# Prevalence of Histology-Agnostic Biomarkers in Pure Squamous Cell Carcinomas of the Genitourinary Tract

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## Background

- Pure squamous cell carcinomas (SCC) of the genitourinary (GU) tract are less responsive to chemotherapy with limited therapeutic options for systemic disease
- SCCs account for 2-8% of bladder cancer cases and treatment mirrors urothelial carcinoma despite significantly lower responses
- There are 8 FDA-approved histology-agnostic treatments based on biomarker profiling: dostarlimab (dMMR/MSI-H), pembrolizumab (dMMR/MSI-H; TMB-H), larotrectinib (NTRK fusion), entrectinib (NTRK fusion), selpercatinib (RET fusion), trastuzumab deruxtecan (HER2 positive), and dabrafenib plus trametinib (BRAF V600E mutation)
- Data are limited on gene alterations associated with SCC of the GU tract. This study aimed to explore the prevalence of biomarkers in pure SCCs of the GU tract.

## Methods

- A retrospective analysis was performed to identify bladder cancer patients with SCCs that underwent comprehensive molecular profiling
- Cases were reviewed by a GU pathologist to confirm pure SCC, and biomarker profiling was conducted to assess prevalence of markers with available histology-agnostic treatments as well as areas of potential future exploration through clinical trials
- NextGen DNA sequencing (592-gene panel or whole exome) was performed at Caris Life Sciences (Phoenix, AZ).
- dMMR/MSI-H was determined by IHC/NGS.
- Tumor mutational burden (TMB) was classified as high if ≥10 mutations per megabase (mt/Mb)
- PD-L1 expression was assessed by IHC (22C3 assay, TPS ≥1+)
- Real-world overall survival (rwOS) information was obtained from insurance claims data and calculated from first of biopsy to last contact. Hazard ratio (HR) was calculated using the Cox proportional hazards model, and P values were calculated using the log-rank test.

**Table 1: Study Demographics**

| Category | Sub-category | Patient count (n) |
|---|---|---|
| Total | Bladder-SCC (after pathology review) | 169 |
| | Bladder-SCC (with outcomes data available) | 166 |
| Sex | Female | 85 (51.2%) |
| | Male | 81 (47.9%) |
| Specimen site | Bladder | 99 (58.6%) |
| | Metastatic sites | 70 (41.4%) |
| Ethnicity | Unknown | 16 (9.5%) |
| | Not Hispanic or Latino | 121 (72.9%) |
| | Hispanic or Latino | 13 (7.7%) |
| Race | Asian or Pacific Islander | 4 (2.4%) |
| | Black or African American | 21 (12.9%) |
| | White | 112 (67.5%) |
| | Other | 5 (2.9%) |
| | Unknown | 8 (4.7%) |

## Results

**Figure 1. Oncoprint and Gene Alteration Prevalences in Squamous Cell Carcinoma of the Bladder in 169 patients**

- Of 8000 bladder cancer cases, 655 (8.2%) were coded as having components of SCC
- 275 (2.4%) cases were reviewed by a GU pathologist, and 169 (2.1%) cases of pure SCC of the bladder were identified

