Non-urothelial bladder cancer: genomic alterations and patient outcomes

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Background

Adenocarcinoma (ADA) and squamous cell carcinoma (SCC) are rare and aggressive subtypes of bladder cancer. For advanced disease, there are limited therapeutic options and no clear standard of care exists. Therefore, novel therapies based on underlying tumor biology are needed. The purpose of this study was to report on survival of patients with ADA and SCC and to identify potential targets and therapeutic options for these subtypes utilizing next generation sequencing (NGS).

Methods

- For survival trends, data were obtained from the SEER Database from 1988 - 2008, with demographic information, pathologic characteristics and 5-year disease-specific survival calculated.
- Using the Caris Life Sciences database, 72 patients (49 with ADA and 23 with SCC) had NGS testing with either hotspot 47 gene panel or a 592 gene assay.

Results

	Local		Regional		Distant	
Cancer Type	Cases	Survival*	Cases	Survival	Cases	Survival
Adenocarcinoma	148	0.78	375	0.61	118	0.23
Squamous Cell Carcinoma	524	0.57	1816	0.39	592	0.07

*Represents 5-year disease specific survival

Table 1 – SEER Database 1988-2008. Of 235,537 cases of bladder cancer, there were 671 ADA and 3096 SCC. For all stages, median OS (mOS) for ADA was 17.9 months and 5-year survival rate was 58% and mOS for SCC was 15 months and 5-year survival rate was 37%.

Histology	Number	Median Age (Range)	Male:Female Ratio	% Metastatic
Adenocarcinoma	49	59 (33 – 82)	3:2	31% (15/49)
Squamous Cell Carcinoma	23	67 (41 – 85)	1:1	52% (12/23)

Table 2 – Specimen information. Bladder specimens were from cystectomy or TURBT. Ten patients with ADA were confirmed as urachal in origin and one patient had urethral ADA.

Results (continued)

ADENOCA

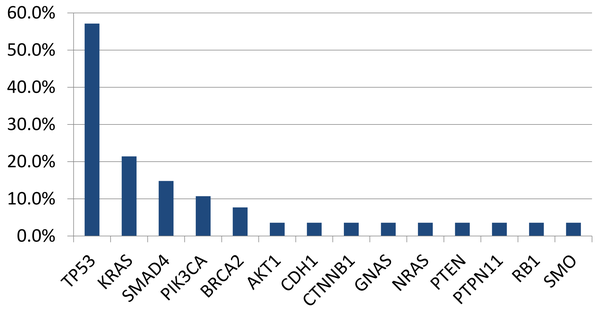

Figure 1 – NGS analysis in ADA (Hotspot, n=28). Majority in the ADA cohort had a *TP53* alteration (57.1%). Other aberrations were detected by NGS, with some being potentially targetable. *PIK3CA* and *BRCA2* alterations were detected in 10.7% and 7.7%, respectively. Most of the 47 genes analyzed were not altered.

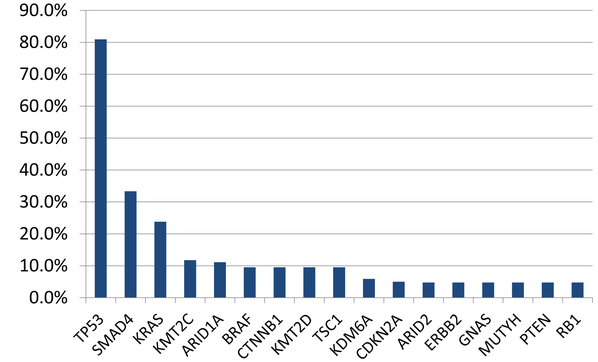

Figure 2 – NGS analysis in ADA (592 gene assay, n=21). Majority in the ADA cohort had a *TP53* alteration (81%). Other potentially targetable mutations include *TSC1* and *CDKN2A*, which were mutated in 9.5% and 5% of cases, respectively. Majority of the genes analyzed in this cohort were not altered.

