Transcriptomic Signatures of *RAD51* and *GATA6* Predict Improved Real-World Overall Survival with Platinum Therapy in *BRCA/PALB2* Wild-Type Metastatic Pancreatic Cancer

Binbin Zheng-Lin[1], Ellen Jaeger[2], Cody Eslinger[1], Stamatina Fragkogianni[2], Unnati Jariwala[2], Arya Ashok[2], Kayla Layng[2], Taro Shibuki[3,4], Daniel Ahn[1], Oluseyi Abidoye[1], Celine Hoyek[1], Angelo Pirozzi[1], Jeremy Jones[5], Christina Wu[1], Mitesh Borad[1], Mohamad Sonbol[1], John Strickler[6], Takayuki Yoshino[4,7], Masafumi Ikeda[3], Tanios Bekaii-Saab[1]

[1]Department of Hematology and Oncology, Mayo Clinic, Arizona, AZ, USA; [2]Tempus AI Inc, IL, USA; [3]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [4]Department for the Promotion of Drug and Diagnostic Development, Division of Drug and Diagnostic Development Promotion, Translational Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan; [5]Division of Hematology and Medical Oncology, Mayo Clinic Cancer Center, Jacksonville, FL, USA; [6]Department of Medicine, Duke University, Durham, NC, USA; [7]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

INTRODUCTION

- Platinum chemotherapy demonstrated efficacy in metastatic pancreatic cancer (mPC) with homologous recombination repair (HRR) deficiencies, yet its clinical application remains confined to a small subset (≤9%) of patients with mutated *BRCA1/2* or *PALB2* genes.
- Emerging data from HRR-proficient ovarian cancer suggest that reduced RNA expression of wild-type *BRCA1/2* may confer platinum sensitivity, indicating a potential role for transcriptional markers of functional HRD.
- We postulated that *BRCA/PALB2* wild-type mPC may similarly exhibit transcriptional HRD phenotypes. To explore this, we analyzed the association between HRR gene expression levels and real-world overall survival (rwOS) and time to next treatment (TTNT) following first-line (1L) platinum therapy in mPC.

METHODS

Tempus Lens was utilized to identify metastatic PC patients. Lens Workspaces is a computational platform embedded within Tempus Lens that enables quick insight extraction from select cohorts of Tempus data using a rich library of tools.

- Wild-type *BRCA1/2* and *PALB2*
- Tempus xT (DNA-seq) testing
- Tempus xR (RNA-seq) testing

Selection criteria (N = 1,068)

- RNA-seq data were normalized to correct for assay/batch effects, quantified as transcripts per million (TPM) and reported as log2(TPM+1) for *GATA6* and 17 HRR genes (*ATM, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, DNMT3A, ERCC1, FANCA, FANCF, NBN, PALB2, RAD51, RECQL4, WRN*).
- Patients were classified as high and low expressors based on gene expression quartiles for univariate analysis and grouped by whether they received 1L platinum therapy (oxaliplatin, cisplatin, or carboplatin).
- rwOS was calculated from 1L start to death or loss to follow up. TTNT was also estimated from 1L start to initiation of 2L therapy or censoring. Risk set adjustment was applied to mitigate immortal time bias. Median rwOS and median TTNT were estimated using Kaplan-Meier and univariate Cox models.
- A multivariate Cox Proportional (CoxPh) model included platinum therapy use, *RAS* mutation status, and expression of selected genes modeled as continuous variables that significantly correlated with rwOS in univariate Cox models.

SUMMARY

- In patients with wild-type *BRCA1/2* and *PALB2* metastatic PC, transcriptomic profiling identified low *RAD51* and high *GATA6* expression as predictors for improved rwOS when treated with platinum therapy
- Integrating these biomarkers may improve development of DNA-damaging therapies beyond canonically defined HRD

Baseline Characteristics

Table 1. Baseline Characteristics of Patients in the Overall, Platinum-naïve, and Platinum-treated cohorts

	Overall N = 1,068‡	Non-platinum N = 459‡	Platinum N = 609‡
Age at diagnosis	66 (60, 72)	70 (63, 75)	63 (58, 69)
Unknown	4	4	0
Female	470 (44%)	222 (48%)	248 (41%)
Race			
White	601 (56%)	263 (57%)	338 (56%)
Unknown	315 (29%)	138 (30%)	177 (29%)
Black or African American	79 (7.4%)	33 (7.2%)	46 (7.6%)
Other Race	47 (4.4%)	15 (3.3%)	32 (5.3%)
Asian	26 (2.4%)	10 (2.2%)	16 (2.6%)
***KRAS* mutation**	930 (87%)	407 (89%)	523 (86%)
Histology			
Adenocarcinoma	569 (53%)	246 (54%)	323 (53%)
Adenocarcinoma, metastatic	397 (37%)	171 (37%)	226 (37%)
Infiltrating duct carcinoma	56 (5.2%)	21 (4.6%)	35 (5.7%)
Other	25 (2.3%)	9 (2.0%)	16 (2.6%)
Mucinous adenocarcinoma	20 (1.9%)	11 (2.4%)	9 (1.5%)
Poorly differentiated carcinoma	1 (<0.1%)	1 (0.2%)	0 (0%)

