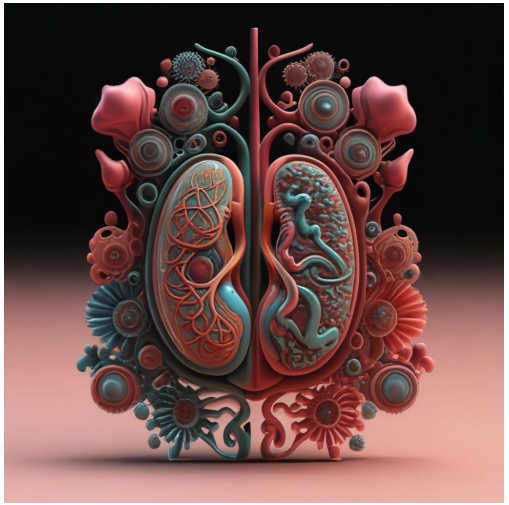
VGO NORTE INTERNATIONAL GU DEBATES

Inhibiting HIF in VHL syndrome:

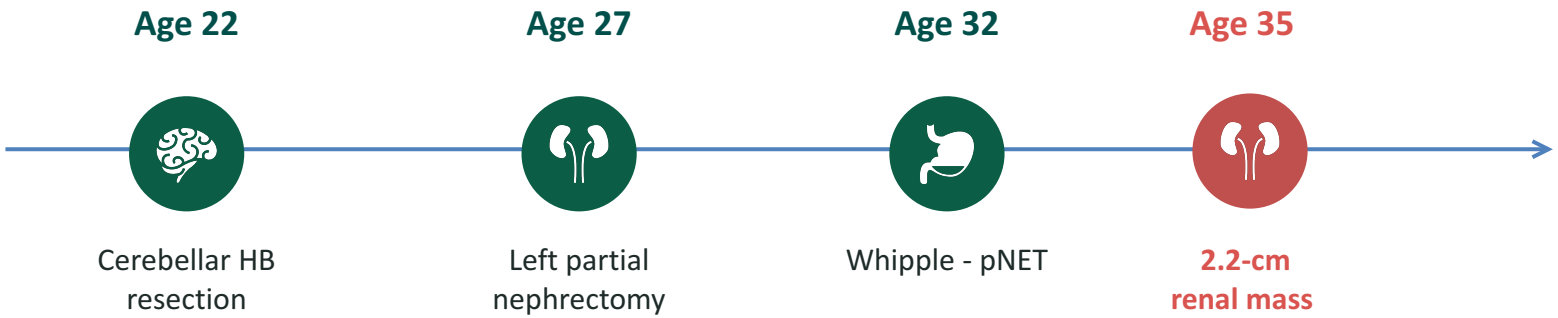
A life changer for patients?



Guillermo de Velasco MD, PhD

Hospital Universitario 12 de Octubre, Madrid

Meet C.: 3 operations — and she is only 35



Every tumour we remove is replaced by the next one.

In VHL, surgery treats the lesion — never the disease.

Illustrative composite patient. HB, haemangioblastoma; pNET, pancreatic neuroendocrine tumour.

One germline hit, a lifetime of tumours

Organ	Tumour	Lifetime risk
Retina	Haemangioblastoma	**25–60%**
CNS	Haemangioblastoma	**60–80%**
Kidney	Clear-cell RCC	**up to 70%**
Pancreas	pNET	**5–17%**
Adrenal	Phaeochromocytoma	**10–20%**
Inner ear	Endolymphatic sac tumour	**10–16%**

1 in 36,000
births carry a germline VHL variant

>90%
penetrance by age 65

~50 years
median life expectancy before HIF-2α inhibition

Lonser RR et al. Lancet 2003; Maher ER et al. Eur J Hum Genet 2011; Tachiki et al. Transl Androl Urol 2025.

The old playbook: watch, wait, cut… repeat



MRI every 6–12 months → Lesion reaches 3-4 cm → Nephron-sparing surgery → A new lesion appears

Cumulative surgery → CKD and dialysis; cerebellar and spinal resections → ataxia and deficits; retinal lesions → blindness.

