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LBA88 Belzutifan versus everolimus in participants (pts) with previously treated advanced clear cell renal cell carcinoma (ccRCC): Randomized open-label phase III LITESPARK-005 study

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Background: Belzutifan is a first-in-class oral HIF-2α inhibitor approved in the US for patients with VHL disease-associated RCC, pNET and CNS hemangioblastoma and has antitumor activity in ccRCC. The phase 3 LITESPARK-005 study (NCT04195750) compares belzutifan vs everolimus in pretreated advanced ccRCC.

Methods: Pts aged ≥18 yrs with KPS ≥70% and advanced ccRCC (1-3 prior systemic regimens including anti−PD-[L]1 mAb and VEGF-TKI) were randomized 1:1 to belzutifan 120 mg QD or everolimus 10 mg QD until progression or unacceptable toxicity. Dual primary endpoints were PFS per RECIST 1.1 by blinded independent central review (BICR) and OS. Secondary endpoints included ORR per RECIST 1.1 by BICR (key), safety and time to deterioration (TTD) per FKSI-DRS. PFS, ORR were formally tested at first interim analysis (IA1).

Results: 374 pts were randomized to belzutifan, 372 to everolimus. At IA1 (median follow up [fu] 18.4 mo; range 9.4−31.7), PFS and ORR were superior with belzutifan vs everolimus (Table); OS did not reach statistical significance. At IA2 (median fu 25.7 mo; range 16.8−39.1), PFS, OS and ORR results were consistent with IA1. Complete responses occurred in 13 (3.5%) vs 0 pts with belzutifan vs everolimus. More pts remained progression-free with belzutifan vs everolimus at 12 mo (PFS rate 33.7% vs 17.6%) and 18 mo (22.5% vs 9.0%). 22.6% vs 5.0% of pts had ongoing treatment; 5.9% vs 14.7% of pts discontinued study therapy due to any AE. Grade 3-5 TRAEs occurred in 38.7% vs 39.4% of pts. TTD for FKSI-DRS favored belzutifan (median not reached vs 12.0 mo; HR 0.53; 95% CI 0.41−0.69; nominal $P<.0001$).

Table: LBA88

	IA1		IA2	
	Belzutifan (n=374)	Everolimus (n=372)	Belzutifan (n=374)	Everolimus (n=372)
Median PFS, mo	5.6	5.6	5.6	5.6
HR (95% CI)	0.75 (0.63−0.90)		0.74 (0.63−0.88)	
P-value	<.001*		Not applicable	
Median OS, mo	21.0	17.2	21.4	18.1
HR (95% CI)	0.87 (0.71−1.07)		0.88 (0.73−1.07)	
P-value	0.09583		0.09941	
ORR, % (95% CI)	21.9 (17.8−26.5)	3.5 (1.9−5.9)	22.7 (18.6−27.3)	3.5 (1.9−5.9)
P-value	<.00001*		Not applicable	

* denotes statistical significance.

Conclusions: Belzutifan was associated with a statistically significant improvement in PFS and ORR vs everolimus for pts with advanced ccRCC after immune checkpoint and anti-angiogenic therapies. The safety profile of belzutifan was consistent with prior reports with no new safety signals.

Clinical trial identification: MK-6482 LITESPARK-005; (NCT04195750).

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