Impact of Tumor Mutational Burden on Clinical Outcomes in Muscle-Invasive Bladder Cancer Patients Treated with Neoadjuvant Chemotherapy

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BACKGROUND

- Neoadjuvant chemotherapy (NAC) remains a standard option for cisplatin eligible muscle-invasive bladder cancer (MIBC) patients.
- The presence of a pathological complete response (pCR) to NAC serves as a surrogate for improved overall survival (OS).[1]
- Increased post-NAC genomic heterogeneity is associated with poor survival in MIBC.[2]
- Whether high tumor mutational burden (TMB) increases genomic heterogeneity and development of chemo-resistant subclones in MIBC is unknown.
- In lung cancer, high tumor mutational burden (TMB) has been associated with poor response to chemotherapy.[3-6]
- Based on observations from lung cancer, we hypothesized that high TMB may increase the probability of development of chemo-resistant subclones and inferior clinical outcomes in MIBC patients.

METHODS

Study Design

- Study hypothesis: High baseline TMB identifies patients unlikely to benefit from NAC as measured by the presence of pathological residual disease.
- MIBC patients within the Atrium Health Wake Forest Baptist Comprehensive Cancer Center network between 2009 and 2023 were included.
- All patients received cisplatin-based NAC followed by cystectomy.
- Pre-NAC diagnostic transurethral resection of bladder tumor (TURBT) specimens were used for genomic analysis.
- Genomic analysis was performed using the Tempus xT (DNA; 648 genes) assay.[7,8]
- TMB was correlated with clinicopathologic outcomes using logistic regression, Cox proportional hazards models and Kaplan-Meier techniques.
- Since clinically significant TMB thresholds are unknown in MIBC, high TMB was defined as the upper TMB quintile for the cohort.

Statistical Plan

- Based on historical observations of a pathological residual disease rate of 0.65 in all patients, the study was powered based on an assumed pathological residual disease rate of 0.57 and 0.95 in the TMB non-high and high cohorts, respectively.
- Using a two-sided alpha of 0.05, a cohort size of 83 evaluable subjects was required to provide at least 90% power to detect this treatment effect size.
- Due to the timing of specimen analysis, the study was over-enrolled beyond calculated target.

OBJECTIVES

Primary

- Assess the impact of high TMB on pathological response rate in patients with MIBC who received NAC

Secondary

- Assess the impact of TMB, co-occurring genomic variants and RNA signatures on additional clinical outcomes, including pathologic complete response (pCR) rate, relapse-free survival (RFS) and overall survival (OS) in this cohort.

RESULTS

Table 1. Patient Characteristics

	N = 91
Race, N (%)	
White	80 (88)
Black or African American	10 (11)
Sex	
Male	63 (69)
Female	28 (31)
Treatment Regimen	
Gemcitabine + Cisplatin	59 (65)
MVAC or ddMVAC	32 (35)
Adjuvant ICI	4 (4)

- Median follow-up for the cohort was 63.6 months.
- pCR (ypT0 ypN0) occurred in 29 (31.9%).
- 38 (41.8%) relapsed with a median time to relapse of 5.3 (IQR: 3.0-12.5) months.
- For those who achieved pCR, RFS [HR 5.575, p < 0.001] and OS [HR 7.214, p < 0.001] were significantly improved compared to those with pathologic stage 1+ tumors.

Table 2. TURBT TMB Characteristics (Mutations/Mb)

	N = 91
Mean	10.6
Median	8.9
Upper Quintile	14.7
Maximum	27.9
Minimum	1.1

Table 3. Pathologic stage by TMB group

	pCR	Non-pCR
N	29	62
High TMB (Upper quintile)	9 (47.4%)	10 (52.6%)
Non-high TMB (Lower four quintiles)	20 (27.8%)	52 (72.2%)
TMB < 10	12 (23.1%)	40 (76.9%)
TMB ≥ 10	17 (43.6%)	22 (56.4%)

- Unexpectedly, patients with high TMB (upper quintile) trended towards improved pCR, [OR 0.43, p = 0.165]
- Since results of the primary analysis were contrary to our initial hypothesis, we also assessed TMB by a threshold of 10.
- Patients with TMB ≥ 10 had improved pCR rate, [OR 0.39, p = 0.044]