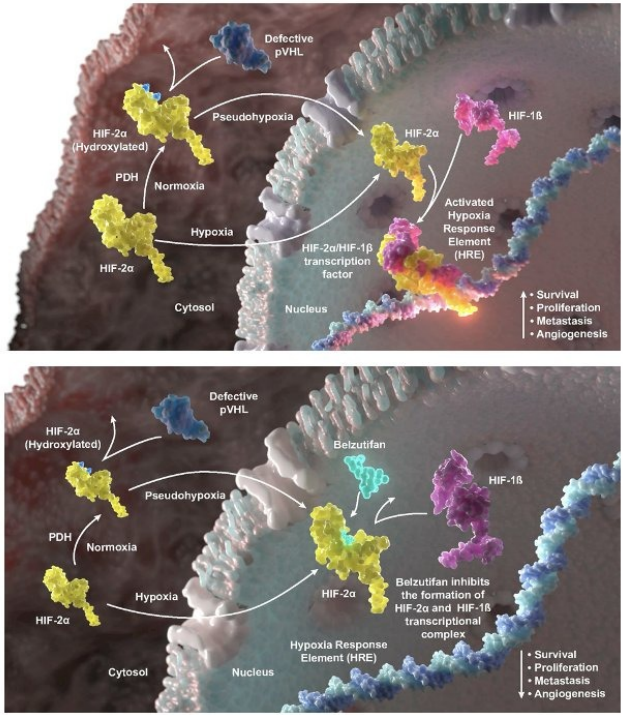
75%

of LITESPARK-004 patients underwent ≥1 VHL procedure in the 5 years before belzutifan

97 procedures in 46 of 61 patients

Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024).

How belzutifan works: switching off pseudohypoxia



Normal cell: HIF-2α is hydroxylated by PHD and destroyed via VHL.

VHL loss: HIF-2α accumulates, pairs with HIF-1β and switches on VEGF, cyclin D1, GLUT1, EPO.

Belzutifan: binds HIF-2α and blocks the HIF-2α/HIF-1β complex.

Every VHL tumour runs on this single switch.

3 milestones to get to belzutifan… 25 years

1993

The gene



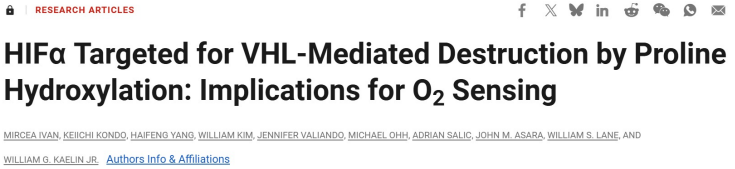
REPORT

Identification of the von Hippel-Lindau Disease Tumor Suppressor Gene

FARIDA LATIF, KALMAN TORY, JAMES GNARRA, MASAHIRO YAO, FUH-MEI DUH, MARY LOU ORCUTT, THOMAS STACKHOUSE, IGOR KUZMIN, WILLIAM MODI, [...], AND MICHAEL I. LERMAN +23 authors Authors Info & Affiliations

2001

The mechanism



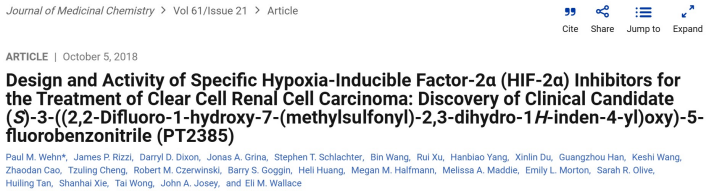
RESEARCH ARTICLES

HIFα Targeted for VHL-Mediated Destruction by Proline Hydroxylation: Implications for O_2 Sensing

MIRCEA IVAN, KEIICHI KONDO, HAIFENG YANG, WILLIAM KIM, JENNIFER VALIANDO, MICHAEL OHH, ADRIAN SALIC, JOHN M. ASARA, WILLIAM S. LANE, AND WILLIAM G. KAELIN JR. Authors Info & Affiliations

2018

The drug



Journal of Medicinal Chemistry > Vol 61/Issue 21 > Article

Cite Share Jump to Expand

ARTICLE | October 5, 2018

Design and Activity of Specific Hypoxia-Inducible Factor-2α (HIF-2α) Inhibitors for the Treatment of Clear Cell Renal Cell Carcinoma: Discovery of Clinical Candidate (*S*)-3-((2,2-Difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1*H*-inden-4-yl)oxy)-5-fluorobenzonitrile (PT2385)

Paul M. Wehn*, James P. Rizzi, Darryl D. Dixon, Jonas A. Grina, Stephen T. Schlachter, Bin Wang, Rui Xu, Hanbiao Yang, Xinlin Du, Guangzhou Han, Keshi Wang, Zhaodan Cao, Tzuling Cheng, Robert M. Czerwinski, Barry S. Goggin, Heli Huang, Megan M. Halfmann, Melissa A. Maddie, Emily L. Morton, Sarah R. Olive, Huiling Tan, Shanhai Xie, Tai Wong, John A. Josey, and Eli M. Wallace

2019 Nobel Prize · **2021** FDA (VHL) · **2025** EMA · **2026** reimbursed in Spain

Latif F et al. Science 1993; Ivan M et al. Science 2001; Wehn PM et al. J Med Chem 2018.

