Validation of PDACai v2.0 in predicting relative benefit from frontline FOLFIRINOX (FFX) and gemcitabine/nab-paclitaxel (GA) for patients (pts) with metastatic pancreatic cancer (mPDAC)

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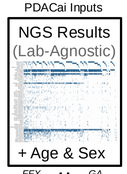
Background

- Nearly 50% of pts with mPDAC never receive a 2nd line therapy for metastatic disease following frontline FFX or GA
- Genomic alterations in the DDR pathway[2] (e.g. BRCA1/2) are associated with longer progression-free survival (PFS) on platinum-containing regimens (e.g. FFX). PDACai uses the full NGS profile to predict benefit from GA and/or FFX in mPDAC.
- PDACai v2.0 redefines the mutational landscape in mPDAC by removing ATM mutations from the DDR pathway (top FFX feature) and adding new variant-level features (e.g. TP53 GOF).

PDACai Methods & Examples



Predicted Response Group	Percentile
FOLFIRINOX: **Upper**	80%
Gem/nab-P: **Middle**	40%

Your PDACai Guidance (Top Alternative)
1st Line FOLFIRINOX (FOLFOX or Gem/Cis)
2nd Line Gem/nab-P (+/- New Trial Agent)
3rd Line Clinical Trial (see Perthera Report)

Predicted Response Group	Percentile
FOLFIRINOX: **Middle**	50%
Gem/nab-P: **Lower**	20%

Your PDACai Guidance (Top Alternative)
1st Line FOLFIRINOX (FOLFIRI or FOLFOX)
2nd Line Clinical Trial (see Perthera Report)
3rd Line Gemcitabine (+/- nab-Paclitaxel)

Predicted Response Group	Percentile
FOLFIRINOX: **Lower**	30%
Gem/nab-P: **Upper**	70%

Your PDACai Guidance (Top Alternative)
1st Line Gem/nab-P (+/- New Trial Agent)
2nd Line FOLFIRI (FOLFOX or FOLFIRINOX)
3rd Line Clinical Trial (see Perthera Report)

PDACai Output Normalized to Population (For Physicians Receiving a Perthera Report)

PDACai Response Groups
- Upper Tertile (67-100%)
- Middle Tertile (33-67%)
- Lower Tertile (0-33%)

NOTE: A Perthera Report's ranked therapy options may differ from these examples based on a patient's
- multi-omic actionability for certain therapies,
- eligibility for nearby/accessible clinical trials,
- previous clinical/treatment history

PDACai predictions were analyzed retrospectively for pts who received a Perthera Report. Outcomes were captured via the Perthera Registry. US pts whose physicians order a Perthera Report may be eligible to participate in prospective efforts to validate PDACai (frontline/adjuvant, non-interventional).

Figure 1 – PDACai learned to predict outcomes based on NGS testing results from Training Cohorts where pts received either FFX & GA in the 1st line setting. PDACai predictions were independently analyzed for FFX & GA Validation Cohorts.

1st Line PFS Stratified by Normalized PDACai Predictions

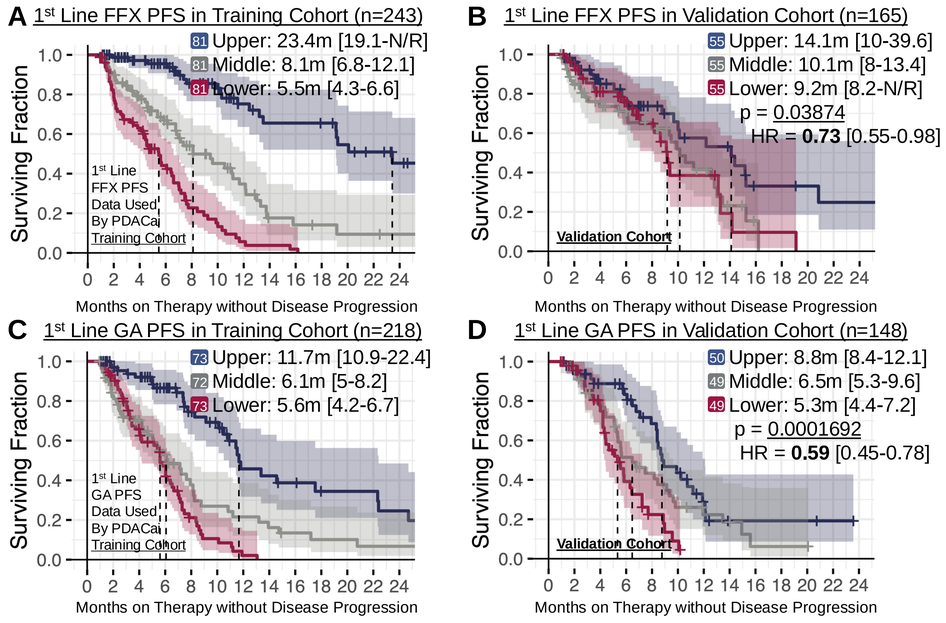


Figure 2 – KM curves of PFS on 1st line therapies from pts allocated to independent training (A,C) and validation (B,D) cohorts. Actual median PFS [plus 95% CI] in months were summarized in pts assigned to lower, middle, or upper thirds based on PDACai response group predictions (see **Fig 1**). The 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]).

