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Reply from Authors re: Ananya Choudhury, Peter J. Hoskin. Predictive Biomarkers for Muscle-invasive Bladder Cancer: The Search for the Holy Grail Continues. Eur Urol 2019;76:69–70

Towards Biomarker-Informed Management of Muscle-Invasive Bladder Cancer

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We thank Drs. Choudhury and Hoskins [1] for their interest in our article [2] and for raising several important issues related to our findings. Identification of predictive biomarkers to guide therapy for muscle-invasive bladder cancer (MIBC) is a pressing unmet clinical need, and we believe that our work represents a significant advance in defining the association between the tumor microenvironment and clinical response following trimodal therapy (TMT) or neoadjuvant chemotherapy and radical cystectomy. However, as we emphasize throughout our manuscript, these findings require validation in additional cohorts before consideration can be given to clinical implementation. Indeed, our hope is that our study will motivate and inform subsequent efforts to further define the role of immune and stromal features in determining response to definitive therapies for MIBC.

Drs. Choudhury and Hoskins reiterate several important challenges in MIBC biomarker studies that were discussed in our manuscript, including the difficulty in separating the prognostic versus predictive implications of a biomarker when comparing outcomes across imperfectly matched cohorts. However, given that no randomized trials of TMT versus cystectomy have been successfully completed and that few large cohorts of patients treated with the current TMT standard of care (concurrent chemotherapy and radiation) are available, our study, although retrospective, does represent one of the largest genomic analyses performed in this context to date.

Owing to a lack of available banked samples (many patients underwent diagnostic transurethral resection of bladder tumor at outside institutions), insufficient tumor quantity or purity, or poor-quality RNA because of sample age or other factors, we excluded many samples to ensure that our final analyses included only samples with high quality transcriptomic data. Reassuringly, there were no significant differences in clinical characteristics between samples that underwent transcriptional analysis and those that did not (Table 1).

We apologize for any confusion regarding the significance of the T-cell and IFN-γ immune signatures in the multivariable models. As shown in Table 2 of our manuscript [2], both signatures were statistically significant in separate models that included clinical factors ($p = 0.002$ for T-cell inflamed signature and $p = 0.012$ for the IFN-γ signature).

As described in Section 3.2 and shown in Supplementary Figure 2 [2], we initially separated immune signature scores into quartiles, which revealed that patients in the first quartile had significantly worse disease-specific survival than those in the others. We subsequently used the same quartile approach to analyze all cohorts and signatures. In the case of the stromal signature, the quartile with the highest signature scores was the clear outlier and was compared to all other quartiles. This quartile approach has been used in other biomarker studies, including the work that identified an association between MRE11 protein levels and MIBC outcomes following radiotherapy [3,4].

Ongoing efforts by our group are focused on validating the association between immune/stromal signatures and outcomes in additional TMT cohorts, combining existing signatures to develop more sophisticated scoring systems, and applying novel signatures that may provide additional biological insights and predictive power [5,6]. To this end, a National Cancer Institute – approved effort is under way to analyze TMT cases from completed RTOG clinical trials, and gene expression profiling is among the rich set of correlative

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Table 1 – Clinical characteristics of the subset of MIBC patients with tumor transcriptional profiling compared to the total MIBC cohort receiving trimodal therapy at the Massachusetts General Hospital

Characteristic	Total cohort (n = 475) [8]	TTP subset (n = 136) [2]	p value
Median age, yr (interquartile range)	67.3 (60.2–74.6)	70.2 (61.8–77.4)	>0.9
Gender, n (%)			0.3
Male	357 (75)	109 (80)	
Female	118 (25)	27 (20)	
Clinical T stage, n (%)			0.6
T2	317 (66)	97 (71)	
T3	134 (29)	33 (24)	
T4	24 (5)	6 (4.4)	
Transurethral resection of bladder tumor extent, n (%)			0.7
Complete	332 (70)	93 (68)	
Incomplete	138 (29)	43 (32)	
Hydronephrosis, n (%)			0.5
Present	57 (12)	20 (14)	
Absent	418 (88)	115 (83)	

MIBC = muscle-invasive bladder cancer; TTP = tumor transcriptional profiling.

studies that will be performed for cases accrued to the phase 3 SWOG/NRG 1806 trial (NCT03775265) investigating TMT with or without concurrent atezolizumab (anti-PD-L1) [7], which will open across the USA in the coming months.

Conflicts of interest: The authors have nothing to disclose.

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