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Retifanlimab (Anti–PD-1 mAb) alone or in combination with Anti-LAG3 ± Anti-TIM3 mAbs In previously untreated, recurrent and/or metastatic (R/M) PD-L1+ HNSCC: A double-blind randomised controlled phase II trial

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Background

PD-1 inhibitors improve survival in patients (pts) with previously untreated R/M PD-L1+ HNSCC. The study assessed whether dual and triple immune checkpoint blockade improves efficacy in pts vs anti–PD-1 treatment (tx) alone.

Methods

Pts were randomised (1:1:1) to retifanlimab (RETI) alone, or RETI with tuparstobart (anti-LAG3 mAb; doublet tx) or RETI + tuparstobart and verzistobart (anti-TIM3 mAb; triplet tx). Tx continued for up to 2 years or until investigator-determined progression by RECIST 1.1, unacceptable toxicity or withdrawal of consent. Primary endpoint: progression-free survival (PFS). Two primary hypotheses were tested: superiority of doublet and/or triplet tx, each vs RETI; 140 PFS events were needed for 80% power to test these hypotheses at 1-sided α of 0.05. Secondary endpoints included objective response rate (ORR), duration of response (DOR), overall survival (OS) and safety.

Results

176 pts were randomised (RETI n=59, doublet tx n=60, triplet tx, n=57): central PD-L1 CPS ≥20, 57%; central LAG3 expression ≥5%, 55%; HPV+, 14%. At data cutoff (28 Jan 2025; estimated median follow-up time, 14 months [mo]), median PFS was 5.8 mo (95% CI, 3.7, 7.6) with doublet tx vs 5.6 mo (95% CI, 3.5, 9.7) with RETI alone (HR, 1.05; 95% CI, 0.66, 1.67; *P*=0.59), and 5.3 mo (95% CI, 2.1, 7.9) with triplet tx (HR vs RETI alone, 1.09; 95% CI, 0.69, 1.72; *P*=0.64). Confirmed ORR was numerically higher with triplet (32% [95% CI, 19.9, 45.2]) and doublet tx (30% [95% CI, 18.8, 43.2]) vs RETI (20% [95% CI, 11.0, 32.8]). Difference in ORR was 11.2% (95% CI, –4.8, 26.6) for triplet vs RETI and 9.7% (95% CI, –6.1, 24.7) for doublet vs RETI. DOR and OS data are not mature. In the RETI, doublet and triplet tx groups, respectively, grade 3/4 tx-related AEs occurred in 16%, 12% and 21% of pts; any-grade immune-related AEs occurred in 38%, 43% and 47% of pts.

Conclusions

This randomised phase 2 trial showed that adding anti-LAG3 ± anti-TIM3 did not significantly improve PFS vs RETI alone in pts with previously untreated R/M PD-L1+ HNSCC. Median PFS with RETI alone exceeded historical data from studies of other anti–PD-1 tx in R/M HNSCC.

Clinical trial identification

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Disclosure

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