Multiplatform molecular profiling of pancreatic adenocarcinomas identifies BRCA1/2 mutations and PD-1/PD-L1 status with therapeutic implications

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Abstract (No. 11108)

Please note, below is a revised version of the abstract

Background: Pancreas adenocarcinoma (PAC) is a challenging disease with overall single digit 5-year survivorship. BRCA1 and BRCA2 germline mutations are associated with increased risk of PC. Recent retrospective studies have described response of BRCA patients to platinum agents and PARP inhibitors. Additionally, immune therapies targeting the programmed cell death pathway in other cancers have shown promise; evaluating the incidence of aberrations of these markers in PAC impact therapeutic decisions.

Methods: 450 PAC's were evaluated at a commercial CLIA laboratory using a combination of sequencing (Sanger or next generation sequencing (NGS)) and protein expression (immunohistochemistry). BRCA1/2 mutations that could be germline or somatic, co-incidence with other mutations identified in the tissue, and expression levels of PD-L1 and PD-1 tumor infiltrating lymphocytes (TIL's) were evaluated.

Results: Mutations (MT) in BRCA1 and BRCA2 were identified in 5 and 17% percent of tissues, respectively. BRCA1 and BRCA2 MT had different rates of concurrence with other gene alterations, which was also different from the general PC population (table). Overexpression of PD-L1 and PD-1 TIL's were also identified in 7% and 37% of PAC cases, respectively. BRCA2 MT cases had a higher incidence of PD-1 TIL's, while BRCA1 MT cases had a higher percent of overexpressed PD-L1 than the overall population.

Biomarker MT	BRCA1 MT	BRCA2 MT	Overall PC Population
	% Coincidence		
APC	14	0	3
BRAF	0	0	1
KRAS	71	77	85
PIK3CA	14	0	3
SMAD4	0	10	16
TP53	43	60	59
PD-1	38	50	37
PD-L1	13	8	7

Conclusions: The different frequencies of KRAS, TP53, PIK3CA and SMAD4 MT between the overall PAC population and BRCA MT populations may inform driver differences and may help select drugs and refine treatment decision making for certain patients. Evaluating the profiles of the BRCA MT populations with clinical outcomes will provide valuable insight into the clinical behavior in genomically defined subsets and may facilitate in developing rational combinations of targeted agents in PAC.

Methods

An additional 106 patients were identified to be included in the analysis since the submission of the abstract

All 556 pancreatic cancer cases underwent molecular profiling at Caris Life Sciences between 2014- 2015. From this original cohort, three subgroups were used for further analysis: BRCA1 + (positive for BRCA1 mutations), BRCA2+ (positive for BRCA2 mutations) and BRCA1/2 (-) (wildtype BRCA1 and BRCA2). The original diagnosis of pancreatic cancer was obtained from the ordering physician and verified by a pathology team at Caris Life Sciences. Testing on formalin-fixed, paraffin-embedded tumor samples (this implies BRCA mutations may be of somatic or germline origin, we did not confirm on blood samples) included a combination of immunohistochemistry (IHC), in situ hybridization (ISH) performed by either fluorescent or chromogenic methods, and Sanger or next-generation sequencing (NGS). All IHC results were read by a board-certified pathologist by measuring the intensity of the stain and percent staining. The KRAS testing included both Sanger and NGS. FISH was interpreted by a molecular cytogeneticist, while CISH was read by a board-certified pathologist. Clinical molecular geneticists provided the NGS interpretation. Statistical analysis was performed using JMP.

Results

Patient & Tumor Characteristics

Mean Age: 63 years

Figure 1. Percent of male and female patients included in this analysis, and mean age.

Specimen Sites Utilized for Tumor Profiling

Liver	33.8%	Lower lobe, lung	0.9%
Pancreas, NOS	28.8%	Diaphragm	0.7%
Head of pancreas	8.3%	Pleura, NOS	0.7%
Omentum	3.2%	Upper lobe, lung	0.7%
Peritoneum, NOS	2.9%	Common bile duct	0.5%
Lung, NOS	2.7%	Ovary	0.5%
Body of pancreas	1.8%	Supraclavicular lymph node	0.5%
Tail of pancreas	1.4%	Abdominal wall, NOS	0.4%
Duodenum	1.3%	Ampulla of Vater	0.4%
Retroperitoneal lymph node	1.1%	Colon, NOS	0.4%
Connective, subcutaneous soft tissues of abdomen	0.9%	Connective, subcutaneous soft tissues of abdominal wall	0.4%

Table 1. Specimen Sites Utilized for Tumor Profiling, liver, was the most common site (33.8%).

