Penile squamous cell carcinoma with high and very high tumor mutational burden: A genomic landscape and real-world clinical outcome study

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ABSTRACT

Background: TMB is an established biomarker of efficacy with immune-checkpoint inhibitors (ICI) in a pan-cancer indication. TMB, however, has not been specifically considered for penile squamous cell carcinoma (PSCC).

Methods: We analyzed 397 PSCC cases to identify genomic alterations (GA) in >300 cancer-associated genes, genomic signatures, and TMB using a hybrid capture-based comprehensive genomic profiling (CGP) assay. TMB was categorized as low (<10 mutations/Mb), high (10-19), and very high (>20). Tumor cell programmed cell-death ligand-1 (PD-L1) expression was determined by immunohistochemistry (IHC, Dako 22C3) and defined as tumor proportion score (TPS) ≥21. Germline status of GA was predicted using a validated somatic-germline computational method. Separately, real-world clinical outcomes (RWCOs) of data patients with metastatic penile cancer receiving first-line ICI were obtained from the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine clinic-genomic database (FH-FMI CSDB), which originated from approximately 280 US cancer clinics (~800 sites of care).

Results: There were 339 (85.4%) TMB-low, 40 (10.1%) TMB-high and 18 (4.5%) TMB-very high PSCC. TMB ≥10 vs TMB-low PSCC revealed an enrichment of GA of PIK3CA (48.3% vs 18.3%, p<0.001) and KMT2D (25.9% vs 7.7%, p<0.001), and less frequent GA of CDKN2A (25.3% vs 45.7%, p=0.050). Most of these GA did not co-occur. PD-L1 expression was not impacted by TMB status. HPV identification was more frequent as TMB increased: 28.3% for the TMB-low, 50% for the TMB-high and 58.8% for the TMB-very high groups. In total, 95/1,377 (6.9%) GA were predicted to be of germline nature. In the FH-FMI CSDB cohort, 10 patients receiving ICI, 4 (40%) had a real-world overall survival (rOS) >12 months with sustained benefit in 3/3 patients with TMB ≥10 mut/Mb.

Conclusions: Evaluation of advanced/metastatic PSCC by CGP based on TMB level revealed significant differences in biomarkers for the near 15% of cases that have high and very high TMB ≥10 mut/Mb. These PSCC cases represented a distinct tumor subgroup deserving further clinical investigation.

MATERIALS AND METHODS

- ≥50 ng DNA extracted from 40 µm of FFPE sections
- Sequencing performed for up to 324 cancer-related genes and introns from 28 genes commonly rearranged in cancer
- Hybrid capture-based sequencing using adaptor ligation-based libraries
- Mean coverage depth >600X
- Tumor mutational burden (TMB): calculated from 0.8-1.1 Mb sequenced DNA
- Predominant Ancestry was determined using a SNP-based approach (Connelly et al. AACR 2018). An ancestry classifier was trained and validated using the 1000 Genomes data and the applied to the assay used in this study.
- PD-L1 expression was measured by IHC (Dako22C3).

RESULTS

- Landscape of GA in the entire cohort. N=397
- Figure 1. Distribution of TMB scores by category.
- Landscape of GA in TMB-high PSCC (n=18)
- Landscape of somatic vs germline GA in PSCC

CONCLUSIONS

- Evaluation of advanced/metastatic PSCC by CGP based on TMB level revealed significant differences in biomarkers for the near 15% of cases that have high and very high TMB ≥10 mut/Mb.
- These PSCC cases represented a distinct tumor subgroup deserving further clinical investigation.

Table 1. Comparison of clinical and genomic features by TMB-high vs TMB-low