Abstract 784: Multiomic analysis and oncologic outcomes in pancreatic cancer by *PIN1* expression

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Background

- **Proline isomerase (PIN1)** regulates multiple cancer pathways and its expression in pancreatic ductal adenocarcinoma (PDAC) is associated with worse survival.
- PIN1 is overexpressed in both stromal (cancer associated fibroblasts) and cancer cell compartments.
- Genetic or pharmacologic ablation of PIN1 in combination with anti-PD1 immune checkpoint blockade leads to eradication of PDAC in pre-clinical models.
- The relevance of these findings in metastatic PDAC patients is unclear.
- To further understand the implications of targeting PDAC stroma, we characterized PIN1 expression and its impact on the Tumor Immune Microenvironment (TIME) and survival.

Cohort Characteristics

Patient Characteristics	All Observations	stratified by PIN1 expression <2.99	 2.99-3.23	 3.24-3.49	 3.5+	 p-value
Number of Observations	N=2,122	N=531	N=530	N=530	N=531	
Age at Sample Collection (years)						
Median (Q1, Q3)	67 (60, 73)	67 (61, 73)	68 (60, 73)	67 (59, 73)	66 (59, 73)	0.227
Min. - Max.	25 - 88	25 - 86	38 - 88	29 - 86	31 - 85	
Missing Observations	5	0	1	1	3	
Sex, N (%)						
Male	1,168 (55%)	271 (51%)	308 (58%)	303 (57%)	286 (54%)	0.081
Female	954 (45%)	260 (49%)	222 (42%)	227 (43%)	245 (46%)	
Race, N (%)						
White	1,185 (56%)	300 (56%)	302 (57%)	293 (55%)	290 (55%)	0.161
Black or African American	135 (6.4%)	31 (5.8%)	28 (5.3%)	40 (7.5%)	36 (6.8%)	
Asian	40 (1.9%)	7 (1.3%)	14 (2.6%)	15 (2.8%)	4 (0.8%)	
Other Race	108 (5.1%)	25 (4.7%)	33 (6.2%)	28 (5.3%)	22 (4.1%)	
Unknown	654 (31%)	168 (32%)	153 (29%)	154 (29%)	179 (34%)	
Ethnicity, N (%)						
Not Hispanic or Latino	878 (41%)	240 (45%)	213 (40%)	222 (42%)	203 (38%)	0.342
Hispanic or Latino	103 (4.9%)	27 (5.1%)	23 (4.3%)	24 (4.5%)	29 (5.5%)	
Unknown	1,141 (54%)	264 (50%)	294 (55%)	284 (54%)	299 (56%)	
Smoking Status, N (%)						
Never-smoker	865 (41%)	210 (40%)	201 (38%)	213 (40%)	241 (45%)	0.009
Ex-smoker	405 (19%)	92 (17%)	108 (20%)	115 (22%)	90 (17%)	
Current-smoker	269 (13%)	87 (16%)	69 (13%)	66 (12%)	47 (8.9%)	
Unknown	583 (27%)	142 (27%)	152 (29%)	136 (26%)	153 (29%)	
Cancer Characteristics						
Overall Stage at Sample Collection, N (%)						
Stage 1	30 (1.5%)	8 (1.6%)	9 (1.8%)	7 (1.4%)	6 (1.2%)	0.026
Stage 2	65 (3.2%)	9 (1.8%)	19 (3.7%)	25 (4.7%)	12 (2.4%)	
Stage 3	74 (3.7%)	9 (1.8%)	20 (3.9%)	25 (4.7%)	20 (4.0%)	
Stage 4	1,844 (92%)	475 (95%)	460 (91%)	442 (89%)	467 (92%)	
Missing Observations	109	30	22	31	26	
Number of Metastatic Sites, N (%)						
0	91 (4.3%)	16 (3.0%)	21 (4.0%)	27 (5.1%)	27 (5.1%)	0.172
1	1,150 (54%)	309 (58%)	303 (57%)	271 (51%)	267 (50%)	
2	518 (24%)	122 (23%)	123 (23%)	138 (26%)	135 (25%)	
3	363 (17%)	84 (16%)	83 (16%)	94 (18%)	102 (19%)	
Histology, N (%)						
Adenocarcinoma	1,770 (83%)	447 (84%)	447 (84%)	434 (82%)	442 (83%)	0.781
Infiltrating duct carcinoma	255 (12%)	58 (11%)	65 (12%)	69 (13%)	63 (12%)	
Carcinoma	46 (2.2%)	14 (2.6%)	11 (2.1%)	12 (2.3%)	9 (1.7%)	
Mucinous adenocarcinoma	32 (1.5%)	6 (1.1%)	7 (1.3%)	11 (2.1%)	8 (1.5%)	
Adenosquamous carcinoma	18 (0.8%)	6 (1.1%)	5 (0.9%)	4 (0.8%)	3 (0.6%)	
Signet ring cell carcinoma	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	

