and resources for insurance approvals within healthcare systems. Moreover, centralised delivery of care would allow the necessary volume of patients for implementation of investigator-led clinical trials to explore alternative dosing, combination with other agents, optimising management of AEs and integrating translational research. The advent of telemedicine could overcome geographical barriers to this care model, providing an opportunity for centralised oncology advice based on imaging review with only occasional as-required in-person review [44,45]. Critical to the success of these efforts will be engagement with patient advocacy groups and other stakeholders to ensure that relevant, patient focussed questions are being addressed.

While involvement of medical oncology would accelerate these therapeutic opportunities, the monitoring of treatment response should remain within the 'parent' MDT where the need for surgery or other definitive intervention can be evaluated. Embedding a translational research program into this paradigm would allow mechanisms of treatment resistance to be explored with multicentre collaboration to conduct this at a meaningful scale.

In summary, efficacy and safety data of HIF-2α antagonists make a compelling case for the use of these agents in the management of localised VHL disease. We advocate for the establishment of national and international collaborative research networks and engagement with patient advocacy groups to realise the therapeutic opportunity of HIF-2α antagonists in the treatment of this challenging disease.

Author contributions

Scott TC Shepherd: Writing – original draft, Visualisation, Writing – review and editing.

William M Drake: Writing – review and editing, Supervision.

Samra Turajlic: Writing – review and editing, Supervision, Decision to submit.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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