Biomarkers of response to immunotherapy in pancreatic ductal adenocarcinoma (PDAC) with homologous recombination deficiency (HRD)

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Background

- PDAC is associated with a paucity of immune effector cells, low antigenicity, and immunosuppressive factors in the tumor microenvironment (TME). Treatment of unselected PDAC patients with immune checkpoint inhibitors (ICIs) has been ineffective
- PDAC typically has very low tumor mutation burden levels. When associated with pathogenic BRCA alterations, the TMB levels are almost three-fold higher than in tumors with wild-type BRCA. Thus, the subset of BRCA-mutant PDAC exhibits a molecular profile associated with response to ICI therapy (1,2)
- Recent data from the TAPUR trial and other retrospective reports show a 14-42% objective response rate to dual PD1/CTLA4 ICI therapy in PDAC patients with pathogenic mutations in HRD genes - Both germline and somatic (3,4)

Methods

Murine Model Generation:

- *BRCA2* was silenced using shRNA in a PDAC cell line from a KPC mouse; Cisplatin resistance was induced in vitro by chronically exposing these KPC-shBrca2 cells to cisplatin
- Whole transcriptomic sequencing (WTS) was performed on these cisplatin-resistant and sensitive tumor cells, along with secretome analysis
- Cisplatin-resistant or sensitive cells were inoculated into the flanks of syngeneic mice which were treated initially with gemcitabine/cisplatin followed by a PD1 and CTLA4 inhibitor combination

Human PDAC Genomic/Transcriptomic Study:

- DNA (592-panel or WES) and RNA (WTS) sequencing was performed on 6396 human PDAC tumor samples submitted to Caris Life Sciences (Phoenix, AZ)
- Samples harboring pathogenic or likely pathogenic (P/LP) *BRCA1*, *BRCA2* or *PALB2* mutations were classified HRD, the remaining samples homologous repair proficient (HRP). Microsatellite instability-high neoplasms excluded
- Immune cell infiltration of the tumor microenvironment (TME) was estimated from WTS measurements using QuanTIseq
- Cohort differences were tested using Mann-Whitney U, Fisher's Exact, or Chi-squared tests with multiple comparisons correction applied as appropriate. Hazard ratios (HR) and associated p-values were calculated using Cox proportional hazard model and log-rank test

Results: Murine model

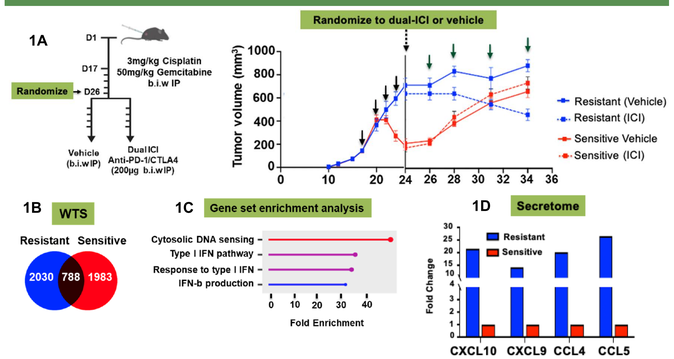

Figure 1: Murine model of HRD-PDAC. Syngeneic mice inoculated with cisplatin-resistant or sensitive KPC-shBrca2 cells were treated with gemcitabine/cisplatin, then randomized to either Vehicle control or Dual ICI (1A). WTS on resistant vs sensitive cells revealed ~2000 differentially expressed genes which enriched for multiple pathways related to type 1 interferon and cytosolic DNA sensing (1B &1C) leading to downstream induction of T-cell attractant chemokines (1D)

KEY TAKEAWAY POINTS

- **PDAC tumors associated with canonical HRD variants (*BRCA1/2*, *PALB2*) have distinct genomic, transcriptomic, and TME features**
- **These characteristics help explain the sensitivity of this subgroup of patients to ICI therapy**
- **Understanding the underlying mechanisms of the immune-permissive characteristics may help inform strategies to broaden the impact of ICI in this population**

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Results: Human PDAC Genomic/Transcriptomic Study

Table 1a: Prevalence of HRD mutants in cohort

Prevalence of HRD mutation		
NGS-BRCA2	172/6396	2.7%
NGS-BRCA1	57/6396	0.9%
NGS-PALB2	38/6396	0.6%

Table 1b: Studied cohort patient demographics

	HRP (N=6130)	HRD (N=266)	p-value
Age			
Median age (range)	68 (23 - 90+)	66 (33 - 90+)	0.0006
Sex			
Male	52.5% (3221/6130)	54.5% (145/266)	0.5295
Female	47.5% (2909/6130)	45.5% (121/266)	
Primary tumor site			
Pancreas, Head	34.5% (2112/6130)	27.1% (72/266)	0.0520
Pancreas, Neck	0.9% (57/6130)	1.1% (3/266)	
Pancreas, Body	12.3% (753/6130)	9.8% (26/266)	
Pancreas, Tail	12.2% (749/6130)	12.8% (34/266)	
Pancreas, NOS	39.9% (2446/6130)	48.9% (130/266)	
Other	0.2% (13/6130)	0.4% (1/266)	

Figure 2: Genomic differences between HRD vs HRP cohort. Compared to the HRP cohort, the HRD cohort had lower prevalence of *TP53*, *CDKN2A*, *RNF43* mutations, and was more frequently PD-L1+, TMB-H, and gLOH-H.