Conclusions

Contrary to published literature, ***higher PIN1 expression*** *in metastatic pancreatic ductal adenocarcinoma patients was associated with* ***better overall survival*** *and* ***enrichment of both pro- and anti-tumor immune subsets.***

Methods

- **Database:** Tempus LENS de-identified database (n=2122).
- **Inclusion:** Stage 1-4 PDAC sequenced prior to 1L therapy.
- **Assay:** Tempus xT DNA and/or xR whole transcriptome analysis.
- **RNA-seq Analysis:** Corrected RNA-sequencing data were normalized by computing log2(TPM+1) (TPM = transcripts per million).
- **Deconvolution:** Immune cell proportions were estimated using quanTIseq. PD-L1 was assessed by IHC (22C3).
- **Survival:** Adjusted Cox proportional hazards (CoxPH) models tested the associations between PIN1 and real-world overall survival (rwOS).

Results

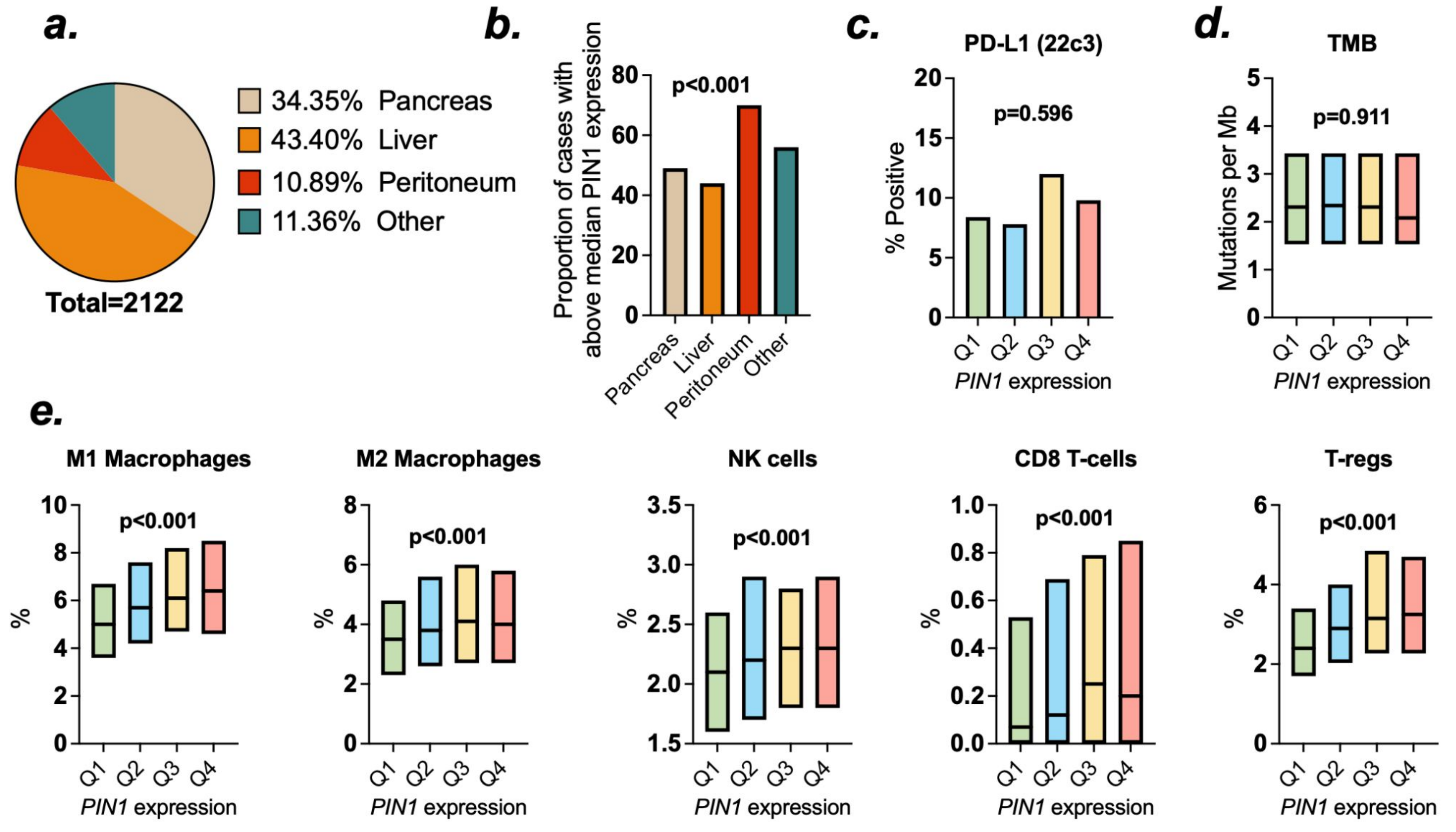
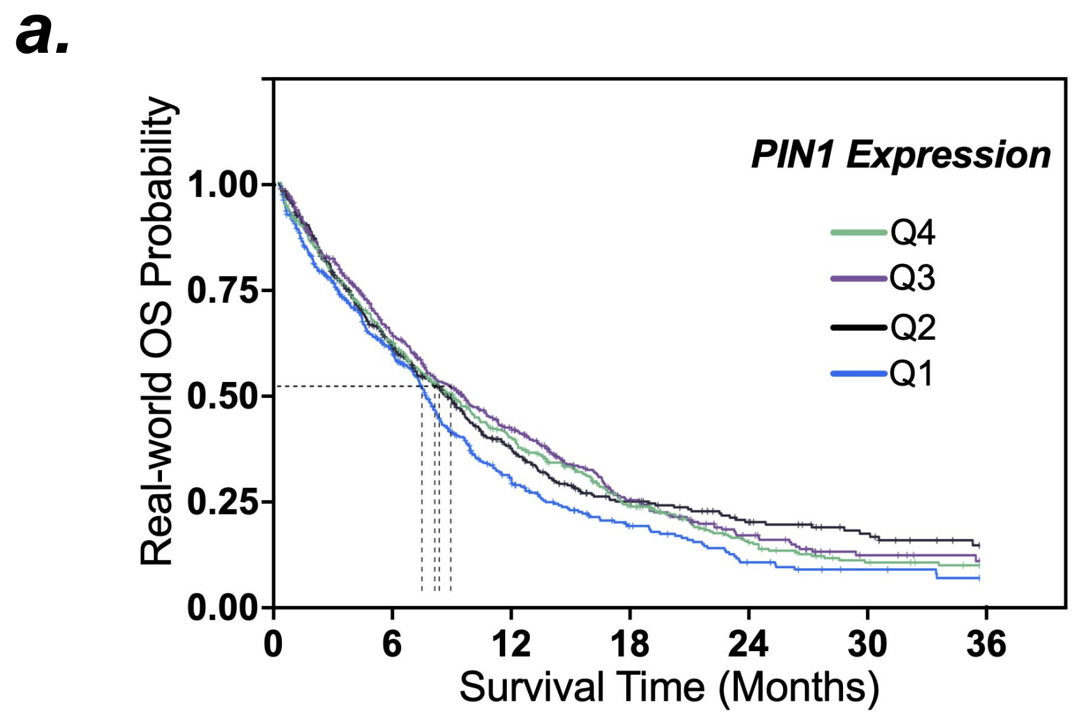