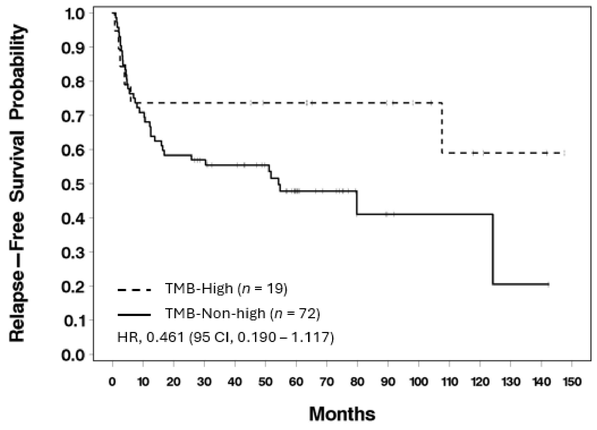
RESULTS

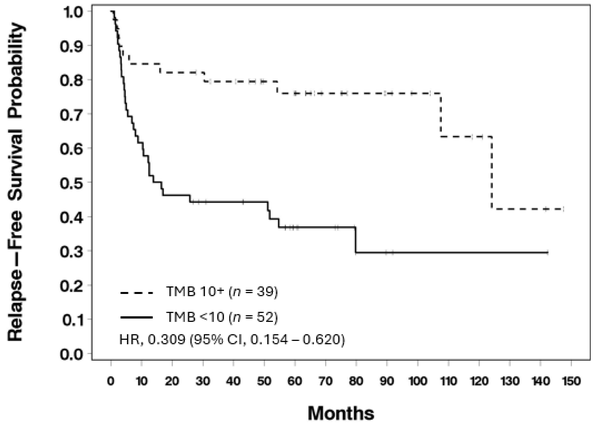
Table 4. Relapse Rate by TMB group

Relapsed	Yes	No
N	38	53
High TMB (Upper quintile)	4 (21.1%)	15 (79.0%)
Non-high TMB (Lower four quintiles)	34 (47.2%)	38 (52.8%)
TMB < 10	29 (55.8%)	23 (44.2%)
TMB ≥ 10	9 (23.1%)	30 (76.9%)

- Low TMB (Lower four quintiles) strongly trended towards increased risk of relapse, [OR 3.35, p = 0.065]
- TMB < 10 was associated with increased risk of relapse, [OR 4.2, p = 0.003]

Figure 1. Relapse-free survival by TMB

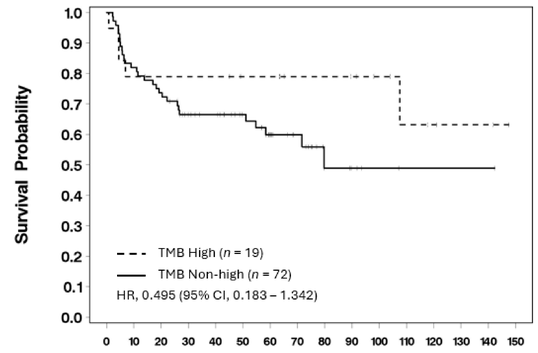


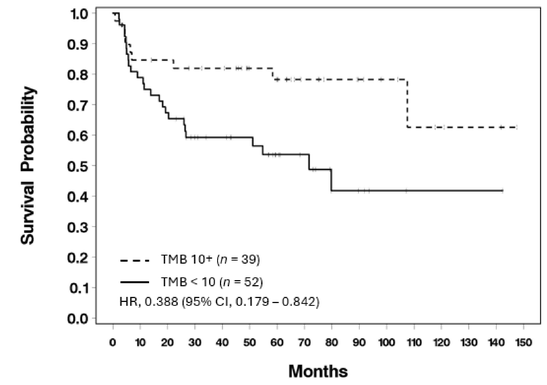


- High TMB (upper quintile) [HR 0.461, p = 0.08) and ≥ 10 [HR 0.309, p < 0.001) were associated with improved RFS as shown in Figure 1.
- TMB ≥ 10 was associated with improved OS [HR 0.388, p = 0.013] as shown in Figure 2.

RESULTS

Figure 2. Overall survival by TMB





CONCLUSIONS

- Contrary to our initial hypothesis, we found that TMB ≥ 10 was associated with improvements in pCR, relapse rates and survival in MIBC patients who received neoadjuvant cisplatin-based chemotherapy in a mature cohort collected before widespread low peri-operative ICI use.
- Our findings suggest TMB ≥ 10 improves sensitivity to cisplatin-based chemotherapy and require validation in a contemporary cohort.
- Associated genomic findings will be reported separately.

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