Table. Summary and time to first onset of adverse drug reactions

[a]Includes patients with adverse events of anemia and decreased hemoglobin.

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Belzutifan versus everolimus for previously treated advanced clear cell renal cell carcinoma: Subgroup analysis of the phase 3 LITESPARK-005 study

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Background: Belzutifan monotherapy is approved for the treatment of adult patients with advanced renal cell carcinoma (RCC) following a PD-(L)1 inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI) based on the results of the phase 3 LITESPARK-005 study (NCT04195750). In LITESPARK-005, belzutifan improved progression-free survival (PFS; HR 0.75; 95% CI, 0.63-0.90; $P < 0.001$) and objective response rate (ORR; 21.9% vs 3.5%; $P < 0.00001$) versus everolimus at first interim analysis (IA1); overall survival (OS) did not reach statistical significance at IA2 (HR 0.88; 95% CI, 0.73-1.07; $P = 0.1$). We present efficacy outcomes by prespecified subgroups from IA2.

Methods: Patients with clear cell RCC whose disease progressed after anti–PD-(L)1 and VEGF-targeted therapies and who had 1-3 prior systemic regimens were randomly assigned 1:1 to belzutifan 120 mg by mouth once daily or everolimus 10 mg by mouth once daily until progression or intolerable toxicity. The dual primary end points of PFS by central review per RECIST v1.1 and OS and the key secondary end point of ORR were evaluated by prespecified baseline characteristic subgroups: IMDC risk (favorable vs intermediate/poor), prior VEGF-TKIs (1 vs 2-3), and number of prior lines of therapy (1 vs 2 vs 3). These analyses were not controlled for multiplicity and no formal statistical testing occurred. The database cutoff date was June 13, 2023.

Results: Overall, 746 patients were assigned to belzutifan (n = 374) or everolimus (n = 372). Baseline characteristics were balanced between groups. Median follow-up was 25.7 months (range, 16.8-39.1). Across analyzed subgroups, PFS and OS results were consistent with the primary analysis (Table). ORR favored belzutifan over everolimus for all subgroups: IMDC favorable risk (22.8% vs 6.0%), IMDC intermediate/poor risk (22.7% vs 2.8%), 1 prior VEGF-TKI (19.7% vs 3.7%), 2 prior VEGF-TKIs (25.7% vs 3.3%), 1 prior line of therapy (28.3% vs 5.8%), 2 prior lines (19.1% vs 2.4%), and 3 prior lines (24.6% vs 3.9%).

Conclusions: Consistent with the intention-to-treat population of LITESPARK-005, PFS and ORR favored belzutifan over everolimus

Table.

	IMDC Favorable		IMDC Intermediate/ Poor		1 Prior VEGF-TKI		2-3 Prior VEGF-TKIs		1 Prior Line		2 Prior Lines		3 Prior Lines[a]	
	Bel	Eve	Bel	Eve	Bel	Eve	Bel	Eve	Bel	Eve	Bel	Eve	Bel	Eve
n	79	83	295	289	187	190	187	182	46	52	157	166	171	154
PFS, HR (95% CI)	0.74 (0.51-1.09)		0.74 (0.61-0.89)		0.77 (0.61-0.98)		0.73 (0.57-0.93)		0.54 (0.34-0.87)		0.81 (0.62-1.05)		0.77 (0.60-1.00)	
OS, HR (95% CI)	0.75 (0.47-1.21)		0.90 (0.73-1.10)		0.87 (0.67-1.13)		0.89 (0.68-1.16)		0.83 (0.46-1.50)		0.84 (0.63-1.10)		0.93 (0.70-1.24)	

Bel, belzutifan; Eve, everolimus.
[a]Included 2 patients in the belzutifan arm and 4 patients in the everolimus arm who had 4 prior lines of therapy and protocol violations.

across prespecified subgroups. These results support belzutifan as a new treatment option for patients with advanced clear cell RCC after prior anti–PD-(L)1 and VEGF-targeted therapies.

Keywords: belzutifan, HIF-2α, renal cell carcinoma

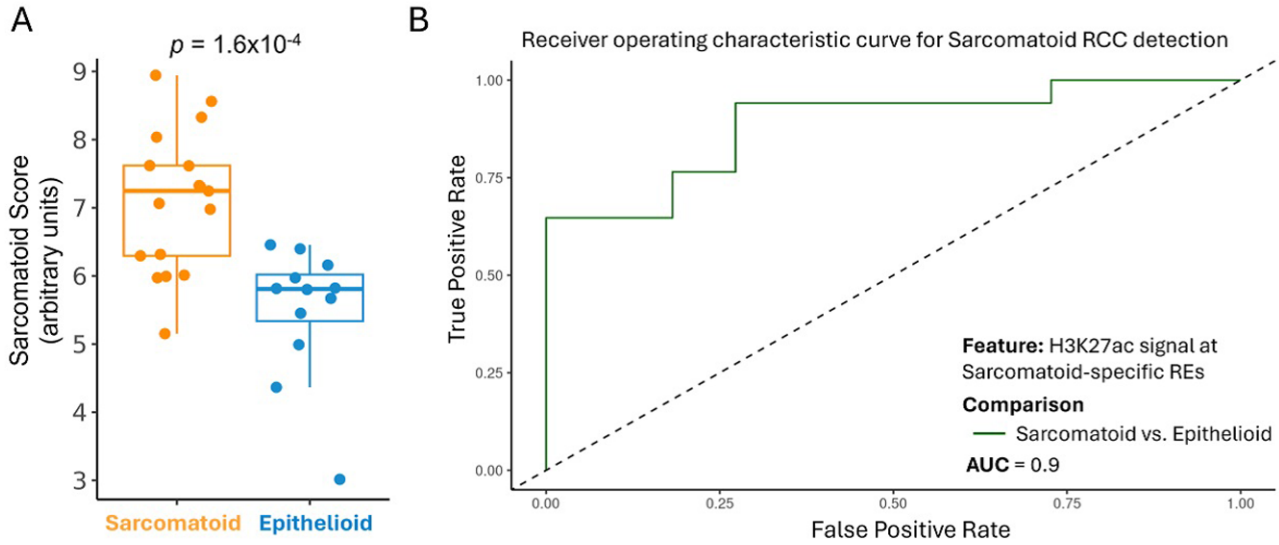

Figure 1. (A) Sarcomatoid Score in plasma from patients with RCC at sarcomatoid-specific REs, comparing sarcomatoid (orange) and epithelioid RCC (blue). (B) ROC curves for distinguishing sarcomatoid from epithelioid RCC plasma samples using H3K27ac cell-free ChIP-seq signal at sarcomatoid-specific REs. 'AUC' indicates area under the ROC curve.