Phase II trial of durvalumab plus tremelimumab with concurrent radiotherapy (RT) in patients (pts) with localized muscle invasive bladder cancer (MIBC) treated with a selective bladder preservation approach: IMMUNOPRESERVE-SOGUG trial.

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Background: Bladder-preserving combined-modality therapies constitute an alternative to radical cystectomy for selected pts with MIBC. In preclinical studies, combination of radiation and dual checkpoint blockade appears to activate non-redundant immune mechanisms, potentiating antitumor activity. The purpose of the present study is to explore feasibility, toxicity and activity of this approach in MIBC.

Methods: Pts with localized MIBC in clinical stages T2-4a N0 M0, ECOG 0-1, without contraindications to immunotherapy, who either wished for bladder preservation or were ineligible for cystectomy, were included in this phase II study. Treatment consisted of initial transurethral resection (TUR) of the tumor, followed by durvalumab 1,500 mg i.v. plus tremelimumab 75 mg i.v., every 4 weeks for 3 doses. Normofractionated external-beam RT was started 2 weeks later, at doses of 46 Gy to minor pelvis and 64-66 Gy to bladder. Pts with either residual or relapsed MIBC were offered salvage cystectomy. The primary endpoint was complete response (CR) defined as absence of MIBC at post-treatment tumor site biopsy. A 2-stage sequential design was used (CR rate P0=5, P1=0.7, α=0.10, β=0.20) requiring at least 6 CR in the first 12 pts to expand to a second cohort of 20 pts.

Results: From 1/2019 to 8/2020, 32 pts were enrolled at 6 centers. Median age was 71 years (49-91). PS was 0 in 24 pts, 1 in 8. 25 were males. Clinical stage was T2 in 28 pts, T3 in 3 and T4a in 1. All pts received at least two immunotherapy cycles. The median dose of RT administered was 64 Gy (60-65). CR at post-treatment biopsy was documented in 26 (81%) pts, 2 pts had residual MIBC and 4 pts were not evaluated due to resection (1), clinical impairment (1), death from COVID 19 (1) and a suspected treatment-related death from peritonitis (1). After a median follow up of 6.1 months (2.5 - 20.1), 2 pts underwent salvage cystectomy because of MIBC and T1 relapses, respectively. The estimated 6-months rates for disease-free survival (DFS) with bladder intact, DFS and overall survival were 76% (95%CI, 61%-95%), 80% (95%CI, 66%-98%) and 93% (95%CI, 85%-100%), respectively. A total of 31 (97%) pts experienced adverse events related to RT and/or immunotherapy, with diarrhea (41%) and urinary disorders (37.5%) as the most frequent. Grade 3 or 4 adverse events related to therapy were reported in 31% pts, being the most frequent gastrointestinal toxicity (12.5%), acute kidney failure (6%) and hepatitis (6%).

Conclusions: A combined-modality approach including durvalumab + tremelimumab with concurrent RT is feasible and safe, showing high efficacy in terms of response and eliciting bladder preservation in a large number of pts. Further research on this approach as an alternative to cystectomy is warranted. Clinical trial information: NCT03702179. Research Sponsor: AstraZeneca, Spanish Oncology Genitourinary Group (SOGUG).