871P Identification of genomic features underlying response of muscle-invasive bladder cancer (MIBC) to neoadjuvant sorafenib, gemcitabine, and cisplatin (SGC) in an open-label, single-arm, phase 2 study

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Background: Genomic analyses demonstrated that MIBC can be grouped into molecular subtypes that portend different outcomes with neoadjuvant chemotherapy (NACT). SGC was active in MIBC, showing a response rate (downstaging to pT < 2) of 54.3% in 46 patients (pts) in a phase 2 trial (NCT01222676, *Necchi et al, GU ASCO 2017*). We analyzed gene expression profiles (GEP) and copy number variations (CNV) of transurethral resections (TURB) from these pts.

Methods: We analyzed 25 pts, 18 responders (R) and 7 non-responders (NR). GEP and CNV profiles were generated using Affymetrix Clariom^{TM} D and OncoScan^{TM} assays. Samples were assigned to claudin-low (CL), basal (B) or luminal (L) subtypes according to the BASE47 and BCL40 signatures. Genes differentially expressed or amplified/deleted between NR and R were functionally analyzed using Ingenuity Pathway Analysis (IPA) and Gene Set Enrichment Analysis.

Results: Transcriptional subtypes were robustly assigned to 24/25 pts: 13 were classified as L, 10 CL and 1 B. A significant association between subtypes and therapeutic response was observed ($p = 0.002$), with all L samples falling in the R group while CL were split between R and NR (5 *vs* 5). To avoid confounding related to the subtype we restricted the comparison of R and NR to CL samples. Through the use of IPA we identified activation of an IRF7-driven transcriptional program ($p = 3.88E-12$) in NR samples. In the NR group we found a positive enrichment of gene sets related to mRNA processing, cell cycle and oxidative phosphorylation and a negative enrichment of defensins. In addition, 19 genes were both significantly overexpressed and amplified in NR whereas copy number gains on chromosome 17, 18 and 20 characterized R samples. Limitations include the unassessable role of S contribution to GC.

Conclusions: Altogether, the results indicate that L tumors are responsive to SGC. Comparisons between R and NR within the CL group outlined potential genomic predictors of response. Once validated, pt selection criteria for NACT may be substantially improved. Comparison with profiling of response to NA pembrolizumab will be shown (NCT02736266).

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