Results (continued)

SCC

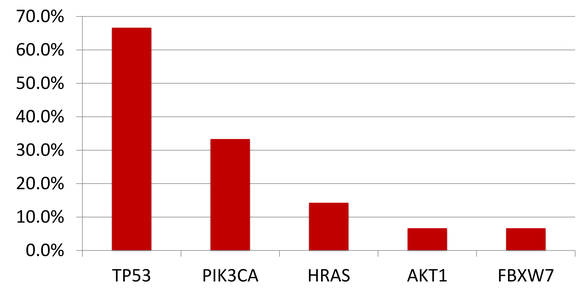

Figure 3 – NGS analysis in SCC (Hotspot, n=15). Majority in the SCC cohort had a *TP53* alteration (66.7%). There was dysregulation along the PI3K/AKT/mTOR pathway, given relatively high rates of mutations in *PIK3CA* (33.7%), AKT1 (6.7%), and FBXW7 (6.7%). Most of the 47 genes analyzed were not altered.

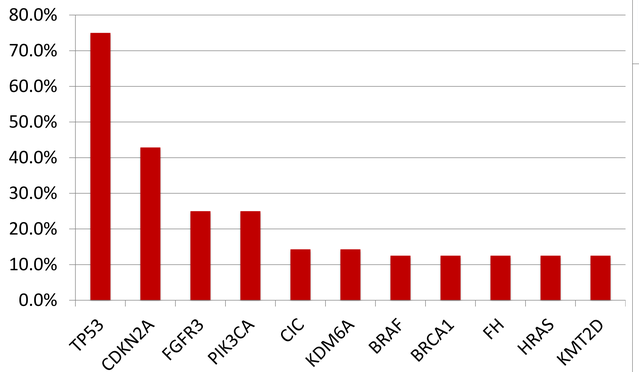

Figure 4 – NGS analysis in SCC (592 gene assay, n=8). Majority in the SCC cohort had a *TP53* alteration (75%). Other potentially targetable mutations include *CDKN2A, FGFR3, PIK3CA, BRCA1*, which were mutated in 42.9%, 25%, 25%, and 12.5% of cases, respectively. Majority of the genes analyzed in this cohort were not altered.

Results (continued)

A

	ADA (%)	UC (%)
TP53	57.1	49.4
KRAS	21.4	4.2
SMAD4	14.8	2.2
PIK3CA	10.7	22.7
BRCA2	7.7	11.3

B

	SCC (%)	UC (%)
TP53	66.7	49.4
PIK3CA	33.3	22.7
HRAS	14.3	5.1
FBXW7	6.7	9.3
AKT1	6.7	2.2

C

	ADA (%)	UC (%)
TP53	81	49.4
SMAD4	33.3	2.2
KMT2C	23.8	21.8
ARID1A	11.8	27.1
BRAF	11.1	3.4
CTNNB1	9.5	3.4
KMT2D	9.5	30.8
TSC1	9.5	10.3
KDM6A	5.9	29.3
CDKN2A	5	7.1

D

	SCC (%)	UC (%)
TP53	75	49.4
CDKN2A	42.9	7.1
FGFR3	25	14.7
PIK3CA	25	22.7
CIC	14.3	4.2
KDM6A	14.3	29.3
BRAF	12.5	3.4
BRCA1	12.5	5.1
FH	12.5	2.0
HRAS	12.5	5.1
KMT2D	12.5	30.8

Table 3 – Comparison of alterations between ADA (A: Hotspot n=28, C: 592 Gene Panel, n=21), SCC (B: Hotspot, n=15, D: 592 Gene Panel, n=8) and UC (data from The Cancer Genome Atlas, n=409). The most common mutation in ADA and SCC is *TP53*. The PI3K/AKT/mTOR pathway is mutated across all 3 histologic subtypes. *BRCA1* is mutated in SCC and UC and *BRCA2* is mutated in ADA and UC. *BRAF* alterations seen in ADA and SCC are not the *V600E* activating subtype. *FGFR3* alteration is seen in SCC and UC, but not in ADA.

Conclusions

- Adenocarcinoma and squamous cell carcinoma of the bladder are rare, aggressive subtypes which represent <5% of bladder cancer diagnoses
- Genomic profiling can identify differences in underlying tumor biology of bladder adenocarcinoma and squamous cell carcinoma
- Alterations in the *PI3K/AKT/mTOR* pathway are similar to what has been reported in UC. Ongoing clinical trials in UC are investigating the use of targeted agents against this pathway.
- Future analyses of these rare subtypes should investigate the emerging actionable targets, such as *TSC1, PIK3CA, FGFR3, BRCA1/2, CDKN2A* and *BRAF*

References

1. Aragon-Ching, et al. *J Clin* Oncol 36, no. 6_suppl (2018) 425-425.
2. The Cancer Genome Atlas Research Network. (2017). "Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer." Cell 171, 540–556.