LITESPARK-004: 61 patients, one pill, 5 years

Key Eligibility Criteria

- Diagnosis of VHL disease, based on germline alteration
- ≥1 measurable RCC tumor
- No RCC tumor or other VHL tumor that necessitates immediate surgery[a]
- No prior systemic anticancer therapy
- No metastatic disease
- ECOG PS 0 or 1

N = 61

Belzutifan
120 mg orally once daily[b]

Tumor Assessments

- At screening and every 12 weeks for a minimum of 3 years, then every 24 weeks thereafter

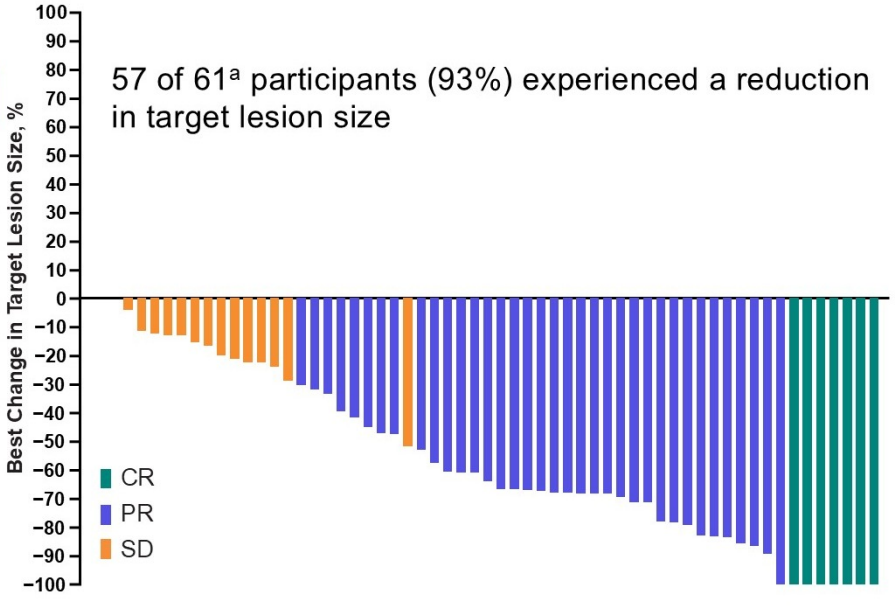
End Points

- Primary: ORR in VHL disease–associated RCC per RECIST v1.1 by IRC
- Secondary: ORR in other VHL disease–associated neoplasms; DOR; TTR per RECIST v1.1 by IRC; and safety

Jonasch E et al. N Engl J Med 2021; Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024).

RCC: 70% respond, 93% shrink — 0 progressions

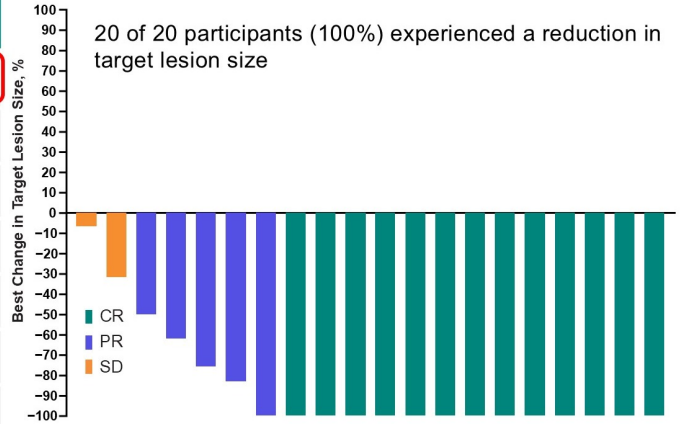
	RCC N = 61
ORR, % (95% CI)	70 (57-81)
Best response n (%)	
CR	7 (11)
PR	36 (59)
SD	17 (28)
PD	0
NE[a]	1 (2)



Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024).

Not just the kidney: every VHL organ responds

	pNETs n = 20
ORR, % (95% CI)	90 (68-99)
Best response n (%)	
CR	13 (65)
PR	5 (25)
SD	2 (10)
PD	0
NE	0



90%

pNET ORR — 65% complete responses

50%

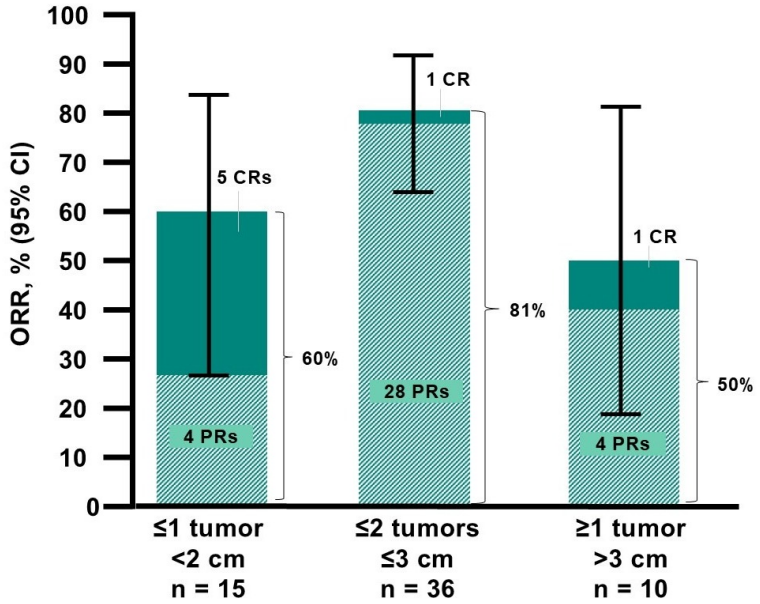
CNS haemangioblastoma ORR

14/14

retinal haemangioblastomas improved

Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024).

