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Phase II multicenter, randomized study to evaluate efficacy and safety of avelumab with gemcitabine/carboplatin (CG) vs CG alone in patients with unresectable or metastatic urothelial carcinoma (mUC) who are ineligible to receive cisplatin-based therapy

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Background

In mUC, avelumab has demonstrated OS improvement as maintenance treatment in patients that benefit from first line (1L) CT. Based on retrospective data (Szabados B. Eur Urol. 2018) that IO before CT was superior than the reverse sequence, we tested the hypothesis that induction avelumab followed by its combination with CG, followed by avelumab maintenance may enhance clinical benefit in patients unfit for cisplatin.

Methods

CT-naïve, unresectable/mUC patients ineligible for cisplatin, as defined by Galsky criteria, were randomized to arm A: 2 cy of induction avelumab 10mg/kg Q2W followed by 6 cy of CG + avelumab (C 5AUC day 1, G 1000mg/m^2 day 1 and 8 and avelumab 10mg/kg day 15) Q3W, followed by avelumab 10mg/kg Q2W (n=42) until progressive disease or intolerance, compared with arm B: CG alone for 6 cy (n=43). The primary endpoint was ORR. Secondary endpoints were PFS, OS, duration of response (DoR) and safety.

Results

Baseline characteristics were generally balanced: median age 74 years, visceral metastasis (65%), renal impairment (60%) and ECOG-PS 2 (35%). The ORR was 57% (24/42) in arm A and 53% (23/43) in arm B (p= 0.73). 13 p (31%) in arm A progressed or died before the 1st response assessment (including 6 deaths in the 1st month) vs. 4 p (9.3%) in arm B. Median PFS was 6.9 m (95% CI, 2.2 to 8.4) in arm A vs. 7.4 m (95% CI, 5.8 to 9.7) in arm B (p=0.712). Median OS was 10.5 m (95% CI, 6.9 to NR) with avelumab/CG and 13.2 m (95% CI, 12.5 to 18.4) with CG (p=0.264). The 15-months OS rate was 45% (95% CI, 29 to 60) with avelumab/CG *vs.* 39% with CG (95% CI, 22 to 56). Treatment-related adverse event of ≥ Grade 3 occurred in 71% of patients in arm A and in 65% in arm B.

Conclusions

The previous hypothesis that IO before CT might optimize subsequent CT response was not proven. Early progression was higher in the induction avelumab arm (31% *vs.* 9.3%). However, despite the follow-up being immature, superior percentual OS benefit was observed in the avelumab/CT arm followed by avelumab maintenance. Induction IO alone before CT/IO is not an adequate strategy. Ongoing phase III trials are looking at different sequencing/combination approaches.

Clinical trial identification

NCT03390595; EudraCT: 2017-004260-36.

Legal entity responsible for the study

Associació per a la Reserca Oncològica Associació per a la Reserca Oncològica.

Funding

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Disclosure

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