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OP20 Three year-survival outcomes after neoadjuvant pembrolizumab and radical cystectomy: Final results from the PURE-01 study

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Background: Survival outcomes of patients with muscle-invasive bladder cancer (MIBC) treated with neoadjuvant pembrolizumab before radical cystectomy (RC) within the PURE-01 study (NCT02736266) showed promising results. Herein, we report the three year-survival outcomes.

Methods: The intention-to-treat (ITT) population included 155 patients, whereas patients receiving neoadjuvant pembrolizumab and RC without additional chemotherapy were 125. Median follow-up was calculated using the reverse Kaplan-Meir method. Event-free survival (EFS) was defined as the time from the first cycle of pembrolizumab to radiographic disease progression precluding RC, initiation of neoadjuvant chemotherapy (NAC), recurrence after RC, or death from any cause. Other end points were recurrence-free survival (RFS) and overall survival (OS). Multivariable Cox regression analyses (MVA) evaluated clinical and biomarkers predictors of events after treatment.

Results: Overall, 143 (92.3%) patients underwent RC, 57 patients (39.9%) achieved an ypT0ypN0 and 83 patients (58%) achieved a pathologic downstaging to ypT1/a/isypN0. After a median [interquartile range (IQR)] follow-up of 39 (30-47) months, three-year EFS was 74.4% [95% confidence interval (CI): 67.8-81.7] in the ITT. The 36-month OS in the ITT population was 83.8% (95% CI: 77.8- 90.2). Within the cohort of patients who did not receive additional chemotherapy (n=125), three-year RFS (95% CI) was 96.3% (91.6- 100) for ypT0ypN0, 96.1% (89-100) for ypT1/a/is ypN0, 74.9% (60.2-93) for ypT2-4ypN0, and 58.3% (36.2-94.1) for ypTanyypN+. According with biomarker analysis, 36-months EFS rates were 89% (82.5-96) and 78.2% (68.4-89.4) in those patients with CD8+ $\geq$ 10% (n=82) and <10% (n=60), respectively. Overall, 8 patients refused RC, of those 5 achieved ypT0, 1 ypTa and 1 had MIBC at second TURBT. To date none had relapse. Higher PD-L1 CPS [hazard ratio (HR): 0.98, 95% CI: 0.96-0.99; P=0.01] was associated with lower rates of events, while cT3-4 (HR: 2.55, 95% CI: 1.18-5.51; P=0.02) was associated with higher rates of events at MVA.

Conclusions: The three-year PURE-01 survival results confirm the prolonged efficacy of neoadjuvant pembrolizumab in MIBC. Biomarkers confirmed their clinical utility to identify those patients who may benefit the most from neoadjuvant pembrolizumab.

Keywords: *Neoadjuvant, Urothelial Cancer, Immunotherapy*

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PP159 Differences in unique molecular characteristics of bladder cancer and upper tract urothelial carcinoma in Korean patients from the K-MASTER project

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Background: Urothelial carcinoma differs in response to treatment and prognosis depending on the site of occurrence. This may be due to the unique biodiversity of the site of origin. This study aimed to compare the genomic properties of bladder cancer (BC) and upper tract urothelial carcinoma (UTUC) using the next-generation sequencing (NGS) of K-MASTER project in Korea.

Methods: This study included patients with unresectable or metastatic UC (bladder, ureter, renal pelvis), who were enrolled in the K-MASTER screening system between Jun 2017 and Jul 2021. Molecular profiling was performed on tumor tissue with the K-MASTER NGS panel.

Results: Our study included 231 patients (175 BC and 56 UTUC). In the BC group, there were 148 men and 27 women, whereas 40 men and 16 women in the UTUC group. In the whole, median number of variants per sample was 11. C to T (C>T) substitutions were the dominant mutation type in both BC and UTUC. There was a marked difference of between molecular characteristics of BC and UTUC. The most frequently mutated genes were TP53 (48%), KMT2D (30%), ARID1A (22%), ATM (20%) and ERCC2 (17%) in BC, whereas KMT2D (63%), TP53 (59%), BRCA2 (24%), CREBBP (24%) LRP1B (17%) were most frequently observed in UTUC. Restricting only those that were statistically significant ($p < 0.05$), the genomic alterations observed more frequently in UTUC than in BC were BRIP1 (Odds ratio, OR 0.142), FLT3 (OR 0.18), CDH5 (OR 0.152), BCORL1 (OR 0.327), and FANCL (0.103), whereas ERCC2 (OR 4.903) and ERBB2 were observed more frequently in BC. Interestingly, our data differed significantly from the TCGA data. TP53 (59%, 22%) was more observed and FGFR3 (18%, 46%) was less observed in our UTUC cohort compared to TCGA UTUC cohort. There was no significant difference of signaling pathway alterations between the TCGA data and our data. However, the cell cycle and TP53 pathway (71.4%, 73.2%) were found to be higher in our UTUC, whereas the RTK-RAS pathway accounted for 76.5% in TCGA UTUC, showing a significant difference. In mutational signature analysis, Signature 3 (DNA double-strand break) was highly dominant in both BC and UTUC. Signature 13 (activity of APOBEC Cytidine Deaminase) was mainly observed in BC, while Signature 18 (damage by reactive oxygen species) was mainly observed in UTUC.

Conclusions: This study showed significant differences in genomic properties between BC and UTUC. It has been confirmed that there are unique characteristics depending on race. These results imply that it is necessary to comprehensively understand the unique genomic characteristics in treating Korean BC and UTUC.

Keywords: *Bladder Cancer, Upper Tract Urothelial Carcinoma, Genomic Characterization*

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