Urology Journal Club

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau (VHL) Disease.

PMID:	34818478
Trial Registry:	NCT03401788 (Jan, 2018)
Funding:	Merck Sharp and Dohme
Journal	NEJM

Trial description: The Belzutifan trial included patients with VHL disease and small renal masses between 1-3cm were surgery is still not indicated. The trial tried to show if this drug is safe and effective for delaying the growth of VHL-related tumors.

The average patient included in this trial is 41 years old and was diagnosed with VHL 10 years before; 84% had VHL type 1; 97% of them had already received at least one surgical or ablative treatment for VHL-related tumors. 75% of them had already undergone ablative or surgical management for a renal tumor, 66% of all patients had undergone 4 or more procedures.

Scenario	Adults patients with VHL disease and renal masses between 1-3cm that are candidates for surveillance.
Trial Design	Phase 2, single arm, open label
Inclusion criteria	VHL disease + at least 1 measurable localized renal tumor 1-3cm with no metastasis (radiologic or histologic diagnosis, biopsy not required), ≥18 years. ECOG 0-1
Exclusion criteria	Prior anti-VEGF therapy, major cardiovascular event within 6 months.
Sample size	N=61
Interventions	Belzutifan 120mg daily (three 40mg tablets, once daily)
Primary outcome	Objective response rate (RECIST 1.1)
Secondary outcomes	Duration of response, time to response, and progression free survival, response in other VHL-related tumors.
Follow-up	21.8 months (median)

Results: 30 patients had partial response (ORR 49%), 30 patients had stable disease (49%) and 3 patients had disease progression. No complete response was seen.

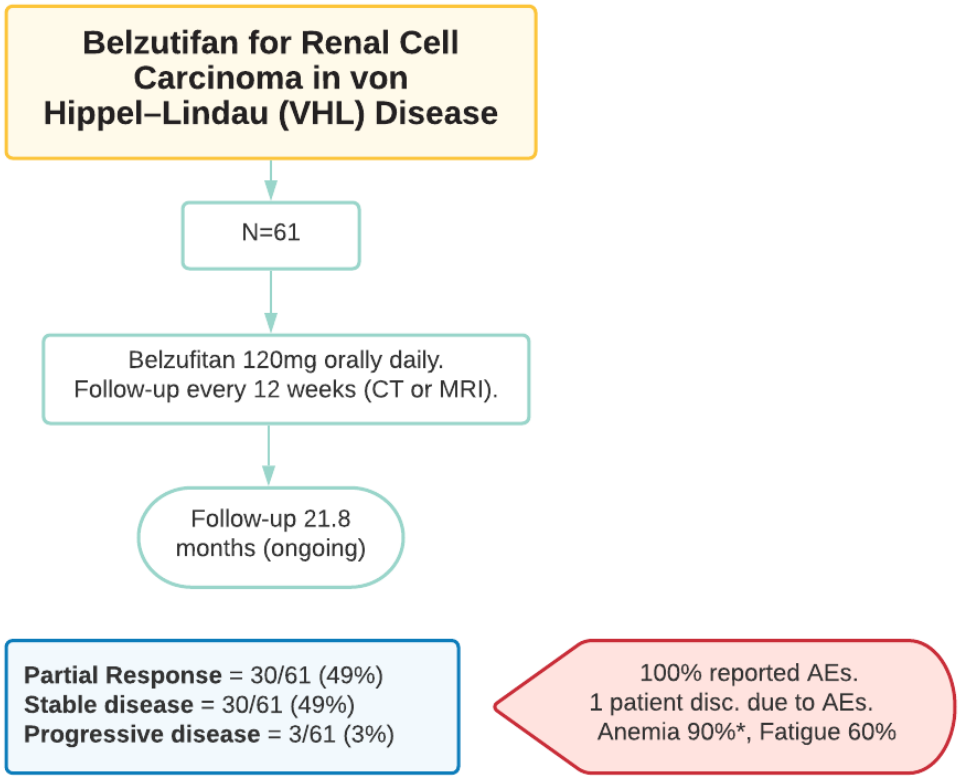
All patients with partial response were still on treatment at data cutoff. 24/30 patients with stable disease were continuing treatment at the time of data cutoff.

All patients (N=61) had concomitant pancreatic lesions, 77% showed confirmed response including 6 patients (10%) with complete response.

Adverse events (AE): All patients (100%) reported treatment related AEs, 33% reported Grade 3-5 AEs, only 1 patient discontinued due to AEs, no treatment-related deaths.

Assessment	Every 3 months with CT or MRI
Number of tumors per patient	Median 3 (1-5)
Time to response	The median time to response was 8.2 months (range, 2.7 to 19.1)
Duration of response	Still not reached, trial ongoing.
Remarks - Pitfalls	4 patients (6.5%) "voluntarily discontinued treatment" (adverse events? why discontinue if working? no details in appendix)

Conclusion: Belzutifan is a novel oral hypoxia-inducible factor (HIF)-2α inhibitor. Showed a high objective response rate and most of those without response did not progress (short follow-up, trial ongoing). Other VHL-related tumors also showed a high response rate and the AE profile seems to be tolerable and fair considering this drug may delay the need for further invasive procedures related to their tumors. These results are encouraging but have not proven to reduce any meaningful outcome (number of procedures, survival, etc)



*Four patients (7%) received blood transfusions owing to anemia; one of the patients received three blood transfusions.
A total of 12 patients (20%) received erythropoietin stimulating agents, with a median of 2.5 administrations (range, 1 to 17)
3 of the 12 patients received both an erythropoietin-stimulating agent and a blood transfusion.

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