RACIAL DIFFERENCES IN TMB MEASURES BETWEEN PAIRED TUMOR/NORMAL AND TUMOR-ONLY SEQUENCING ACROSS ENDOMETRIAL, BLADDER, AND NON-SMALL CELL LUNG CANCERS

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Background Tumor mutational burden (TMB), defined as the number of somatic mutations per megabase of a tumor, is routinely used as a predictive biomarker for immunotherapy response in metastatic cancer patients. Sequencing of paired tumor and normal specimens allows for correction of TMB estimates with patient-specific germline variants. For tumor only assays, TMB estimates are corrected using germline variant annotations derived from population-scale germline variant surveys. These surveys often underrepresent minorities and individuals of non-European descent, leading to potential inaccuracies in TMB estimates in these populations.

Methods Our cohort includes patients who underwent tumor genomic profiling with the Tempus xT Next Generation Sequencing (NGS) assay and diagnosed with non-small cell lung (NSCLC, n=4,583) endometrial (n=3,084), or urothelial (n=2,806) cancer. We used 654 ancestry informative markers selected to overlap the target regions of the 648-gene Tempus xT NGS assay to infer global continental ancestry proportions and imputed race/ethnicity categories using ancestry admixture thresholds. TMB differences in paired sequencing (PS) and tumor-only sequencing (TOS) were evaluated for each imputed race/ethnicity category and cancer type. Statistical comparisons of TMB distributions were assessed using the Kruskall-Wallis test.

Results Among the entire cohort, 6,126 patients had PS performed, and 4,347 had TOS performed. The imputed ethnicities were 4% Asian (A), 10% Black (B), 5% Hispanic/Latino (H) and 81% White (W). In NSCLC, median TMB for A, B, H, and W patients was 1.9, 4.2, 3.2, and 3.8 for PS and 4.9, 7.6, 4.9, and 5.4 for TOS. Among endometrial cancers, median TMB for A, B, H, and W patients was 2.1, 2.7, 2.6, and 3.5 for PS and 5.0, 5.4, 5.4, and 5.4 for TOS. Median TMB for A, B, H, and W patients was 3.1, 3.5, 3.5, and 4.2 for PS and 7.3, 6.1, 6.9, and 5.6 for TOS in urothelial cancers. Differences across PS and TOS were significant in each cancer type (p<0.0001). When all cancer types were combined, the mean inflation of TMB median values was 1.7 for White whereas non-White patients was 3.4 (p<0.0001).

Conclusions Paired tumor sequencing reduces estimated TMB compared to tumor-only sequencing across all racial groups, more significantly for non-White patients.