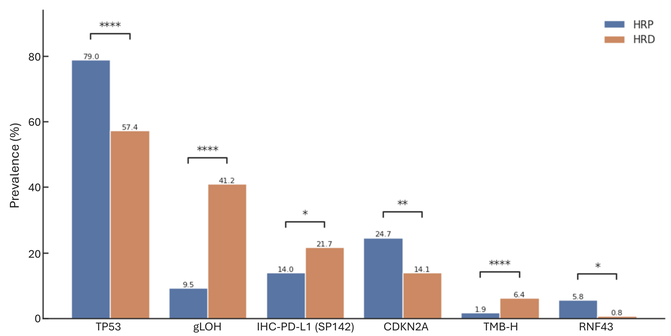


Figure 3: HRD Cohort validation platinum responsiveness, TMB, and genomic scar score (GSS). HRD PDAC cohort had significantly longer OS with platinum therapy (3A). HRD cohort had higher TMB (3B) and GSS values (3C and 3D).

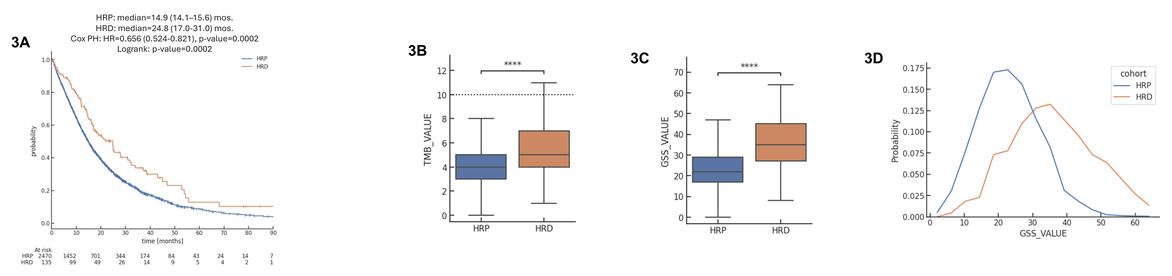


Figure 4 : Immune cell infiltration in the tumor microenvironment. Median infiltration of M1 macrophages was higher in the HRD cohort (6.2% vs 5.3%, p = 0.0028), while that of M2 macrophages was lower (2.9% vs 3.3%, p = 0.0081).

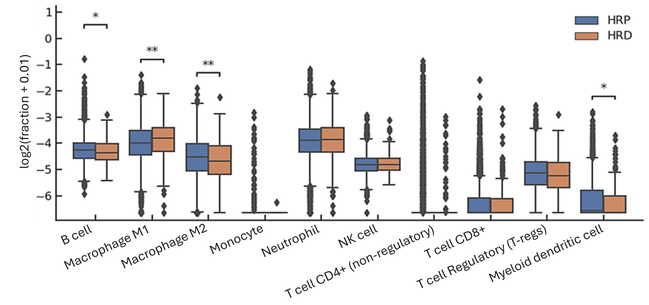
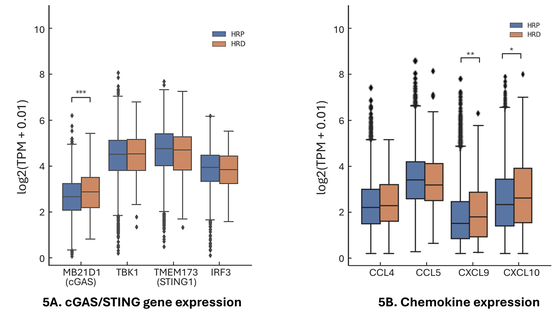


Figure 5: cGAS/STING gene expression and chemokine expression. The HRD cohort demonstrated higher median expression measured in transcripts per million of *CGAS* (5A). The HRD cohort demonstrated higher median expression measured in transcripts per million of *CXCL9*, and *CXCL10*, phenocopying observations in the murine model (5B). This is consistent with other reports of a chemokine signature associated with ICI responsiveness (5).



5A. cGAS/STING gene expression **5B. Chemokine expression**

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