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First-line pembrolizumab + lenvatinib + belzutifan or MK-1308A + lenvatinib in advanced RCC: Randomized open-label phase 3 LITESPARK-012 study

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Background

The phase 3 LITESPARK-012 study (NCT04736706) evaluated efficacy and safety of 1L pembrolizumab + lenvatinib + belzutifan or MK-1308A (coformulated quavonlimab [anti-CTLA-4]/pembrolizumab) + lenvatinib vs standard-of-care (SOC) pembrolizumab + lenvatinib in clear cell RCC (ccRCC).

Methods

Adults with untreated advanced ccRCC were randomized 1:1:1 to Arm A: pembrolizumab (400 mg Q6W, ≤18 cycles) + lenvatinib (20 mg QD) + belzutifan (120 mg QD); Arm B: MK-1308A (quavonlimab/pembrolizumab 25 mg/400 mg Q6W, ≤18 cycles) + lenvatinib; or Control: pembrolizumab + lenvatinib; and treated until progression, unacceptable toxicity, or withdrawal from study (pembrolizumab or MK-1308A treatment for max 2 yrs). Dual primary endpoints were PFS by blinded independent central review (BICR) per RECIST 1.1 and OS, tested in all randomized pts for Arm A vs Control, and pts with IMDC intermediate/poor risk or all pts for Arm B vs Control. ORR by BICR and safety were secondary endpoints.

Results

1688 pts were randomized. As of Feb 4, 2026, median follow-up was 43.6 mo (range, 31.8–57.4). Triplet therapy (Arm A, Arm B) did not improve efficacy vs Control (Table). Median duration of each drug therapy was as follows - Arm A: pembrolizumab (14.1 mo) + lenvatinib (18.1 mo) + belzutifan (18.6 mo); Arm B: MK-1308A (11.8 mo) + lenvatinib (15.2 mo); and Control: pembrolizumab (21.2 mo) + lenvatinib (22.2 mo). All cause AEs led to discontinuation of any drug in 51.6% of pts in Arm A, 51.4% in Arm B, and 36.2% in the Control arm. All cause grade ≥3 AEs occurred in 87.2%, 88.7%, and 84.8% of pts, respectively.Table: 35860

	N	Median PFS, mo	PFS HR (95% CI) and <i>p</i> -value vs control	Median OS, mo	OS HR (95% CI) and <i>p</i> -value vs control	ORR, % (95% CI)
Arm A, all pts	560	20.8	1.08 (0.93–1.26); <i>P</i> =.84	52.0	1.04 (0.87–1.25); <i>P</i> =.66	69.1 (65.1–72.9)
Arm B, all pts	562	20.7	1.07 (0.92–1.25); <i>P</i> =.82	NR	1.12 (0.94–1.35); <i>P</i> =.90	69.0 (65.0–72.8)

	N	Median PFS, mo	PFS HR (95% CI) and <i>p</i> -value vs control	Median OS, mo	OS HR (95% CI) and <i>p</i> -value vs control	ORR, % (95% CI)
Control, all pts	566	23.7		NR		76.3 (72.6–79.8)
Arm B, IMDC intermediate/poor risk	429	20.5	1.12 (0.94–1.33); <i>P</i> =.90	39.1	1.17 (0.96–1.42); <i>P</i> =.94	66.9 (62.2–71.3)
Control, IMDC intermediate/poor risk	429	23.5		46.2		75.5 (71.2–79.5)

NR, not reached.

Conclusions

Neither addition of HIF-2α inhibitor belzutifan nor of CTLA-4 blockade to pembrolizumab + lenvatinib in advanced RCC improved efficacy; pembrolizumab + lenvatinib remains a 1L SOC. Higher discontinuation rate of pembrolizumab, MK-1308A, and lenvatinib due to AEs in the investigational arms may have limited drug exposure and partly impacted efficacy.

Clinical trial identification

NCT04736706; LITESPARK-012.

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