Treat earlier? Smaller tumours respond better



81%

ORR with ≤2 tumours ≤3 cm

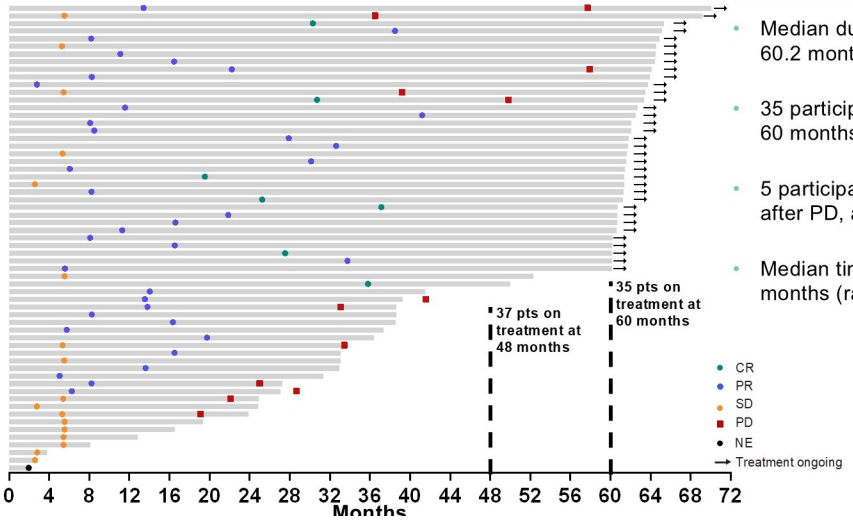
50%

ORR with ≥1 tumour >3 cm

Waiting for 3 cm may mean waiting too long.

Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024).

Responses last: 35 patients still on drug at 5 years



- Median duration of therapy was 60.2 months (range, 1.9-70.1)
- 35 participants remained on treatment at 60 months
- 5 participants were ongoing treatment after PD, as of the data cutoff date
- Median time to response[a] was 8.5 months (range, 2.7-41.2)