Figure 1:
a. Distribution of biopsy sites.
b. PIN1 expression by metastatic site.
c. PD-L1 positivity rate stratified by PIN1 expression.
d. Tumor mutation burden (TMB) stratified by PIN1 expression.
e. TIME components stratified by PIN1 expression. PIN1 quartiles (Q1= <2.99, Q2=2.99-3.23, Q3=3.24-3.49, Q4=3.5+)



b.

Characteristic	HR[1]	95% CI[1]	p-value
First-Line Therapy			
Folfirinox	—	—	
Gemcitabine + Paclitaxel	1.28	1.14, 1.44	<0.001
PIN1 Expression			
<2.99	—	—	
2.99-3.23	0.79	0.67, 0.94	0.007
3.24-3.49	0.77	0.65, 0.91	0.002
3.50+	0.82	0.70, 0.96	0.015
N events	1,170		

[1] HR = Hazard Ratio, CI = Confidence Interval

Figure 2:
a. *KM Curve showing real-world overall survival by PIN1 expression quartiles.*
b. *Multivariable CoxPH model*

Future Directions for Research

- Ongoing work is validating these results using PIN1 proteomics. These studies will unravel the implications of compartment-specific PIN1 targeting.
- These findings underscore the complexity of PDAC stromal targeting via PIN1.

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