279P: Transcriptomic Analysis of Homologous Recombination Repair Genes in *BRCA1/2* and *PALB2* Wild-Type Metastatic Pancreatic Cancer Suggests Potential Platinum Sensitivity

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BACKGROUND

- DNA-damaging agents enhance outcomes in metastatic pancreatic cancer (mPC) with homologous recombination repair (HRR) deficiency (HRD), though their use is limited to less than 6-9% of patients.
- In patients with *BRCA1/2* wild-type ovarian cancer, platinum therapy showed survival benefit in those with low RNA expression of wild-type *BRCA1/2* gene.
- We hypothesized that *BRCA/PALB2* wild-type mPC may exhibit HRD phenotype based on HRR gene expressions.
- We correlated HRR gene mRNA levels with real-world overall survival (rwOS) from first line (1L) platinum therapy in mPC.

METHODS

- From the Tempus database, we retrieved de-identified records of patients diagnosed with mPC who underwent both Tempus xT DNA and xR RNA assays (Figure 1).
- In the *BRCA1/BRCA2/PALB2* wild-type cohort, based on log2(TPM+1) expression for each gene of interest, patients were classified into two groups: high expressors (≥ 75th percentile of RNA expression) and low expressors (≤ 25th percentile of RNA expression).
- Analyzed genes included: *ATM, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, DNMT3A, ERCC1, FANCA, FANCF, NBN, PALB2, RAD51, RECQL4, WRN,* and a non-HRR gene, *GATA6*.
- rwOS was calculated from treatment start to last follow-up or death from any cause. We compared rwOS based on the HRR gene expression levels and the receipt of 1L platinum therapy (defined as any regimen containing cisplatin, carboplatin, or oxaliplatin).
- Risk set adjustment was used to account for immortal time bias.

RESULTS

- The median age at diagnosis was 63 years in the platinum group, compared to 70 years in the platinum-naïve group. Additionally, the platinum group had a lower proportion of females (41% vs 48%).

We observed differences in rwOS based on 1L platinum treatment and the RNA expression for the following genes (Table 1):

CHEK2 (Figure 2):

- In low ***CHEK2*** expressors, the median rwOS was longer in patients treated with 1L platinum therapy than those without, which were 12.7 (95% CI 10.2-13.9) vs 8 months (95% CI 6.3-9.5), respectively.
- In contrast, in high *CHEK2* expressors, median rwOS were similar between the platinum-treated and platinum-naïve groups: 8.8 m (95% CI 7.4-9.6) vs 8 m (95% CI 5.5-9.9), respectively.

BRCA1:

- In low ***BRCA1*** expressors: median rwOS was longer at 13 months (95% 10.5-15.7) if platinum-treated vs 8 months (95% CI 5.5-9.5) if platinum-naïve.
- In high BRCA1 expressors: median rwOS were similar between platinum-treated and platinum-naïve groups which were respectively 8.4 (95% CI 7.2-9.8) vs 6.8 months (95% CI 5.0-9.3).

GATA6:

- In high ***GATA6*** expressors: median rwOS was longer at 13.5 months if treated with platinum (95% CI 11.4-15.8) vs 9.3 months (95% CI 8-11.3) if platinum-naïve.
- Of note, among patients with wild-type *BRCA1, BRCA2,* and *PALB2*, those with a low *BRCA1* expression (n=277) had similar median rwOS compared to patients with a mutated *BRCA1, BRCA2* or *PALB2* (n=70), which were respectively 10.5 and 13.4 months (HR 0.79, 95% 0.6-1.1, p=0.2).

NBN:

- In high ***NBN*** expressors: median rwOS was longer if treated with 1L platinum at 9.6 (95% CI 8.1-11.4) vs 6.1 months (95% CI 4.3-7.6) if platinum-naïve.

Figure 1. Patient Inclusion Flow Diagram

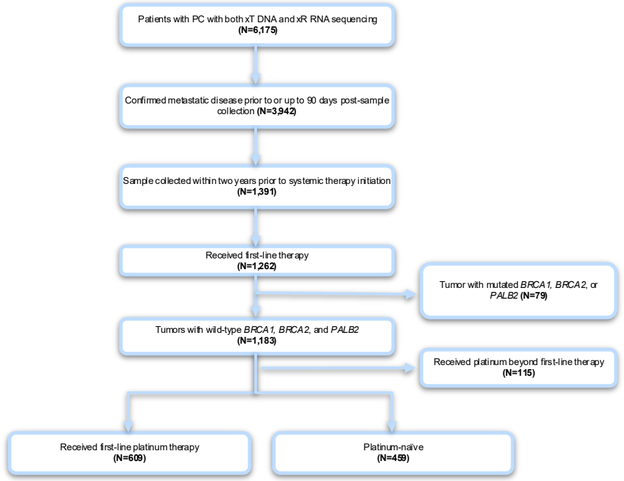

Figure 2. Kaplan-Meier Estimate of rwOS Based on *CHEK2* Expression Levels and Treatment with First-Line Platinum Therapy

