Advanced pancreatic adenocarcinoma outcomes in patients with DDR deficiencies outside of *BRCA1/2* and *PALB2*

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Background

Pancreatic adenocarcinomas (PDAC) harboring deficiencies in *BRCA1/2* or *PALB2* are more susceptible to platinum chemotherapy regimens and PARP inhibitors. The same is not fully elucidated for PDAC harboring alterations in other genes within the DNA damage repair (DDR) pathway. In this study, we aim to compare outcomes of patients with advanced PDAC harboring mutations in the DDR pathway in genes other than *BRCA 1/2* and *PALB2* treated with platinum- versus non-platinum chemotherapy regimens in the first line (1L).

Methods

- The Tempus Lens Platform (Tempus AI, Inc., Chicago, IL) was used to analyze a cohort of 3,175 de-identified advanced PDAC patients without *BRCA1/2* or *PALB2* mutations who underwent Tempus xT (solid tumor) or xF (liquid biopsy) testing. Briefly, Lens provides access to Workspaces, a computational platform embedded within the Tempus Lens product that enables users to quickly extract insights from select cohorts of Tempus data using a rich library of tools.
- Patients with clinically reportable copy number losses (0 copies), gains (≥8 copies), or pathogenic/likely pathogenic SNVs/indels in any of 67 other DDR genes were classified as DDR-mutated (DDR-mut, N = 783).
- First-line (1L) treatment regimens were categorized as platinum or non-platinum depending on the inclusion of a platinum compound.
- Real-world objective response rate (rwORR) was defined as the proportion of patients with documented complete or partial response after 1L initiation.
- Real-world time to next treatment (rwTTNT) was defined as time from 1L start to start of next treatment or death; real-world overall survival (rwOS) as time from 1L start to death. Patients were censored at loss to follow-up or 18 months.
- Median rwOS and rwTTNT were estimated using Kaplan-Meier curves and compared using Cox proportional hazards likelihood ratio tests.

Conclusions and Future Directions

- This is one of the largest cohorts comparing outcomes in DDR-mutated PDAC treated with platinum versus non-platinum regimens.
- Patients treated with platinum regimens showed a trend toward improved survival, but this was not statistically significant.
- Patients treated with non-platinum regimens had longer rwTTNT, although this was not statistically significant.
- Results are investigational and do not account for treatment duration or performance status. Larger studies are needed to clarify outcome differences, and no conclusions can be made about specific gene mutations due to small sample sizes.

Results

Table 1. Patient demographics for entire cohort

Characteristic	Overall (N = 3,175)[1]	DDR-mut (N = 783)[1]	DDR-WT (N = 2,392)[1]	p-value[2]
Age at diagnosis				0.5
Median (Q1, Q3)	66 (59, 72)	66 (59, 72)	66 (60, 73)	
Min, Max	29, 89	29, 86	29, 89	
Unknown	11	3	8	
Age at sample collection				>0.9
Median (Q1, Q3)	67 (60, 73)	67 (60, 73)	67 (60, 73)	
Min, Max	30, 89	30, 88	30, 89	
Unknown	9	0	9	
Age at 1L treatment start				0.6
Median (Q1, Q3)	67 (60, 73)	67 (60, 73)	67 (60, 73)	
Min, Max	29, 89	29, 86	29, 89	
Unknown	8	0	8	
Sex				>0.9
Male	1,724 (54%)	426 (54%)	1,298 (54%)	
Female	1,451 (46%)	357 (46%)	1,094 (46%)	
Race				0.4
White	1,783 (56%)	433 (55%)	1,350 (56%)	
Unknown	943 (30%)	249 (32%)	694 (29%)	
Black/African American	305 (10%)	77 (10%)	228 (10%)	
Other Race	144 (4.5%)	24 (3.1%)	120 (5.0%)	
Asian	75 (2.4%)	16 (2.0%)	56 (2.3%)	
Ethnicity				0.6
Not Hispanic or Latino	1,503 (90%)	334 (90%)	1,169 (90%)	
Hispanic or Latino	164 (9.8%)	39 (10%)	125 (9.7%)	
Unknown	1,508	410	1,098	
Smoking status				>0.9
Never smoker	1,294 (51%)	309 (50%)	985 (51%)	
Ex-smoker	935 (37%)	228 (37%)	707 (36%)	
Current smoker	332 (13%)	83 (13%)	250 (13%)	
Unknown	614	164	450	

