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Pembrolizumab (P) combined with chemotherapy (C) vs C alone as first-line (1L) therapy for advanced urothelial carcinoma (UC): KEYNOTE-361

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Background

The open-label, phase III KEYNOTE-361 study compares efficacy and safety of 1L P + C vs C for advanced UC (NCT02853305).

Methods

Eligible pts had advanced/unresectable or metastatic UC, ECOG PS 0-2, and no prior systemic therapy for advanced disease. Pts from 201 sites in 21 countries were randomized 1:1:1 to P 200 mg Q3W for ≤35 cycles, P for ≤35 cycles + C for ≤6 cycles (investigator's choice [IC] of gemcitabine + either cisplatin or carboplatin), or IC of C for ≤6 cycles. Randomization was stratified by IC of platinum and PD-L1 combined positive score (CPS) (≥10 vs <10). Dual primary endpoints were PFS by blinded central review and OS. A sequential testing strategy was used, beginning with superiority testing of PFS and OS for P + C vs C in the total population (*P*-value threshold of ≤0.0019 for PFS and ≤0.0142 for OS as adjusted for α spent at interim analyses to maintain overall α=2.5% [one-sided] with 0.5% and 2.0% allocated to PFS and OS, respectively), followed by noninferiority and superiority testing of OS for P vs C in pts with CPS≥10 and total pts only if OS for P + C was statistically superior to C.

Results

1010 pts were randomized between Oct 19, 2016 and Jun 29, 2018: 351 to P + C, 307 to P, and 352 to C. As of Apr 29, 2020, median (range) time from randomization to cutoff was 31.7 (22.0-42.3) mo. Baseline characteristics were generally well-balanced across arms. Median PFS for P + C, P, and C for total pts was 8.3 mo, 3.9 mo, and 7.1 mo, respectively; median OS was 17.0 mo, 15.6 mo, and 14.3 mo, respectively. HR (95% CI) for P + C vs C was 0.78 (0.65-0.93, *P* = 0.0033) for PFS and 0.86 (0.72-1.02, *P* = 0.0407) for OS. ORR was 54.7% for P + C, 30.3% for P, and 44.9% for C. Median DOR (range) was 8.5 (2.0+-35.5+) mo, 28.2 (2.1+-36.1+) mo, and 6.2 (1.8+-36.3+) mo, respectively. 35.3%, 41.0%, and 61.1% of total pts in P+C, P, and C arms received subsequent therapy (6.6%, 4.6%, and 48.0% of total pts received anti–PD-[L]1), respectively. Grade 3-5 TRAE rate was 75.1% with P + C, 16.9% with P, and 71.6% with C; discontinuation rate of any drug due to an AE was 30.9%, 15.9%, and 18.1%, respectively.

Conclusions

PFS and OS benefit upon addition of P to C vs C did not reach statistical significance. Due to statistical design, OS noninferiority/superiority of P vs C was not tested.

Clinical trial identification

NCT02853305, August 2, 2016.

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