BRCA1 +	BRCA2 +	BRCA1/2 (-)
8/199	26/199	165/199
4%	13%	83%

Table 2. Overall incidence of BRCA mutations (+) and BRCA wildtype or (-), in pancreatic adenocarcinomas tested in this analysis. Presence of BRCA2 vs. BRCA1 (p=0.0019).

Results, continued

BRCA1									
Categorization	VUS	P	P	VUS	VUS	VUS	VUS	VUS	VUS
Exon	2	4	5	10	14	14	14	14	14
Protein Change	V1804D	M1775R	Q1756fs	S864L	G275S	T843R	R1028C	E1219D	
BRCA2									
Categorization	VUS	VUS	VUS	VUS	P	P	P	VUS	
Exon	10	10	10	10	10	10	10	11	
Protein Change	D596H	D559N	L629F	C554W	K437fs	Y600X	E510fs	H2074N	
Categorization	VUS	VUS	VUS	VUS	VUS	P	P	VUS	
Exon	11	11	11	11	11	11	11	14	
Protein Change	F1219V	T774A	S1674G	T2250A	S1979R	C711X	S1064fs	P2347Q	
Categorization	VUS	VUS	VUS	VUS	VUS	P	P	P	
Exon	14	17	17	17	19	19	22	23	
Protein Change	K2339N	D2712V	S2670L	A2717S	D2811G	W2788X	Q2960X	T3033fs	
Categorization	VUS	VUS							
Exon	26	27							
Protein Change	P3194Q	V3244I							

Table 3. Characterization of BRCA1 and BRCA2 mutations. All BRCA variants fell into the "variant of unknown significance" (VUS) or "pathogenic" (P) categorization. Exons and protein changes for each variant detected are provided. Pathogenic variants are highlighted in yellow.

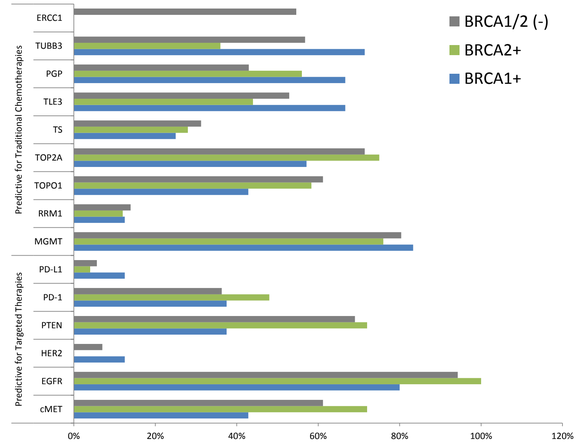

Figure 2. Positive Expression Rates of Predictive IHC Biomarkers across PC patients with wildtype BRCA status or BRCA1/2 (-) (n=165) and compared to BRCA1 + (n=8) and BRCA2+ (n=26). No statistically significant differences exist comparing the subgroups.

BRCA status	HER2	cMET
BRCA1+	0% (0/8)	0% (0/7)
BRCA+	0% (0/26)	4% (1/24)
BRCA1/2 (-)	2% (3/156)	1.3% (2/154)

Table 4. Amplification events in Pancreatic Cancers according to BRCA status

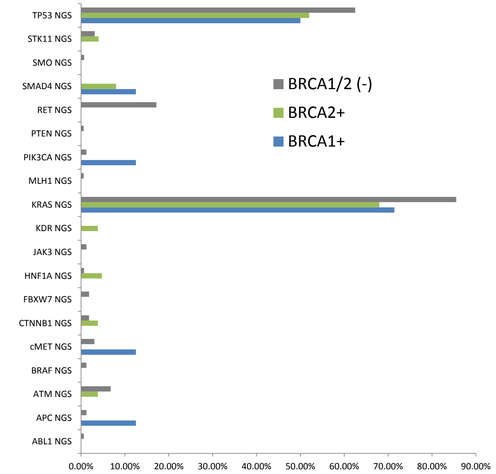

Figure 3. Mutation profiles of BRCA1+ (n=8), BRCA2+ (n=26) and wildtype BRCA status or BRCA1/2 (-) (n=165). No statistically significant differences exist among the subgroups.

Conclusions

- The different frequencies of KRAS, TP53, PIK3CA and SMAD4 MT between the overall PAC population and BRCA MT populations may inform driver differences and may help select drugs and refine treatment decision making for certain patients.
- Evaluating the profiles of the BRCA MT populations with clinical outcomes will provide valuable insight into the clinical behavior in genomically defined subsets and may facilitate in developing rational combinations of targeted agents in PAC.

References

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