Advanced OS Correlates with PDACai Predictions

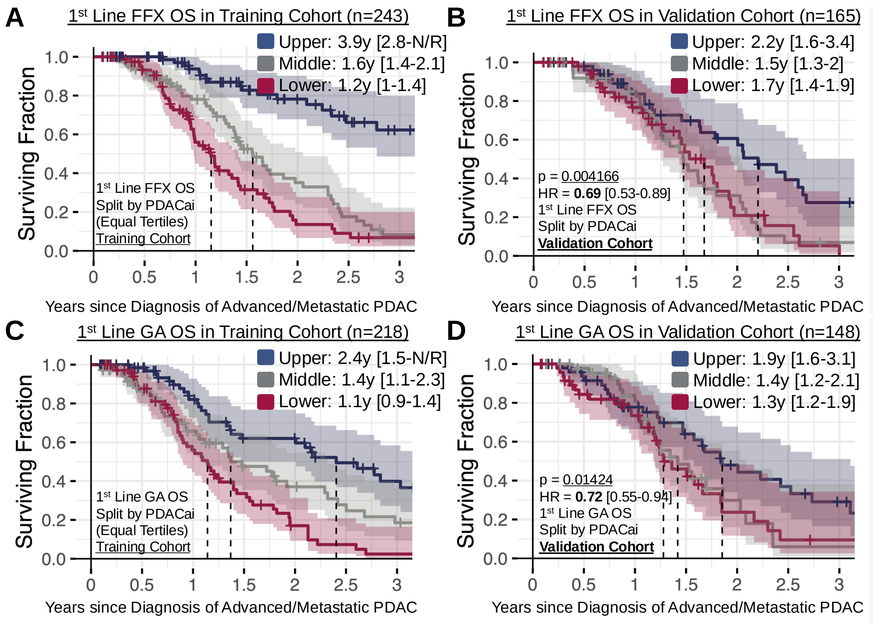


Figure 3 – KM curves of overall survival advanced diagnosis for treatment-specific PDACai predictions within the training (A,C) and validation (B,D) cohorts who received 1st line FFX (A,B) or GA (C,D).

Conclusions

- Response to chemotherapy is heterogeneous and difficult to predict in pts with mPDAC
- PDACai v2.0 successfully predicted differences in PFS for both FFX and GA cohorts (better than v1.0)
- Guidance for 1st line decisions is now feasible with upfront NGS and PDACai v2.0 (faster than v1.0)
- Efforts to validate PDACai predictions for 2nd line variations of FFX (FOLFIRI vs FOLFOX) are ongoing
- Continuous prospective validation of AI/ML models that utilize lab-agnostic NGS results is warranted

PDACai predictions correlated with OS/PFS outcomes for FFX & GA cohorts. PDACai inputs routine NGS results and assigns Upper vs Middle vs Lower "Predicted Response Groups" from normalized FFX & GA scores (0-100%).

Recent Studies Explored Top NGS Features
WNT Pathway Alterations (RNF43/GNAS/APC/CTNNB1)[3]
- Prognostic Associations Observed for FFX & GA Cohorts

TP53 WT vs GOF vs LOF[4] *& More* (KRAS Variants[5], BRCA/DDR[6])
- FFX Cohort: Longer OS for TP53 WT vs GOF/LOF
- GA Cohort: Shorter OS/PFS for TP53 LOF vs GOF/WT

#GI25 Poster #776

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Conflicts of Interest
Perthera is a privately-held precision oncology company delivering multi-omic insights and real-world outcomes to support investigators, sponsors, and health systems[1]

References
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Treatment-Specific PDACai Variables of Importance

Figure 4 – Normalized percentiles for variables of importance calculated from therapy-specific PDACai models which utilized a shared set of inputs including patient sex, age, gene- and variant-specific alterations (e.g. KRAS Mutation, KRAS G12D, KRAS G12R, KRAS Q61), 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 where only a handful of genes are commonly mutated.