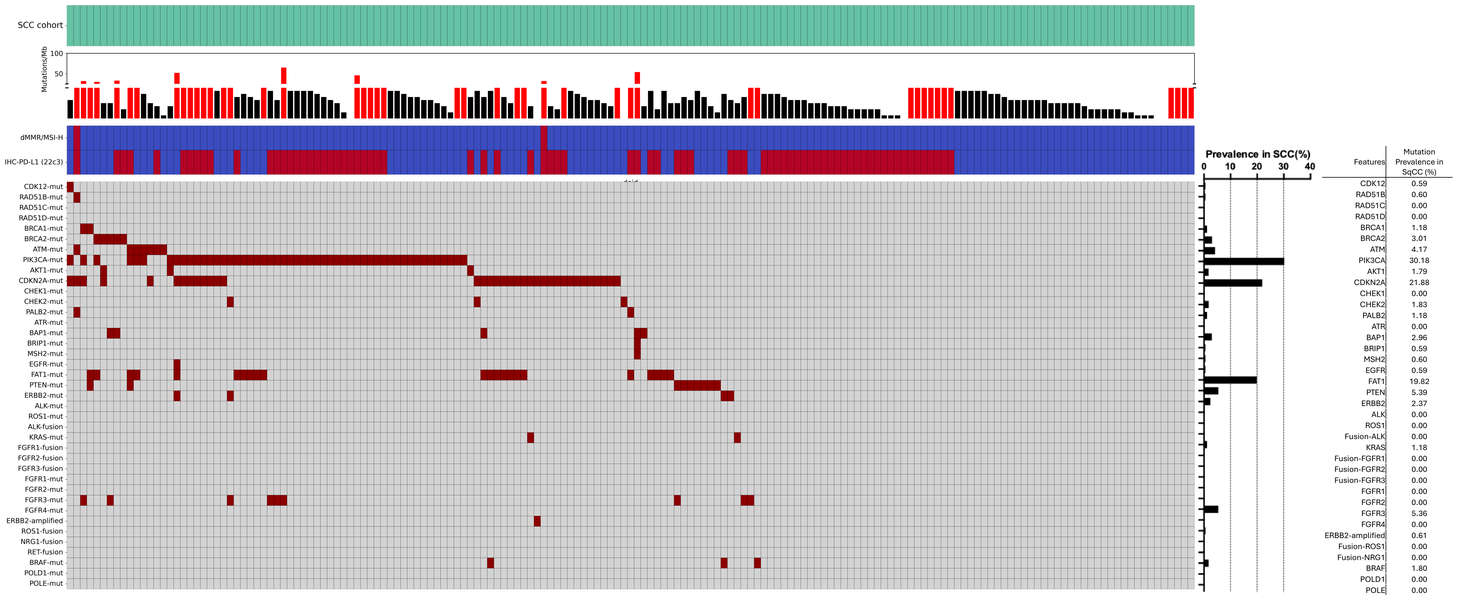
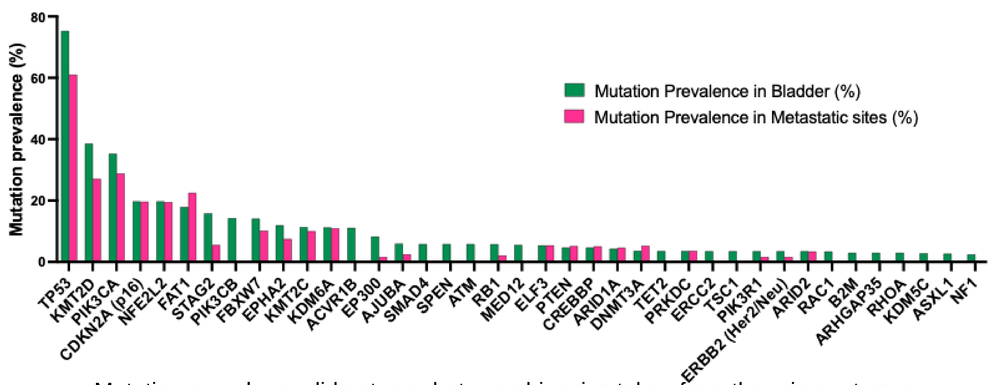


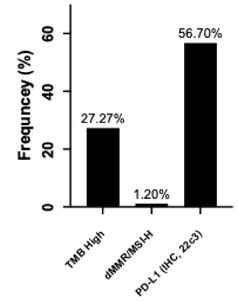

**Figure 2. Mutation Frequencies in Bladder SCC Primary Biopsy Site Versus Metastatic Biopsy Site**




- Mutation prevalence did not vary between biopsies taken from the primary tumor versus metastatic sites

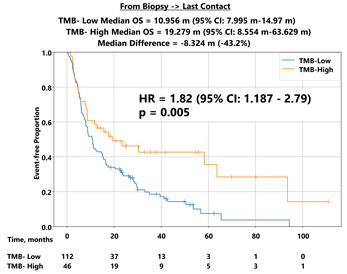
## Results

**Figure 3. Immunotherapy Related Markers in SCC.** TMB-High, PD-L1 and dMMR/MSI-High frequency in SCC of bladder




- TMB-H was noted in 27% of patients with pure SCC of the bladder

**Figure 4. Overall Survival in TMB-High (≧10 mut/Mb) Compared to TMB-Low SCC Tumors**




## Conclusions

- This study provides a comprehensive analysis of the genetic landscape of pure SCC of the bladder that may inform future therapeutic strategies for this rare tumor with limited treatment options
- Almost one-third of patients were TMB-High, reflecting a population that may benefit from immune checkpoint inhibitors monotherapy or combination strategies.
- Other histology-agnostic targets for current therapies were relatively infrequent.

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