Validation of the PDACai Signature in Predicting Relative Benefit from Frontline FOLFIRINOX (FFX) and Gemcitabine/nab-Paclitaxel (GA) for Patients (pts) with Metastatic Pancreatic Cancer (mPDAC)

[1]Michael J Pishvaian, [2]Edik Matthew Blais, [2]Dzung Thach, [3]Jonathan R Brody, [4]Lynn M Matrisian, [2]David C Halverson, [2]Patricia DeArbeloa, [3]Flavio G Rocha, [5]Andrew E Hendifar, [6,2]Emanuel F Petricoin III
[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Washington, DC; [2]Perthera AI, Mclean, VA; [3]Oregon Health & Science University, Portland, OR;
[4]Pancreatic Cancer Action Network, Manhattan Beach, CA; [5]Cedars-Sinai Medical Center, Los Angeles, CA; [6]George Mason University, Manassas, VA

Background

- Nearly 50% of pts with mPDAC never receive a 2nd line of therapy for metastatic disease following frontline FFX or GA.
- Genomic alterations in the DDR pathway[2] (e.g. BRCA1/2) are associated with increased progression-free survival (PFS) on platinum-containing regimens (e.g. FFX), but other biomarkers that predict benefit from GA and/or FFX in mPDAC remain unexplored.
- Here, we used a machine learning approach to gain new data-driven insights from the mutational landscape in mPDAC and validate the PDACai signature in predicting relative benefit from FFX and GA.

Methods

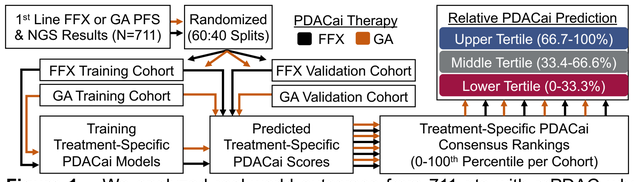

Figure 1 – We analyzed real-world outcomes from 711 pts with mPDAC who underwent clinical genomic profiling via the Know Your Tumor® program or were referred to Perthera by treating oncologists[1]. Chart-abstracted PFS data on either 1st line FFX or GA were split (60:40) into independent training and validation cohorts for each regimen. All models integrate a shared set of 33 clinical and lab-agnostic molecular features derived from clinical NGS testing reports (see **Figure 2** for top variables of importance). PDACai benefit scores predicted by FFX or GA models were evenly binned into three relative prediction groups representing lower, middle, and upper tertiles. Statistical differences in median PFS/OS were evaluated using ordinal Cox regression in each cohort (hypothesis: upper > middle > lower?).

1st Line PFS Stratified by PDACai Predictions

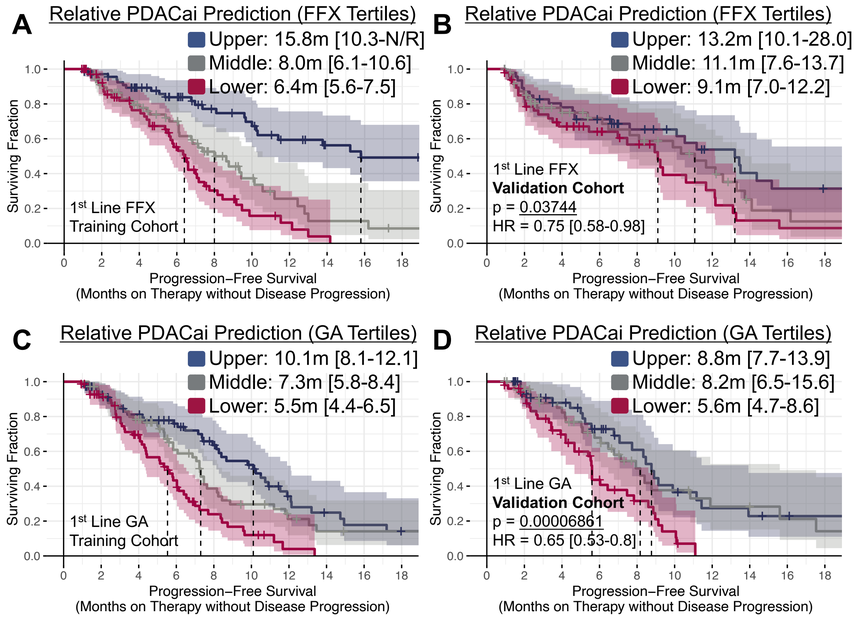

Figure 2 – KM curves of PFS on 1st line therapies from pts allocated to independent training (A,C) and validation (B,D) cohorts. Actual median PFS [plus 95% CI] in months were summarized in pts assigned to lower, middle, or upper thirds based on relative PDACai predictions. The predictive utility of PDACai was confirmed in the independent validation cohorts (B,D) by comparing PFS across tertiles (see p-values and hazard ratios (HR) [plus 95% CI]).