IN RESPONSE AT 48 MONTHS

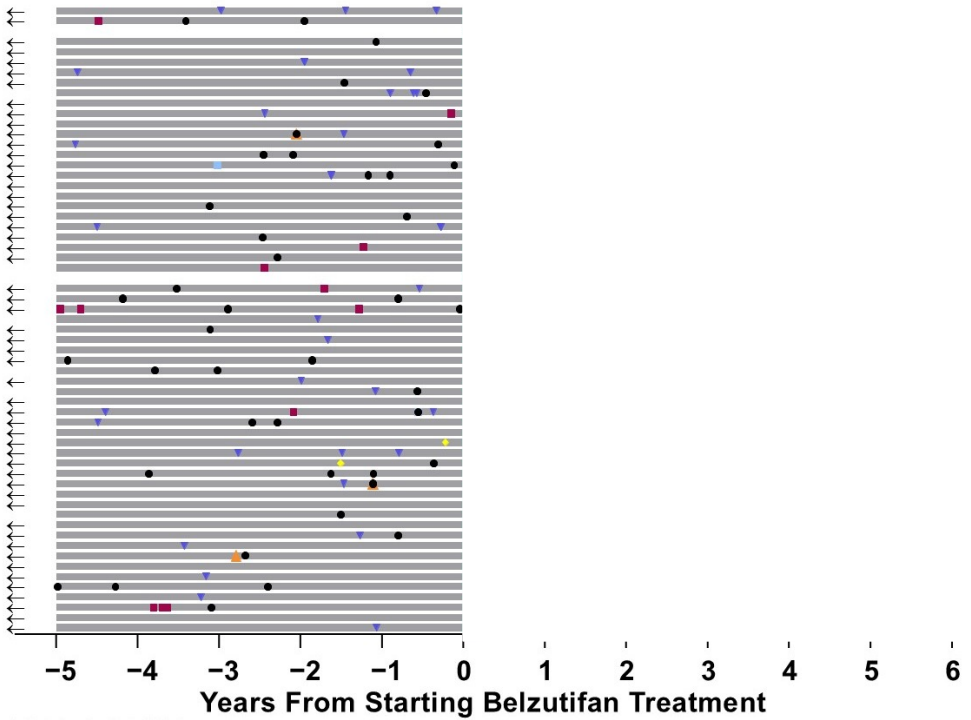
76%
RCC

82%
CNS haemangioblastoma

94%
pNET

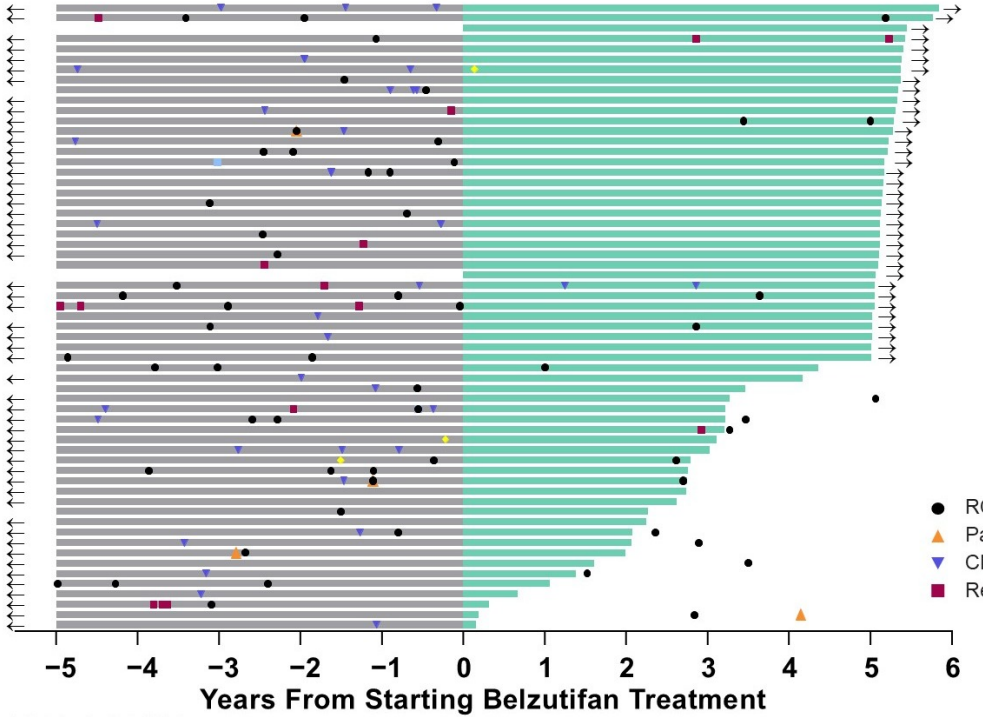
Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024). Median time to RCC response 8.5 months.

The endpoint patients care about: 97 procedures → 24



Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024).

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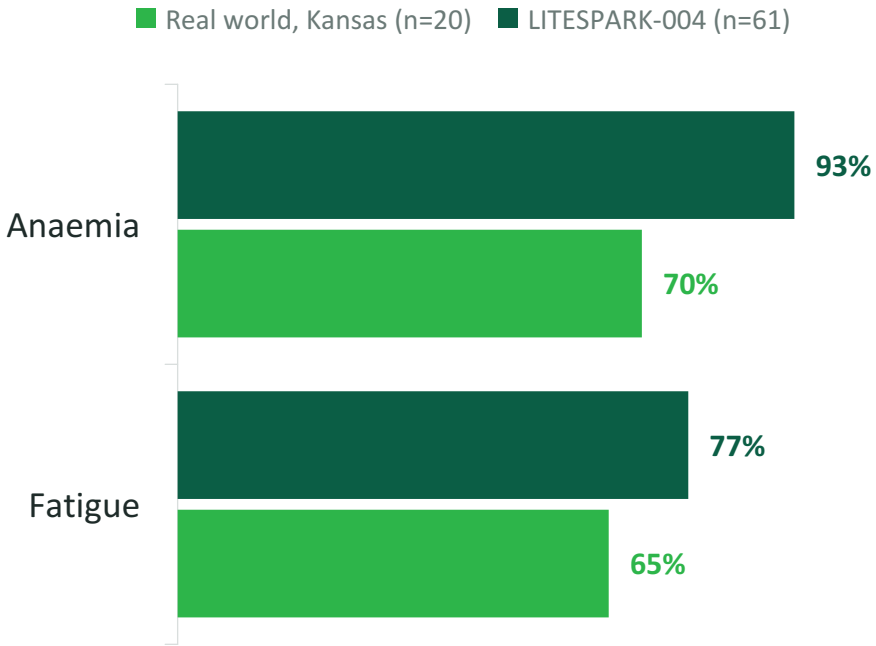


- Within 5 years before starting belzutifan, 46 participants (75%) underwent 97 VHL-related procedures
- After starting belzutifan
  - 19 participants (31%) underwent 24 surgical procedures
    - 17 RCC
    - 3 CNS hemangioblastoma
    - 1 pancreatic lesion
    - 3 retinal hemangioblastoma
  - 1 participant received radiation therapy for CNS hemangioblastoma

RCC
Pancreatic
CNS
Retinal
Other
Radiation
← Participant had ≥1 procedure beyond 5 years
→ Treatment ongoing

Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024).