[1] n (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test

Commonly mutated genes in the DDR-mutant cohort

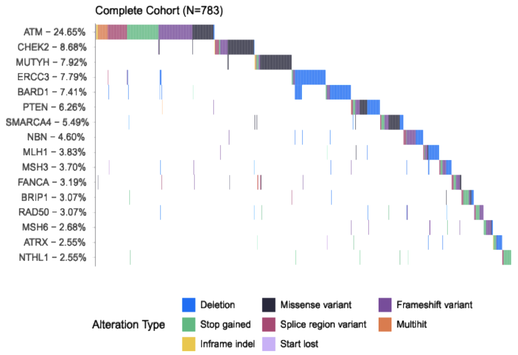

Figure 1: Oncoplot of the top 15 most commonly mutated genes in the DDR-mutant cohort. Mutations in ATM were most prevalent (25%), followed by *CHEK2* (8.7%) and *MUTYH* (7.9%).

Table 2: 1L rwORR in DDR-mut patients treated with platinum vs. non-platinum regimens

Characteristic	Non-Platinum (N = 357)	Platinum (N = 426)	p-value
Objective 1L response			0.6
No response	141 (63%)	154 (60%)	
Response	84 (37%)	101 (40%)	
Unknown	132	171	

[1] n (%)

[2] Pearson's Chi-squared test

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1L rwOS and 1L rwTTNT in DDR-mut patients treated with platinum vs. non-platinum regimens

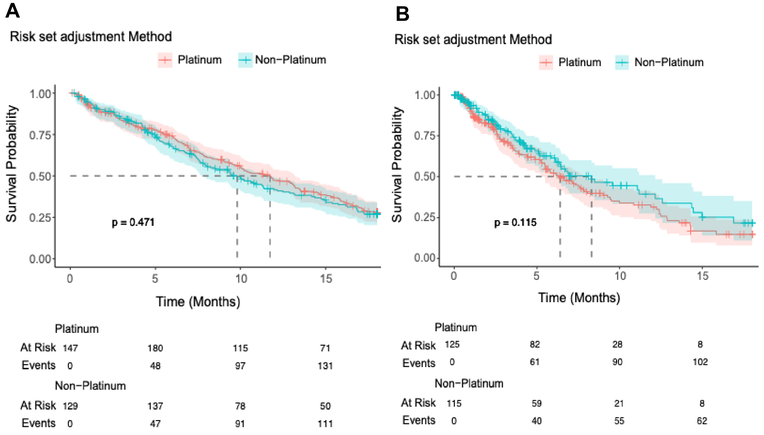

Figure 2: Of DDR-mut pts included in rwOS, 55% (N = 256) received platinum regimens compared to 45% (N = 212) who received non-platinum regimens. Of those receiving platinum regimens, the majority received a triplet regimen rather than a doublet (84% vs 7%). **A)** 1L rwOS for patients in the DDR-mut cohort treated with platinum-vs non-platinum regimens. Although no statistically significant difference was observed in rwOS between platinum and non-platinum regimens in the DDR-mut group, there was a trend toward improved survival starting around 5 months of treatment (median rwOS 11.7 vs 9.8 months, p=0.471). **B)** 1L rwTTNT for patients in the DDR-mut cohort treated with platinum-vs non-platinum regimens. Interestingly, rwTTNT was longer in pts receiving non-Pl (8.3 months vs 6.4, p=0.115).

References:

1. Tempus AI, Inc. Tempus Lens. Tempus AI Website. 2025. Accessed 11/21/2025. https://www.tempus.com/life-sciences/lens/
2. Liu, M. C., MacKay, M., Kase, M., Piwowarczyk, A., Lo, C., Schaeffer, J., Finkle, J. D., Mason, C. E., Beaubier, N., Blackwell, K. L., & Park, B. H. (2022). Longitudinal Shifts of Solid Tumor and Liquid Biopsy Sequencing Concordance in Metastatic Breast Cancer. JCO Precision Oncology, 6(1), e2100321. DOI: 10.1200/PO.21.00321