Genomic and Immune Landscape of Biliary Tract Cancers with *ARID1A*, *PBRM1* and *BAP1* Alterations

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Background

- Alterations in *ARID1A*, *PBRM1* and *BAP1* subunits of the SWI/SNF complex are common in biliary tract cancers (BTCs) and have been implicated in tumor microenvironment (TME) immunomodulation.
- However, there is heterogeneity in outcomes, with *PBRM1* and *BAP1* conferring improved survival vs worse survival with ARID1A. We explored relationships between *ARID1A*, *PBRM1*and *BAP1* alterations with putative immunotherapy biomarkers and genomic co-alterations.

Methods

- We examined BTC patients in the Tempus database with *ARID1A*, *PBRM1* and *BAP1* alterations.
- Co-alterations were identified through next-generation sequencing (NGS) using the Tempus xT assay, a targeted, tumor-normal-matched DNA panel that detects SNVs, indels, and CNVs in 648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity.
- Samples additionally underwent whole transcriptome RNA-seq via the Tempus xR assay (Tempus Labs, Chicago, IL). Immune biomarkers explored include MSI-H, PD-L1, Tumor Mutation Burden (TMB), and immune cell infiltration by RNA sequencing.
- Parameters were analyzed between two groups: BTC with *ARID1A*, vs BTC with *PBRM1* and/or *BAP1* alterations.

Baseline Demographics

- 696 BTC patients, *ARID1A* n=350, *PBRM1* and/or *BAP1* n=346
- Majority of patients with advanced disease (76% stage IV)
- 85% with sample collection for NGS within 3 months of diagnosis

Characteristic	Overall, N = 696[1]	ARID1A, N = 350[1]	PBRM1 and/or BAP1, N = 346[1]	p-value[2]
Age at Diagnosis				0.048
Median (Range)	67 (27, 90)	68 (27, 90)	66 (27, 90)	
Gender				0.069
Female	410 (59%)	218 (62%)	192 (55%)	
Male	286 (41%)	132 (38%)	154 (45%)	
Race				0.4
White	310 (80%)	147 (77%)	163 (83%)	
Black or African American	34 (8.8%)	19 (9.9%)	15 (7.7%)	
Other	30 (7.7%)	18 (9.4%)	12 (6.1%)	
Asian	14 (3.6%)	8 (4.2%)	6 (3.1%)	
Unknown	308	158	150	
Stage within 60 Days of Sample Collection				0.3
Stage 4	299 (76%)	158 (77%)	141 (75%)	
Stage 2	36 (9.2%)	19 (9.2%)	17 (9.1%)	
Stage 3	35 (8.9%)	21 (10%)	14 (7.5%)	
Stage 1	23 (5.9%)	8 (3.9%)	15 (8.0%)	
Unknown	303	144	159	

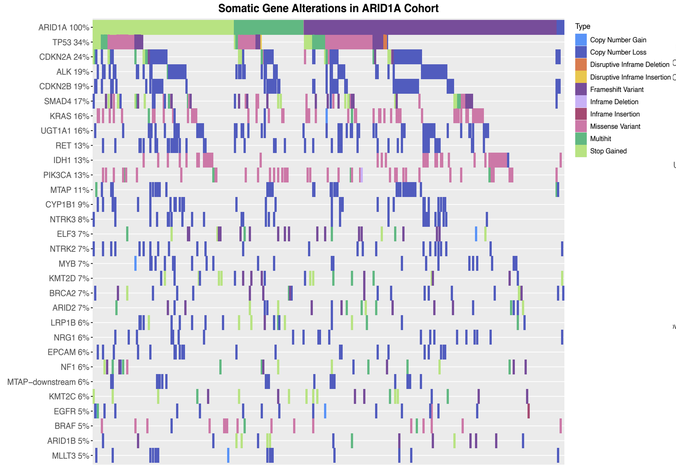
[1] n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test

Results

Somatic Gene Alterations *ARID1A* vs *PBRM1/BAP1*

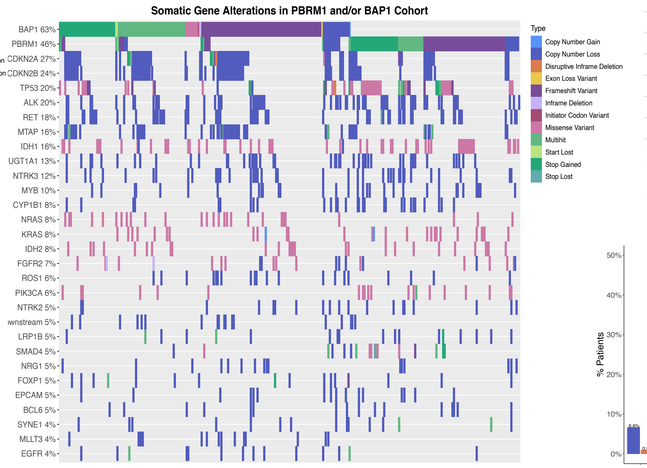
***ARID1A* cohort**

- Alterations in *TP53*, *SMAD4* and *KRAS* more frequent in *ARID1A* BTC
- Quantitatively, more co-alterations seen in *ARID1A* BTC