OS Explained by PDACai Predictions

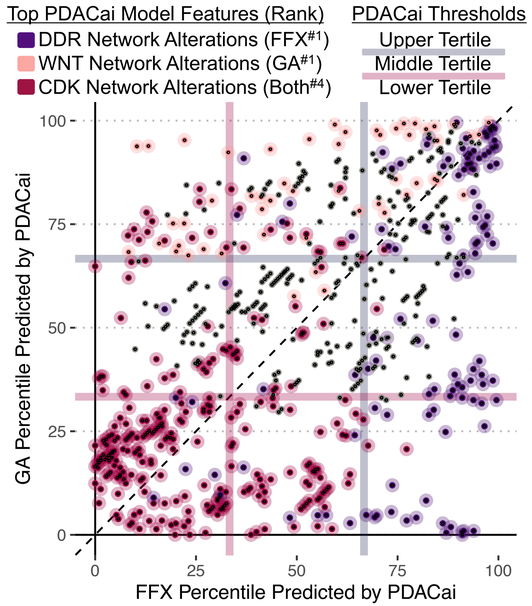

Figure 4 – The landscape of FFX versus GA percentiles across all cohorts highlights how the most important variables for FFX (DDR Network[2]) and GA (WNT Network) are enriched in a treatment-specific manner respectively for pts with higher PDACai values. Top PDACai pathway-level features are highlighted here for patients with genomic alterations in DDR (BRCA1/2, PALB2, CHEK1/2, ATR/ATM, FANC/MRN, etc[2]), WNT (RNF43, APC, GNAS, CTNNB1), or CDK (CDKN2A, CDK4/6, CCND1/2/3, RB1) gene networks.

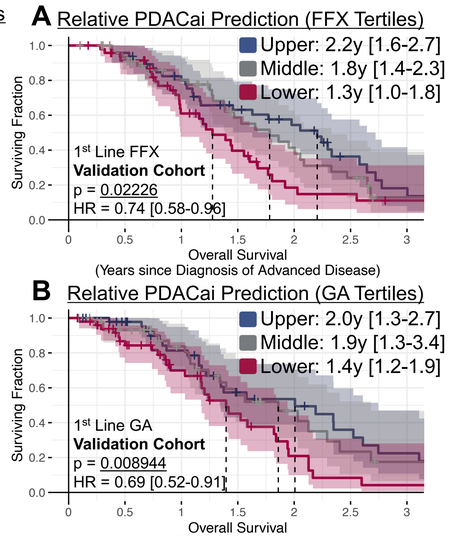

Figure 5 – KM curves of overall survival in years since advanced diagnosis for treatment-specific PDACai predictions within the independent FFX (A) and GA (B) validation cohorts.

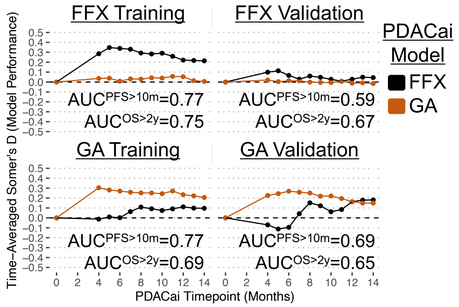

Figure 6 – Time-averaged performance (higher is better) assessed within each cohort comparing PFS against both PDACai model predictions. FFX PDACai was generally more predictive of PFS for FFX outcomes than GA outcomes (and vice versa for GA PDACai).

#ASCO23 Poster #4149

This work was supported by donations to the Pancreatic Cancer Action Network (PanCAN)

Conflicts of Interest

Perthera is a privately-held precision oncology company that facilitates multi-omic testing and captures real-world outcomes to support investigators, sponsors, and health systems[1]

References

1. Pishvaian et al. *The Lancet Oncology*. Mar 2020; PMID: 32135080
2. Pishvaian et al. *JCO Precision Oncology*. Oct 2019 PMID: 35100730

Questions?
eblais@perthera.com

QR CODE

Treatment-Specific PDACai Variables of Importance

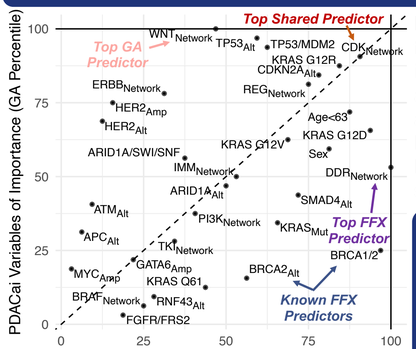

Figure 3 – Relative percentiles of variables of importance calculated from therapy-specific PDACai models which utilized a shared set of inputs including patient sex, age<63 at diagnosis, variant-specific alterations (e.g. KRAS G12D, KRAS G12R, KRAS Q61), gene-level alterations (BRCA2 Alteration), curated pathway clusters (e.g. BRCA1/2), and broader network-level alterations (e.g. DDR Network[2]). This novel approach helps overcome the limitations of sparse NGS data (only a handful of genes are commonly mutated).

Median PFS followed predicted trends generated by PDACai for each therapy option in the training and validation cohorts

Conclusions

- Response to chemotherapy is heterogeneous and difficult to predict in pts with mPDAC.
- Using RWE, PDACai signatures successfully predicted relative differences in PFS for both FFX and GA.
- Further efforts to optimize predictions that distinguish response to 2nd line variations of FFX are underway
- The prognostic/predictive importance of molecular features driving PDACai warrant further exploration.
- This study provides a proof-of-concept framework for the prospective validation of AI/ML models that utilize clinical NGS results to deliver insights for treatment sequencing within standard of care.