Abstract ID# 9027: The Genomic, Transcriptomic, and Immunological Landscape of Sodium-glucose cotrasporter-2 in Lung Cancer and Association with Clinical Outcomes

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Background

- *In vivo* data indicate SGLT2 plays a role in the development of NSCLC.
- SGLT2 inhibitors are associated with a lower incidence of cancer development.
- **Aim:** Characterize the genomic and immunological landscape of tumors with high and low expression of SGLT2-coding gene *SLC5A2* in NSCLC [adenocarcinoma (AC) or squamous cell carcinoma (SCC) histology] and the relationship with clinical outcomes.

Methods

- NSCLC tumors of AC (N = 11,725) or SCC (N = 4,158) histology were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or whole exome) and RNA (whole transcriptome).
- Tumors were divided by *SLC5A2* expression quartiles based of expression in all NSCLC tumors (Q4: *SLC5A2*-H, Q1: *SLC5A2*-L).
- PD-L1 expression (22C3; Positive (+): TPS ≥1%) was assessed by IHC.
- High tumor mutational burden (TMB-H) was defined as ≥10 mutations/MB.
- Mutations were defined as pathogenic SNVs/indels. *SLC5A2*-H and -L expression (transcripts per million) was defined as top and bottom quartile, respectively.
- A transcriptomic signature predictive of response to immunotherapy was applied (T cell-inflamed; Bao, 2020).
- The Mann-Whitney U test was applied as appropriate, with P-values adjusted for multiple comparisons (p < .05).
- Real-world overall survival (OS) data was obtained from insurance claims and Kaplan-Meier estimates were calculated for molecularly defined subpopulations of patients (N = 13,505).

	SLC5A2 Q1	*SLC5A2* Q2	SLC5A2 Q3	*SLC5A2* Q4	Statistic	q-value
Histology						
Adenocarcinoma	46% (2487/5401)	50% 2726/5401)	55% (2994/5400)	65% (3518/5401)	Fisher's Exact	0.00
Squamous cell carcinoma	25% (1331/5401)	22% 1194/5401)	19% (1023/5400)	11% (610/5401)	Fisher's Exact	0.00
Other	29% (1583/5401)	27% (1481/5401)	26% (1383/5400)	24% (1273/5401)	Fisher's Exact	0.00

Table 1: Cohort makeup by histology and *SLC5A2* expression quartile.

Results

1. Genomic Landscape:

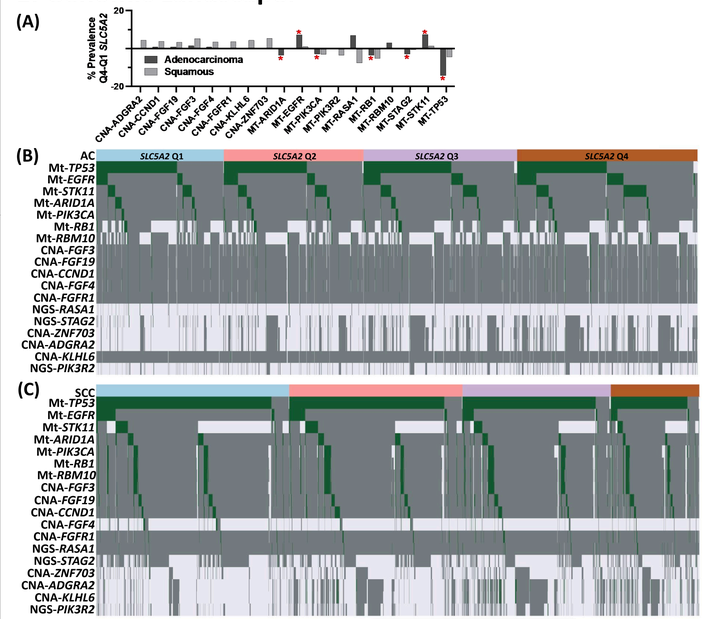

Figure 1: (A) Prevalence of gene alterations with a greater than 3% difference in prevalence between Q1 and Q4 of *SLC5A2* expression (asterisk indicates significance, $q < 0.05$). Oncoprint for AC **(B)** and SCC **(C)** histology.