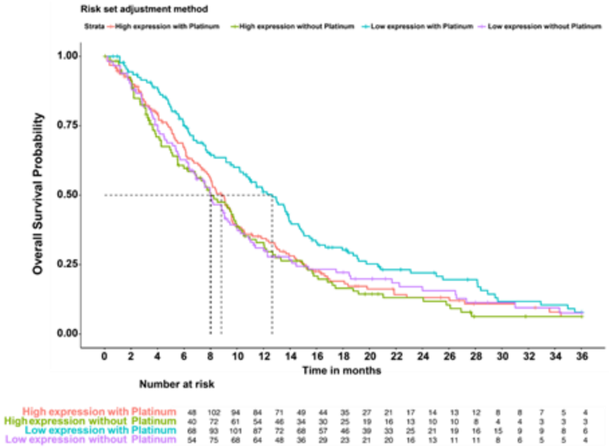

Table 1. Median rwOS of All Analyzed Genes Based Expression Levels and Treatment with First-Line Platinum Therapy

Gene	Expression	1L platinum	Median rwOS	95% CI
BARD1	High	Yes	9.5	8.15 - 10.91
		No	9.6	6.44 - 11.97
	Low	Yes	10.6	9.04 - 12.2
		No	8.1	5.98 - 9.5
BRIP1	High	Yes	8.4	6.9 - 9.76
		No	7.5	5.23 - 10.32
	Low	Yes	11.1	9.53 - 13.64
		No	8.1	5.52 - 9.7
CHEK2	**High**	**Yes**	**8.8**	7.36 - 9.6
		No	**8**	5.52 - 9.89
	Low	**Yes**	**12.7**	10.19 - 13.94
		No	**8**	6.34 - 9.47
FANCA	High	Yes	8.8	7.86 - 10.59
		No	8.7	5.52 - 10.39
	Low	Yes	11.4	8.42 - 13.77
		No	7.5	5.26 - 8.97
ATM	High	Yes	8.9	6.15 - 9.7
		No	8.1	5.69 - 10.32
	Low	Yes	8.8	7.63 - 10.62
		No	8	5.26 - 9.96
BAP1	High	Yes	10.7	8.88 - 13.02
		No	10.5	7.53 - 11.97
	Low	Yes	8.7	7.2 - 9.7
		No	6.9	4.64 - 7.99
BLM	High	Yes	8.1	6.25 - 9.7
		No	7.9	6.08 - 9.99
	Low	Yes	11.9	10.19 - 13.91
		No	8.8	6.34 - 11.34
BRCA1	**High**	**Yes**	8.4	7.23 - 9.76
		No	6.8	5.03 - 9.27
	Low	**Yes**	13	10.49 - 15.68
		No	8	5.52 - 9.47
BRCA2	High	Yes	8.4	6.15 - 9.73
		No	8.7	6.44 - 10.39
	Low	Yes	10.5	8.25 - 12.98
		No	8.2	5.79 - 9.8
DNMT3A	High	Yes	12.2	9.27 - 13.77
		No	10.3	7.3 - 12.23
	Low	Yes	7.9	6.28 - 8.88
		No	6.3	4.31 - 8.05
ERCC1	High	Yes	7.5	5.36 - 8.88
		No	6.2	5.13 - 8.91
	Low	Yes	9.8	8.25 - 13.08
		No	6.7	4.64 - 8.05
FANCF	High	Yes	9.7	7.89 - 12.23
		No	9.3	6.41 - 12.23
	Low	Yes	8.3	6.61 - 10.42
		No	8.2	5.26 - 10.49
GATA6	**High**	**Yes**	13.5	11.44 - 15.75
		No	9.3	7.96 - 11.34
	Low	**Yes**	6.7	5.95 - 7.96
		No	5.7	4.47 - 8.02
NBN	**High**	**Yes**	9.6	8.12 - 11.41
		No	6.1	4.27 - 7.56
	Low	**Yes**	8.3	7.56 - 10.49
		No	10	8.12 - 11.97
PALB2	High	Yes	8.3	7.23 - 9.7
		No	8.8	6.84 - 10.32
	Low	Yes	11.4	8.68 - 13.94
		No	8.7	6.34 - 10.95
RAD51	High	Yes	7.9	6.15 - 9.5
		No	6.9	4.7 - 8.71
	Low	Yes	11.4	7.76 - 13.77
		No	8	5.52 - 9.04
RECQL4	High	Yes	9.1	7.07 - 10.98
		No	8.3	5.49 - 10.45
	Low	Yes	9.6	7.86 - 11.8
		No	6.3	4.64 - 8.81
WRN	High	Yes	9.4	7.23 - 11.8
		No	7.5	5.49 - 9.47
	Low	Yes	8.3	6.71 - 11.08
		No	6.9	4.7 - 8.94

CONCLUSIONS

- Comprehensive transcriptomic analysis suggests that HRR genes beyond *BRCA1/2* or *PALB2* may predict benefit from platinum use in mPC.
- Identifying functional HRR-deficient or proficient phenotypes may better help select for DNA-damaging strategies.
- Multigene interaction models and time-on-treatment analysis are underway.

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Conflict of interest of the presenting author: nothing to declare