Spectrum of Tumor Mutational Load in Genitourinary Cancers

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Background

Immunotherapy (IO) has changed the clinical management of numerous cancer (CA) types such as lung, melanoma, and Hodgkin lymphoma. Recently, clinical trials have demonstrated clinical benefit with IO showing durable responses in certain genitourinary (GU) cancers. Atezolizumab was the first IO approved for urothelial cancer in 20 years, thereby changing the treatment paradigm. Tumor mutational load (TML) has been shown to correlate with responses to IO. TML was measured for tumors sequenced using the NextSeq platform (592 genes and high concordance observed between TML-high and MSI-high in colorectal cancer. The cutoff of TML-high vs. TML-low used was 17 muta/ons/megabase [MB] due to the following differences (Figure 2A).

TML varied amongst GU cancers, with bladder cancer having the highest rate at 14.5%.

Table 1: Demographics of TML-high GU Cancers

Results (continued)...

Table 2C: TML and PD-L1 expression in Penile CA

Table 2E: TML and PD-L1 expression in Kidney CA

Figure 2: Concordance between TML-high and PD-L1 positivity in Bladder CA

Figure 3: Gene mutation frequency in TML-low and TML-high bladder cancer

Methods

We performed NGS on genomic DNA isolated from formalin-fixed, paraffin-embedded tissue using the Illumina NexSeq platform. An Agilent custom-designed SureSelectXT assay was used to enrich 582 whole-gene targets.

The cutoff of TNL-high vs. TNL-low was used 17 mutations/megabase (MB) due to the high concordance observed between TNL-high and MSI-high in colorectal cancer. TML was measured for tumors sequenced using the NexSeq platform (592 genes and 1.4MB sequenced per tumor) by counting all non-synomymous isosense mutations found per tumor that have not been previously described as germline alterations.

PD-L1 (SP142, Ventana) was performed on tumor specimen pending tumor availability. PD-L1 was considered positive if at least 5% of tumor cells exhibited membranous staining. Otherwise, PD-L1 was considered as negative. Immune cell staining was not performed on this cohort.

Results

Total of 544 tumor samples were analyzed. Demographics have been described in Table 1. TML varied amongst GU cancers, with bladder cancer having the highest rate at 14.5%.

Urothelial - squamous histology had a pronounced PD-L1 expression (Table 2A).

A comparison of TML-high (≥15) versus TML-low (<7) urothelial bladder CA showed the following differences (Figure 2A).

1. Bladder - express a higher rate of TML-high
2. Kidney - express a lower rate of TML-high
3. Penile - express a moderate rate of TML-high
4. Prostate - express a low rate of TML-high
5. Testicular - express a very low rate of TML-high

No correlation was found between a high TNL and PD-L1 expression.

Figure 1 – Distribution of TML across GU cancers. TML distributions are shown above. TML mean and ranges in bladder, kidney, penile, prostate, and testicular CA are 134 (1-1,301), 58 (1-1,301), 13 (10-16), 61 (1-1,411), and 5.1 (1-10), respectively.

Table 2: Concordance between TML high and PD-L1 positivity in Bladder CA

References


Figure 2: Concordance between TML high and PD-L1 positivity in Bladder CA

Table 2: Spectrum of TML in Genitourinary Cancers

Table 3: Concordance between TML-high and PD-L1 positivity in Bladder CA

Table 3A: Landscape of TML and PD-L1 expression across GU histologies

Table 3B: Landscape of TML and PD-L1 expression in Bladder CA

Table 3C: Landscape of TML and PD-L1 expression in Kidney CA

Conclusion

Our initial analysis indicates urothelial and squamous cell carcinomas of the bladder may derive the most benefit from checkpoint blockade therapy.

The near absence of TML high in the kidney cancer evaluated, indicates the existence of a separate medical medium accounting for the response to checkpoint inhibitors in these malignancies.

The lack of TML high and low PD-L1 expression observed in some GU CA requires further investigation.

The lack of concordance between TML and PD-L1 suggests a multi-modality approach is needed to ascertain which GU CA derive the greatest benefit from checkpoint blockade therapy.

More studies correlating molecular profiling with clinical outcomes (e.g. ORR, PFS, OS) are required to evaluate response to checkpoint blockade therapy.