2. Immune Landscape:

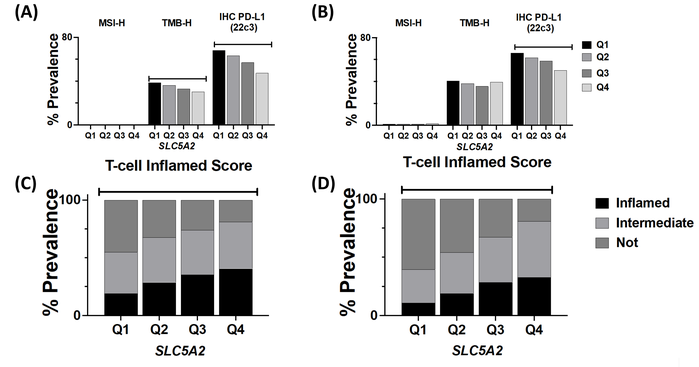

Figure 2: Prevalence of immune biomarkers for AC **(A)** and SCC **(B)** tumors. Prevalence of inflamed tumors (more immunotherapy responsive per the T cell-inflamed score) for AC **(C)** and SCC **(D)** tumors (asterisk indicates significance, $q < 0.05$).

3. Outcome data:

(A)

	Collection-> Last contact						First pembrolizumab -> Last contact						First pembrolizumab->Last pembrolizumab					
Subgroup	**HR**	**Low CI**	**Upper CI**	***p*-value**	**Q4**	**Q1**	**HR**	**Low CI**	**Upper CI**	***p*-value**	**Q4**	**Q1**	**HR**	**Low CI**	**Upper CI**	***p*-value**	**Q4**	**Q1**
Adenocarcinoma	0.787	0.73	0.85	**<0.001**	2784	2335	1.062	0.89	1.28	0.517	509	413	0.898	0.78	1.03	0.133	442	355
AC EGFR WT	0.782	0.72	0.85	**<0.001**	2056	1729	0.879	0.72	1.07	0.207	411	324	0.882	0.75	1.03	0.116	359	277
AC EGFR MT	0.786	0.63	0.99	**0.038**	508	284	1.993	0.77	5.18	0.148	50	16	1.697	0.87	3.33	0.119	39	12
AC KRAS WT	0.852	0.77	0.95	**0.002**	1582	1271	1.094	0.84	1.43	0.509	266	191	1.017	0.83	1.24	0.868	231	166
AC KRAS MT	0.642	0.57	0.73	**<0.001**	949	732	0.72	0.54	0.96	**0.024**	190	151	0.836	0.66	1.06	0.137	163	124
Squamous Carcinoma	0.882	0.78	1.00	**0.045**	546	1347	0.73	0.54	0.99	**0.041**	103	228	0.72	0.56	0.93	0.012	90	185
SCC EGFR WT	0.902	0.79	1.03	0.125	481	1145	0.673	0.49	0.94	**0.018**	90	195	0.713	0.54	0.94	0.015	80	157
SCC EGFR MT	0.42	0.11	1.60	0.189	7	10	ND						ND					
SCC KRAS WT	0.869	0.76	1.00	**0.042**	463	1109	0.66	0.47	0.92	**0.013**	91	186	0.707	0.54	0.93	**0.013**	81	150
SCC KRAS MT	1.456	0.83	2.57	0.189	21	46	ND						ND					

