866PD Comprehensive biomarker analyses and updated results of PURE-01 study: Neoadjuvant pembrolizumab (pembro) in muscle-invasive urothelial bladder carcinoma (MIBC)

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Background: PURE-01 (NCT02736266) is a single-arm, phase 2 study of Pembro preceding radical cystectomy in MIBC. Updated results and exploratory biomarker analyses are presented.

Methods: 71 patients (pts) will be enrolled, with cT $\leq$ 3bN0 MIBC, regardless of cisplatin eligibility. Pembro is given 200mg q3w x3 cycles. Pathologic complete response (pT0) in ITT population is the primary endpoint (EP). The H_1 is pT0 $\geq$25%, H_0 pT0$\leq$15%. 15/71 pT0 are required. Biomarker analyses include: IHC PD-L1 combined positive score (CPS, Dako 22C3), hybrid-capture based comprehensive genomic profiling (CGP, FoundationONE), and expression of a 22-gene "T-cell inflamed" signature via quantitative PCR (qPCR).

Results: As of 05/2018, 65 pts have been enrolled and all underwent CGP from TURB samples: 42% showed DDR genomic alterations (GA). Median CPS was 21%. CPS and qPCR showed a significant correlation ($r = 0.71$, $p < 0.0001$), whereas CPS did not correlate with neither tumor mutational burden (TMB) nor DDR-GA (R=-0.16). 37 pts are evaluable for the primary endpoint. With 15 (40.5%) pT0 responses, the study has already achieved its PE. RB1 and PBRM1 GA were significantly associated with pT0 ($p = 0.014$ and $p = 0.007$). pT0 responses were obtained in 10 (52.6%) pts with CPS$\geq$21% and, most noteworthy, in 13 (61.9%) with DDR or RB1 GA. 8/8 pts (100%) with DDR/RB1 GA and CPS$\geq$21% achieved pT0. The 22 gene T-cell inflamed signature also significantly discriminated pT0 from non-pT0 pts ($p = 0.0032$). 17 pts had matched pre-post Pembro tumor samples analyzed, showing a mean of 51.9% shared GA. Concordant increases in gene expression by qPCR, observed in post- vs pre-Pembro lesions, from at least 5/7 non responding patients, were consistent with promotion of adaptive immunity (IFN-g, CXCL9, CXCR6, CD27, GZMB), being counteracted by strong adaptive resistance mechanisms (CD274, PDCD1, CD276, PDCD1LG2, IDO1).

Conclusions: Pembro has already exceeded the pT0 responses required in this study. Many new observations and the immune-genomic features interplay may contribute identifying those pts who might deserve a bladder-sparing approach. Full results on the entire dataset will be presented.

Clinical trial identification: NCT02736266.

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