Precision Medicine for Pancreatic Cancer Patients: Preliminary Results from the Know Your Tumor Program

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Abstract

Background: To democratize the implementation of precision medicine (PM) in the care of pancreatic cancer patients, the Know Your Tumor (KYT) program was initiated US-wide using a turn-key PM operating system that produces a treatment decision support tool/report.

Methods: Tumor samples were obtained for 932 patients from 287 high-volume academic and local community practices covering 44 states. Our system provides a standardized workflow within an IRB-approved registry protocol from patient intake through multi-omic molecular profiling, integration of treatment history followed by computational analysis to produce a treatment decision support tool of patient-tailored therapeutic options. Longitudinal outcome is collected on every patient along with treatment decisions, and patient experience.

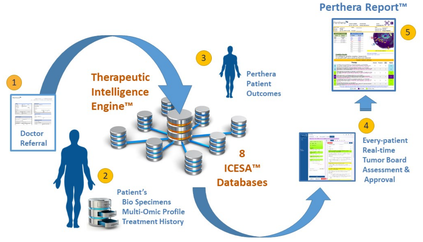
Results: Tumor samples were adequate for next-generation sequencing in 96% and immunohistochemistry in 91% of patients. KRAS mutations were identified in 92% of pancreatic ductal adenocarcinomas. A tumor board reviewed the results for every patient and found actionable genomic alterations in 48% of patients (with 27% highly actionable) and actionable proteomic alterations (excluding chemopredictive markers) in 5%. Highly actionable alterations are defined as those where literature supports clinical evidence of a high response rate in patients with that molecular abnormality in any cancer type. Actionable alterations commonly found were in DNA repair genes (BRCA1/2 or ATM mutations, 8.4%) and cell cycle genes (CCND1/2/3 or CDK4/6 alterations, 8.1%). A subset of samples was assessed for actionable phosphoprotein markers. To date, 126 (19.7%) patients have utilized a molecularly matched therapy. Patients with highly actionable biomarkers who received matched therapy (n = 20) had a median progression-free survival (PFS) of 5.5 months, significantly longer than patients with highly actionable biomarkers who received unmatched therapy (n = 23; PFS = 1.9 months; adjusted P-value = 0.05).

Conclusions: A comprehensive PM system can be implemented in community and academic settings, with highly actionable findings observed in ~25% of pancreatic cancers. Patients whose tumors have highly actionable molecular alterations and who receive matched therapy demonstrated significantly increased PFS. Our findings support expansion and further prospective evaluation of precision oncology in pancreatic cancer.

Background

- Response rates to the current approved therapies for pancreatic cancer are low, with 5-year survival rates among the lowest of all cancers.
- Genomic and proteomic profiling are used to select therapies in other cancer types such as lung, ovarian, and breast, but has had limited success in pancreatic cancer.
- To expand the application of molecular profiling in pancreatic cancer, Perthera, Inc. and the Pancreatic Cancer Action Network have implemented a program designed to provide access to profiling for patients while building an outcomes database to enable detection of molecular correlates of treatment response (1).

Methodologic Details



Perthera Workflow: After referral and consent, Perthera collects patient medical and treatment history, facilitates the process of tumor biopsy, coordinates the multi-omic molecular testing, and reviews the results with the disease-specific medical review panel. A report is then delivered to the treating oncologist and patient, and patients are followed longitudinally for outcomes. Here, labs used were Foundation Medicine for next-gen sequencing and Caris Life Sciences or NeoGenomics for immunohistochemistry of a panel of proteins.

	Total (n=932)	Disease Status	
		Metastatic (n=642)	Localized/ Loc. Adv. (n=290)
Gender			
Male	480 (52%)	339 (53%)	141 (49%)
Female	452 (48%)	303 (47%)	149 (51%)
Age			
< 50	93 (10%)	59 (9%)	34 (12%)
50-59	236 (25%)	168 (26%)	68 (23%)
60-69	390 (42%)	265 (41%)	125 (43%)
≥ 70	213 (23%)	150 (23%)	63 (22%)
Tumor Biopsy Site			
Liver	348 (37%)	348 (54%)	0 (0%)
Pancreas	348 (37%)	78 (12%)	270 (93%)
Lung	55 (6%)	55 (9%)	0 (0%)
Peritoneum	70 (8%)	70 (11%)	0 (0%)
Other	111 (12%)	91 (14%)	20 (7%)
Treatment Setting (n=813)			
High Volume	551 (68%)	396 (69%)	155 (64%)
Community Practice	262 (32%)	174 (31%)	88 (36%)

Table 1: Patient characteristics. In 932 patients receiving reports, demographic characteristics (gender, age) had similar distributions in metastatic and localized/locally advanced cases. The majority of biopsies for metastatic cases were from the liver. Approximately one-third of cases were referred by doctors practicing in the community setting.