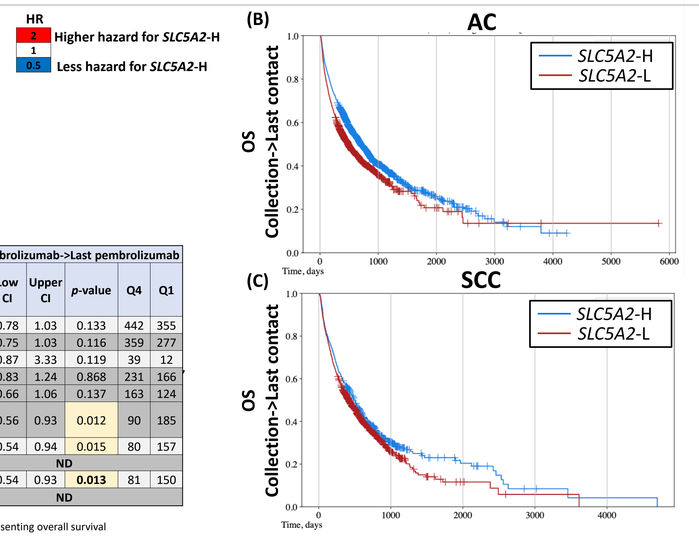

Figure 3: (A) Table of survival data for different NSCLC subpopulations segmented by *SLC5A2*-H vs *SLC5A2*-L. Kaplan-Meier curves representing overall survival for AC **(B)** and SCC **(C)** histology's.

Study Highlights

- In **AC**, *SLC5A2*-H was associated with **higher rates** of ***EGFR*** (20.8 vs 13.5%, $p < 0.05$) and ***STK11*** mutations (20.1 vs 12.9%, $p < 0.05$), but **lower rates** of ***TP53*** (50.8 vs 69.5%, $p < 0.05$) and ***ARID1A*** (8.7 vs 4.6%, $p < 0.05$)
- *AC* and SCC *SLC5A2*-H tumors had a lower prevalence of PD-L1+ (AC: 47 vs 68%, SCC: 50 vs 67%, $p < 0.05$). AC *SLC5A2*-H tumors had a lower prevalence of TMB-H (30 vs 39%, $p < 0.05$), but not in SCC (40 vs 41%, $p = 0.6$).
- In **AC**, *SLC5A2*-H had **longer OS** as compared to SLC5A2-L (HR = 0.787 [0.73-0.85], $p < 0 .001$)
- *SLC5A2*-H **SCC** tumors had significantly **longer OS** (HR 0.88, [0.78-1.00], $p = 0.045$) and **TOT with pembrolizumab** (HR .72 [0.56-.093], $p = 0.01$).
- *SLC5A2*-H**, *KRAS* mutant AC** tumors had significantly **longer OS** (HR 0.64 [0.57-0.73], $p < 0.001$) whereas SLC5A2-H **KRAS mutant SCC** tumors (HR 1.46 [0.83-2.57], $p = 0.19$) trended towards **shorter OS**.

Conclusions

1) *SLC5A2* expression was associated with a highly altered genomic landscape in AC
2) In specific subgroups, high expression of *SLC5A2* was associated with OS and TOT with immunotherapy

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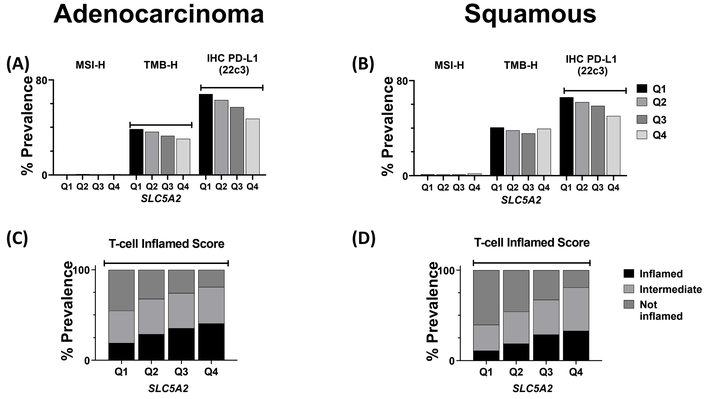
Adenocarcinoma
Squamous
(A)
(B)
(C)
(D)
MSI-H
TMB-H
IHC PD-L1 (22c3)
% Prevalence
80
0
Q1 Q2 Q3 Q4
SLC5A2
Q1
Q2
Q3
Q4
T-cell Inflamed Score
100
Inflamed
Intermediate
Not inflamed