***BAP1* and/or *PBRM1* cohort**

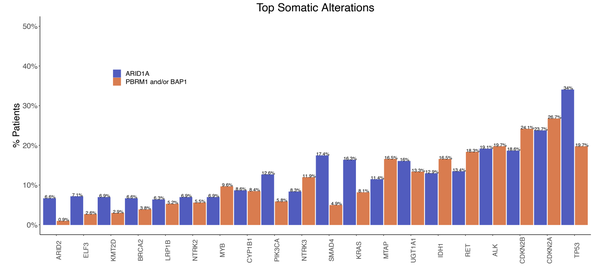
- *TP53* alterations more frequent in *PBRM1* BTC
- *CDKN2A/B* alterations more common in *BAP1* BTC



Somatic Gene Co-alterations *ARID1A* vs *PBRM1/BAP1*

Gene	ARID1A, N = 350[1]	PBRM1 and/or BAP1, N = 346[1]	p-value[2]	q-value[3]
SMAD4	61 (17%)	17 (4.9%)	<0.001	<0.001
TP53	119 (34%)	68 (20%)	<0.001	<0.001
ARID2	23 (6.6%)	3 (0.9%)	<0.001	<0.001
IDH2	7 (2.0%)	28 (8.1%)	<0.001	<0.001
NRAS	8 (2.3%)	28 (8.1%)	<0.001	<0.001
KRAS	57 (16%)	28 (8.1%)	<0.001	0.001
MTAP	40 (11%)	57 (16%)	0.055	0.070
BRCA2	23 (6.6%)	13 (3.8%)	0.094	0.11
IDH1	45 (13%)	57 (16%)	0.2	0.2

[1] n (%)
[2] Pearson's Chi-squared test
[3] False discovery rate correction for multiple testing



Immune Cell Infiltrate Fractions by RNA seq

- Macrophages dominate immune TME (~45 cell fraction),
- CD4+ T-cells second most common (~24 cell fraction)
- Low prevalence of CD8+ T-cells

Immune Cell Proportions	Overall, N = 696[1]	ARID1A, N = 350[1]	PBRM1 and/or BAP1, N = 346[1]	p-value[2]
B cells (%)	6.9 (1.9, 16.0)	9.4 (3.2, 19.5)	5.6 (0.9, 11.7)	<0.001
Macrophages (%)	46.4 (34.7, 57.9)	43.5 (33.0, 56.7)	49.4 (37.6, 59.6)	<0.001
NK cells (%)	12.3 (8.0, 17.5)	12.2 (7.4, 17.3)	12.6 (8.4, 18.0)	0.12
CD8 T cells (%)	4.7 (0.0, 9.8)	5.2 (0.0, 9.8)	4.0 (0.0, 9.8)	0.2
CD4 T cells (%)	23.0 (14.7, 32.1)	23.6 (15.2, 31.2)	22.4 (14.3, 32.5)	0.4
Immune cell (%) of all cells in the sample	14.7 (9.3, 20.3)	14.8 (9.1, 20.6)	14.6 (9.4, 19.7)	>0.9

[1] Median (IQR)
[2] Wilcoxon rank sum test

TMB, PD-L1 in *ARID1A* vs *PBRM1* and/or *BAP1* BTC

- No significant difference in putative immune biomarkers between groups
- Low prevalence of MSI-H, dMMR, TMB-High, PD-L1-positive molecular profiles in the entire cohort and within each group.

Characteristic	Overall, N = 696[1]	ARID1A, N = 350[1]	PBRM1 and/or BAP1, N = 346[1]	p-value[2]
TMB				<0.001
Median (IQR)	2.69 (1.53, 3.87)	2.92 (1.90, 4.23)	2.31 (1.17, 3.43)	
Range	0.00, 50.33	0.00, 50.30	0.00, 50.33	
TMB				0.2
<10	663 (95%)	330 (94%)	333 (96%)	
>=10	33 (4.7%)	20 (5.7%)	13 (3.8%)	
PDL1				0.8
Negative	233 (94%)	109 (95%)	124 (94%)	
Positive	14 (5.7%)	6 (5.2%)	8 (6.1%)	
Unknown	449	235	214	
MSI				0.010
Stable	674 (97%)	333 (95%)	341 (99%)	
High	22 (3.2%)	17 (4.9%)	5 (1.4%)	
MMR Deficiency Based on Internal IHC				0.3
Not Deficient	287 (96%)	146 (95%)	141 (97%)	
Deficient	12 (4.0%)	8 (5.2%)	4 (2.8%)	
Unknown	397	196	201	

[1] n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test

Conclusions

- This is the largest known data set exploring the genomic and immune landscape of BTC with ARID1A, PBRM1 and BAP1 alterations.
- Macrophages were the dominant immune cell TME and may be a target of interest. Co-alteration profile is distinct between ARID1A- vs PBRM1- and/or BAP1-altered BTC.

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Disclosure: Dr. King, as presenter, has no significant conflicts of interest to declare for this presentation
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