The price: anemia



On-target: EPO is a HIF-2 gene → anaemia. ESA or transfusion; reduce dose if needed (30% in real world).

Only 2 of 61 stopped for adverse events at 5 years.

Pregnancy is the red line: embryo-fetal toxicity; hormonal contraception may fail (CYP3A4 induction).

LITESPARK-004 5-year update, ASCO 2025 (any-grade AEs); Chidharla A et al. ASCO 2023 (University of Kansas real-world cohort); belzutifan SmPC.

Not a cure — yet: what we still don’t know

1 When to start?

At 3 cm, or earlier? **Smaller tumours respond better.**

Tachiki et al. Transl Androl Urol 2025; Ministerio de Sanidad, informe público Welireg (belzutifán), junio 2026.

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Lifelong? Drug holidays? What happens when we stop?

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Lesions start in adolescence; paediatric data are scarce.

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A young population planning families.

Tachiki et al. Transl Androl Urol 2025; Ministerio de Sanidad, informe público Welireg (belzutifán), junio 2026.

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6 **Access**

Spain, May 2026: reimbursed with fences — genetic confirmation, no conservative alternative, high-risk lesions, hospital pharmacy.

Tachiki et al. Transl Androl Urol 2025; Ministerio de Sanidad, informe público Welireg (belzutifán), junio 2026.

A life changer? Yes, we now treat the gene, not the tumor

1

It works everywhere

RCC 70% · pNET 90% · CNS 50% · retina 100% — durable at 5 years

2

It takes away the surgery

97 procedures before vs 24 on treatment

3

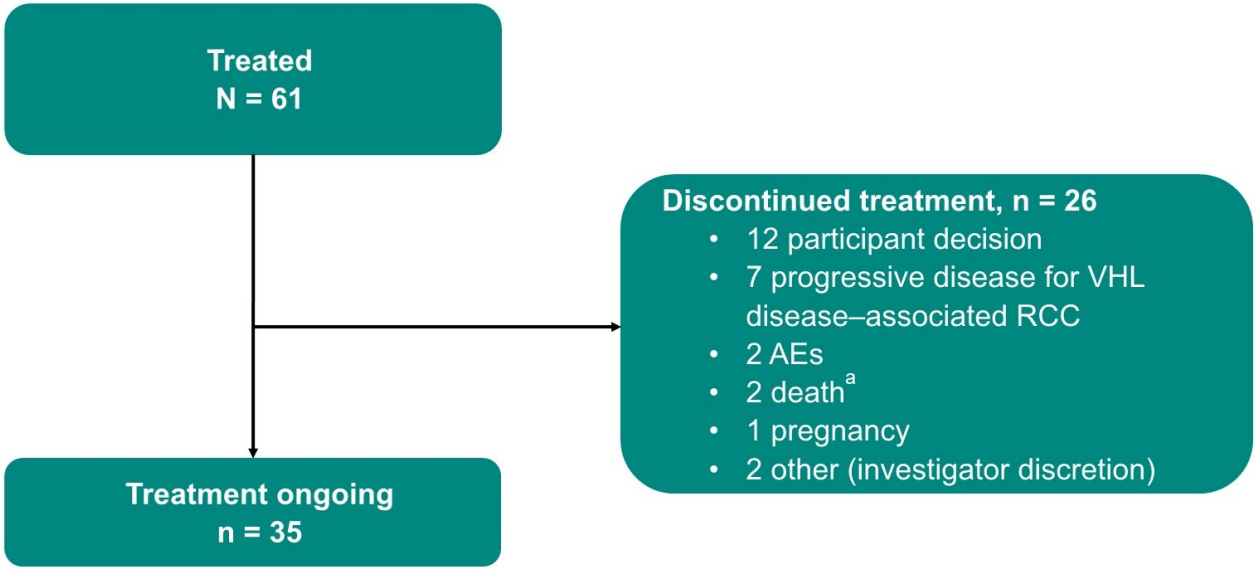
The questions have changed

When to start, how long, for whom — and how to beat resistance

And M.? At 35, instead of a fifth intervention, she starts a pill. Two years later the renal mass has shrunk. **From “when is the next operation?” to “how is the treatment going?”**



BACKUP Who stopped — and why?



[a]2 deaths occurred (death by suicide, acute fentanyl toxicity) that were not attributed to study treatment. Data cutoff date: April 1, 2024.

Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024).