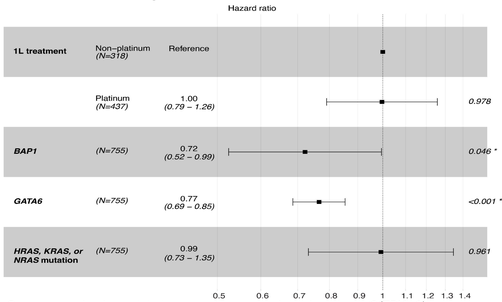
‡ Median (Q1, Q3); n (%)

The total cohort included 1,068 patients with *BRCA/PALB2* wild-type mPC. 609 (57%) received 1L platinum therapy, were younger at diagnosis (63 vs 70 years) and higher proportion were male (59% vs 52%) compared to the platinum-naïve group.

Time-to-Next-Treatment Analysis

- In univariate models with patients treated with first-line platinum therapy, high *GATA6* expression levels correlated with longer TNTT (HR 0.42; p<0.001), whereas high RNA expression of *PALB2* (HR 1.71, *p*=0.011), *BRCA1* (HR 1.51, p=0.048), and *BRIP1* (HR 1.55, p=0.035) were associated with shorter TTNT.
- In multivariate analysis adjusting for selected HRR gene expression levels, *RAS* mutation status, and receipt of platinum therapy, elevated expressions of *GATA6* and *BAP1* emerged as significant predictors of longer TTNT, respective HR were 0.77 (95% CI, 0.69–0.85; *p*<0.001) and 0.72 (95% CI 0.52–0.99; p=0.046), while platinum therapy itself and *RAS* mutation status were not associated with TTNT (*p*>0.9 for both) (Figure 1).

Figure 1. Forest plot with Association Between HRR Gene Expression and TTNT in mPC



Gene expression is modeled as a continuous variable in units log2(TPM+1).

Real-World Overall Survival Analysis

- In univariate analysis, platinum-treated patients with low *RAD51* RNA expression (n=136) experienced significantly longer rwOS compared to platinum-naïve patients (n=112): 11.4 months (95% CI, 7.8–13.8) versus 8.0 months (95% CI, 5.5–9.0), respectively; p=0.028 (Figure 2).
- Conversely, among high *RAD51* expressors, rwOS did not differ meaningfully between platinum-treated (n=150) and platinum-naïve patients (n=97): 7.9 vs. 6.9 months; p=0.236.
- Elevated *GATA6* expression was also associated with improved rwOS in platinum-treated patients relative to platinum-naïve individuals: 13.5 vs. 9.3 months; p=0.011.
- Multivariate modeling (Figure 3) confirmed increasing *GATA6* expression as a positive predictor of rwOS (HR 0.82; 95% CI, 0.76–0.88; p<0.001), while increasing *RAD51* expression remained associated with inferior rwOS (HR 1.18; 95% CI, 1.01–1.39; p=0.043).

Figure 2. Kaplan-Meier Estimate of rwOS in Low *RAD51* Expression Patients Based on 1L Therapy

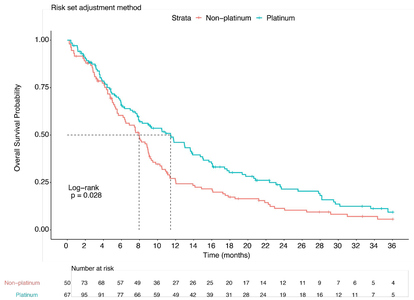
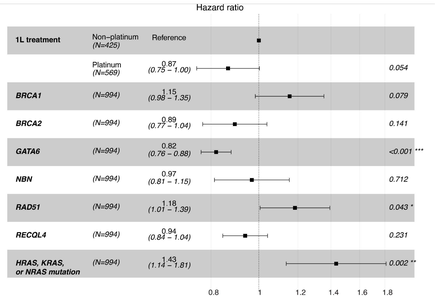


Figure 3. Forest plot of Multivariate Cox Proportional Hazards Model of rwOS in mPC by HRR Gene Expression



Gene expression is modeled as a continuous variable in units log2(TPM+1).

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CORRESPONDENCE

Binbin Zheng-Lin: binbin.zheng@providence.org