LBA6 EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC)

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Background: Platinum-based chemo is the standard of care (SOC) for la/mUC. An unmet need remains as long-term outcomes are poor. Here we present EV-302, a global, phase 3, open-label, randomized study evaluating EV+P in patients (pts) with previously untreated la/mUC who were eligible for cisplatin- or carboplatin-containing chemo.

Methods: Pts with previously untreated la/mUC (regardless of PD-L1 expression) were randomized 1:1 to receive 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1 or gemcitabine with cisplatin or carboplatin. Dual primary endpoints were PFS per RECIST v1.1 by BICR and OS. Select secondary endpoints included overall response rate (ORR) and safety.

Results: 886 pts (EV+P: 442; chemo: 444) were randomized; pt characteristics were balanced between arms. At data cutoff, median follow-up was 17.2 mo. PFS was significantly prolonged with EV+P vs chemo, reducing the risk of progression or death by 55% (median PFS, 12.5 mo vs 6.3 mo, respectively; HR 0.45 [95% CI: 0.38-0.54]; $P<0.00001$). OS was significantly prolonged with EV+P vs chemo, reducing the risk of death by 53% (median OS, 31.5 mo vs 16.1 mo, respectively; HR 0.47 [95% CI: 0.38-0.58]; $P<0.00001$). Confirmed ORR was 67.7% and 44.4% in the EV+P and chemo arms, respectively ($P<0.00001$). Grade $\geq$3 TRAEs occurred in 55.9% with EV+P and 69.5% with chemo; most common were maculopapular rash (7.7%), hyperglycemia (5.0%), and neutropenia (4.8%) for EV+P and anemia (31.4%), neutropenia (30.0%), and thrombocytopenia (19.4%) for chemo. Most common ($\geq$5%) grade $\geq$3 TRAEs of special interest for EV included skin reactions (15.5%), peripheral neuropathy (6.8%), and hyperglycemia (6.1%). Most common ($\geq$5%) grade $\geq$3 treatment-emergent AEs of special interest for P included severe skin reactions (11.8%).

Conclusions: EV+P significantly improved outcomes in pts with previously untreated la/mUC, nearly doubling the median PFS and OS vs chemo. The safety profile was generally manageable with no new safety signals. These results support EV+P as a new SOC for 1L la/mUC.

Clinical trial identification: NCT04223856.

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