BACKUP 97% had prior VHL surgery

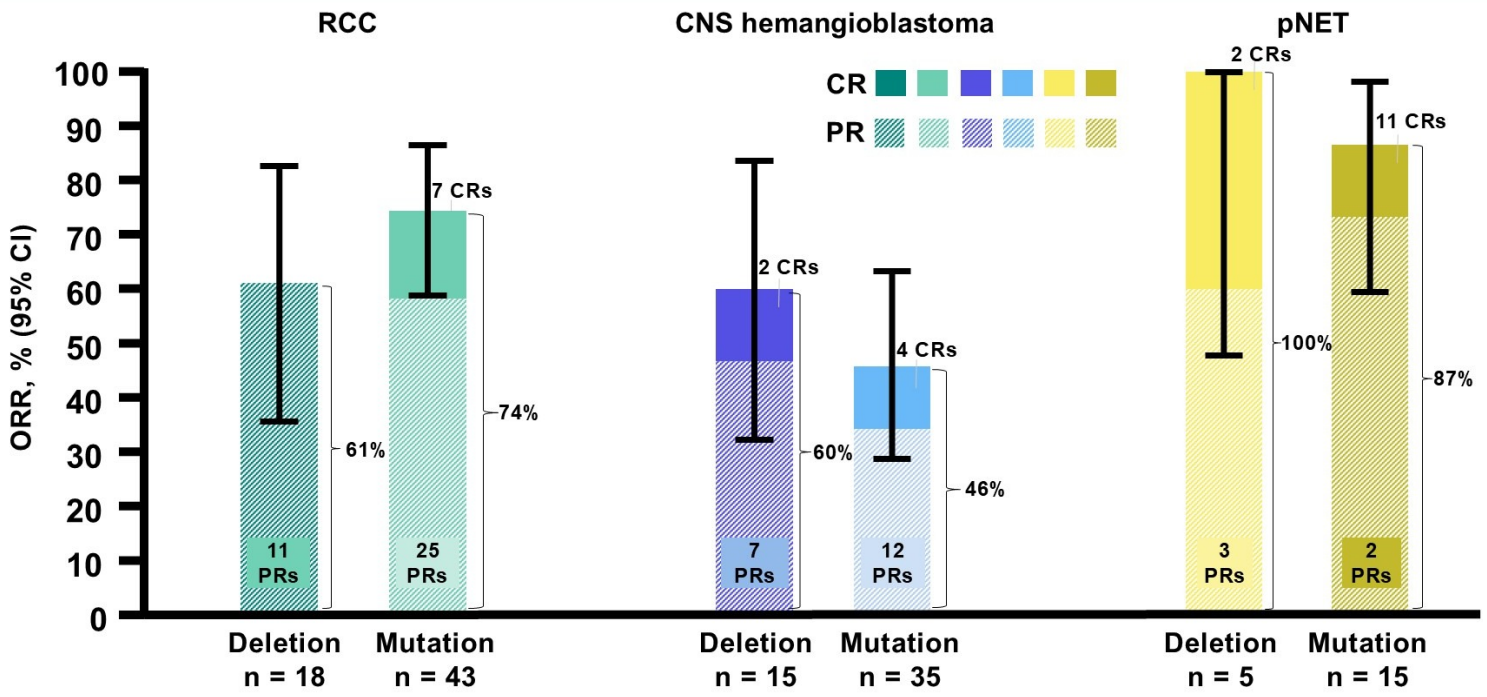
	N = 61
Age, median (range), years	41 (19-66)
Sex, n (%)	
Male	32 (52)
Female	29 (48)
ECOG PS, n (%)	
0	50 (82)
1	10 (16)
2[a]	1 (2)
No. of participants with non-RCC neoplasms[b] per IRC, n (%)	
pNET	20 (33)
CNS hemangioblastoma	50 (82)
Retinal hemangioblastoma	14 (23)

	N = 61
Prior VHL disease–related surgical procedures,[c] n (%)	
No. of participants who had ≥1 prior surgical procedure	59 (97)
RCC	47 (77)
Pancreatic lesions (serous cystadenoma + pNET)	9 (15)
CNS hemangioblastoma	46 (75)
Retinal hemangioblastoma	26 (43)
Size of target lesions,[d] median (range), mm	
RCC	22 (10-43)
CNS hemangioblastoma	17 (10-87)
pNET	19 (10-52)
***VHL* alteration, n (%)**	
Deletion	18 (30)
Mutation	43 (70)

[a]A waiver was requested by the investigator and approved by the institutional review board before enrollment of the participant who had an ECOG PS score of 2. [b]Participants could have more than 1 type of neoplasm. [c]Participants may have undergone surgical procedures for multiple organ systems. [d]Per IRC. Data cutoff date: April 1, 2024.

Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024).

