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## LBA96

# First-line pembrolizumab-based regimens for advanced clear cell renal cell carcinoma: KEYMAKER-U03 substudy 03A

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### Background

Substudy 03A (NCT04626479) of the umbrella phase 1/2 KEYMAKER-U03 trial evaluates novel pembrolizumab (pembro)-based regimens in the first line for pts with advanced clear cell renal cell carcinoma (ccRCC).

### Methods

Adults with advanced ccRCC and no prior systemic therapy were randomized 2:1 to open investigational arms or the reference (ref): coformulated quavonlimab (qmab; anti-CTLA-4)/pembro + lenvatinib (lenva; VEGFR-TKI); coformulated favezelimab (fave; anti-LAG-3)/pembro + lenva; pembro + lenva + belzutifan (bel; HIF-2α inhibitor); coformulated vibostolimab (vibo; anti-TIGIT)/pembro + bel; ref, pembro + lenva. Investigational arms each had a safety lead-in phase of ⊠10 pts. Primary endpoints were safety (in all pts with ≥1 dose study therapy) and ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints included DOR and PFS per RECIST v1.1 by BICR, and OS. Efficacy was evaluated in all randomized pts. Efficacy comparisons to ref were exploratory with no formal statistical testing; HR estimates were ad hoc. Data cutoff date was Mar 31, 2025.

### Results

Substudy 03A enrolled 393 pts (353 in the efficacy phase). Median follow-up for randomized pts across arms ranged from 16 to 39 mo; efficacy is shown in the table. Grade ≥3 TRAEs occurred in 66/90 pts (73%) with qmab/pembro + lenva, 53/61 (87%) with fave/pembro + lenva, 63/90 (70%) with pembro + bel + lenva, 62/90 (69%) with vibo/pembro + bel, and 44/62 (71%) in the ref arm.Table: LBA96

| | Qmab/pembro + lenva n = 80 | Fave/pembro + lenva n = 51 | Pembro + bel + lenva n = 80 | Vibo/pembro + bel n = 80 | Ref n = 62 |
|---|---|---|---|---|---|
| ORR (95% CI), % | 71 (60–81) | 63 (48–76) | 78 (67–86) | 42 (32–54) | 81 (69–90) |
| CR (95% CI), % | 6 (2–14) | 10 (3–21) | 12 (6–22) | 5 (1–12) | 6 (2–16) |
| DOR median (range), mo | 25.0 (2.4–37.1+) | 26.3 (1.4+–34.4+) | 33.4 (2.6–37.6+) | 14.0 (2.7+–18.2+) | 25.6 (1.4+–41.2+) |
| PFS median, mo (95% CI) | 18.0 (11.6–34.3) | 26.0 (8.2–31.8) | 31.8 (26.3–NR) | 15.2 (12.4–NR) | 26.3 (15.3–39.8) |
| PFS HR (95% CI)[a] | 0.96 (0.57–1.61) | 1.26 (0.65–2.42) | 0.45 (0.25–0.83) | 1.42 (0.75–2.67) | - |
| 24-mo OS rate, % (95% CI) | 73 (60–83) | 76 (62–86) | 86 (73–92) | NR | 77 (60–87) |

NR, not reached. [a]HR for each arm estimated against concurrently enrolled pts in the ref.

## Conclusions

Pembrolizumab + lenvatinib + belzutifan showed promising early efficacy and is being explored in the randomized phase 3 LITESPARK-012 study. Other regimens did not show improved ORR and PFS compared with pembrolizumab + lenvatinib, yet the duration of follow-up was insufficient to detect long-term contributions to OS. Safety profiles were consistent with the profiles of the individual drugs in each regimen.

## Clinical trial identification

NCT04626479.


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## Legal entity responsible for the study

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## Disclosure

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