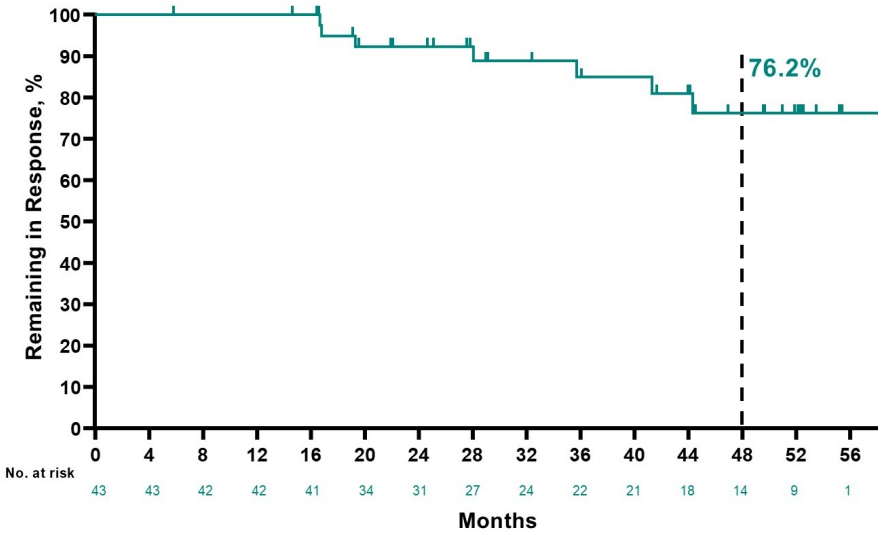
BACKUP Deletion or mutation: every genotype responds



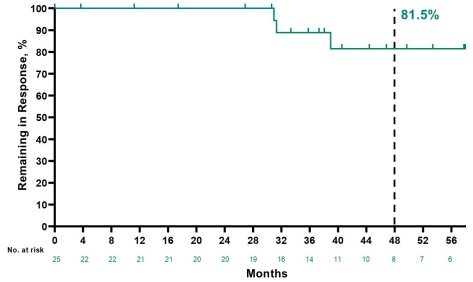
Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024).

BACKUP Durable in every organ: response at 48 months

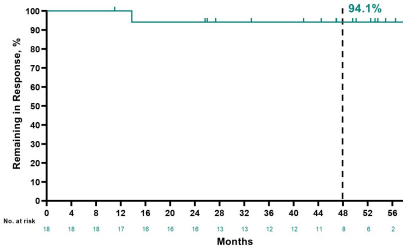
76.2% RCC



81.5% CNS haemangioblastoma

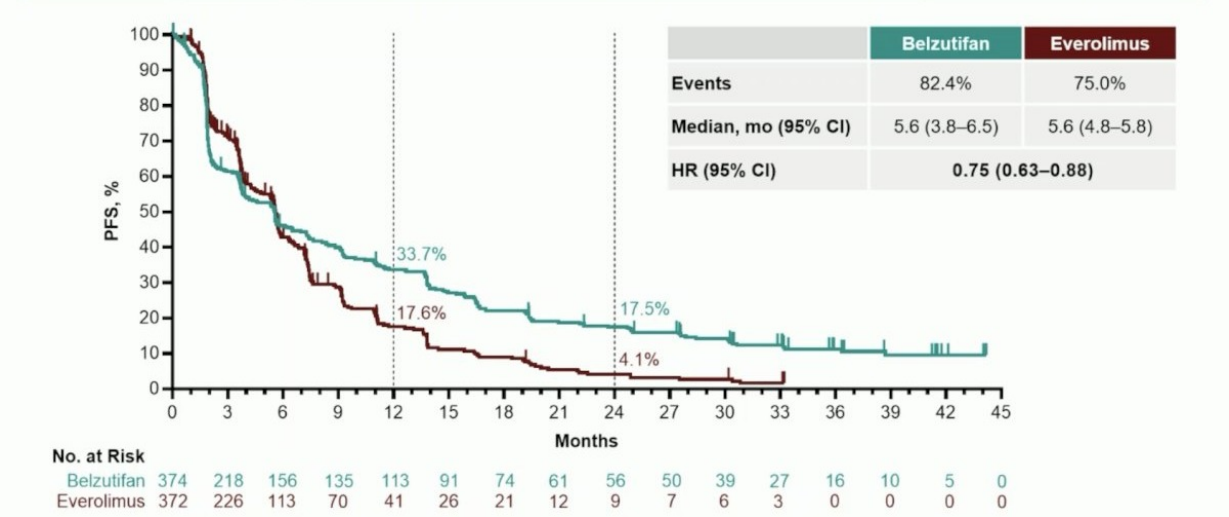


94.1% pNET



Narayan V et al. ASCO 2025 (LITESPARK-004 5-year update; median follow-up 61.8 months; data cutoff 1 Apr 2024). Duration of response per RECIST v1.1 by IRC.

BACKUP Beyond VHL: sporadic ccRCC (LITESPARK-005)



	Belzutifan	Everolimus
Events	82.4%	75.0%
Median, mo (95% CI)	5.6 (3.8–6.5)	5.6 (4.8–5.8)
HR (95% CI)	0.75 (0.63–0.88)	

HR 0.75

PFS vs everolimus, post-IO and VEGF-TKI

ORR 22.7% vs 3.5%

OS HR 0.92 (NS)

Same target, different disease: in VHL the driver is pure; in sporadic RCC it is diluted.

Rini BI et al. ESMO 2024; Choueiri TK et al. N Engl J Med 2024.