Patient Characteristics

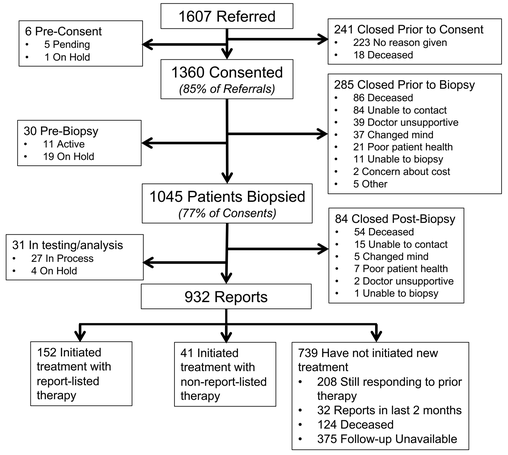


Figure 2: Patient referrals, consents, and reports generated. As of May 23, 2018, 1,607 referrals have led to 932 completed reports with therapy options matched based on genomic and proteomic profiling. 152 patients have gone on to receive a report-listed therapy, while 41 patients have received therapies not listed on the report. Data will likely become available in the future for many patients who have not yet initiated a new therapy.

Actionability

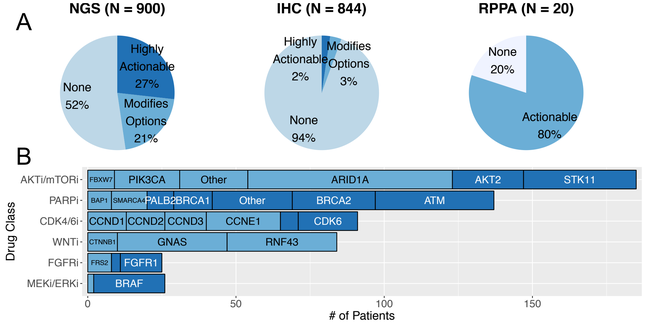


Figure 3: Actionable recommendations by assay type and drug class. (A) Approximately half of patients had actionable findings by NGS, while 5% had protein markers suggestive of benefit from molecular targeted therapy (note that nearly all patients had chemopredictive IHC markers). (B) Number of patients with actionable alterations in specific genes. Dark blue indicates highly actionable alterations.

Outcomes

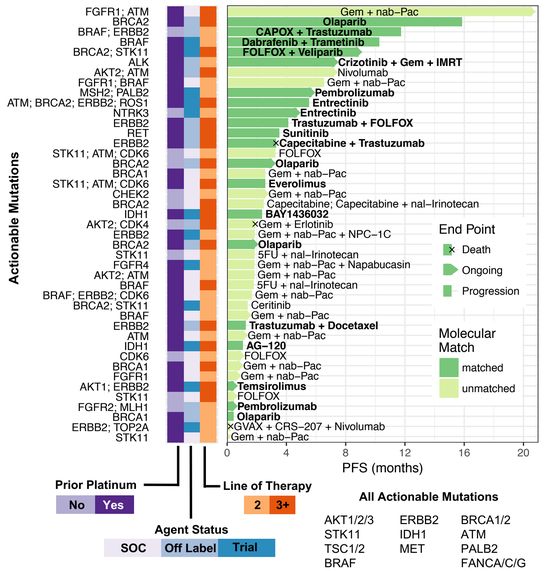


Figure 4: Progression-free survival in patients with highly actionable alterations. Bars correspond to PFS on matched therapies (dark green) and unmatched therapies (light green) for all patients with highly actionable alterations who received therapy post-report. The most frequent matched therapies were PARP inhibitors (olaparib and veliparib) and HER2 inhibitors (trastuzumab). Immunotherapies (nivolumab and pembrolizumab) were given in both matched (one patient with an MLH1 mutation and one with an MSH2 mutation) and unmatched scenarios. ALK, ROS1, and NTRK1/2/3 fusions, while rare overall, were targeted with crizotinib or entrectinib in three patients.

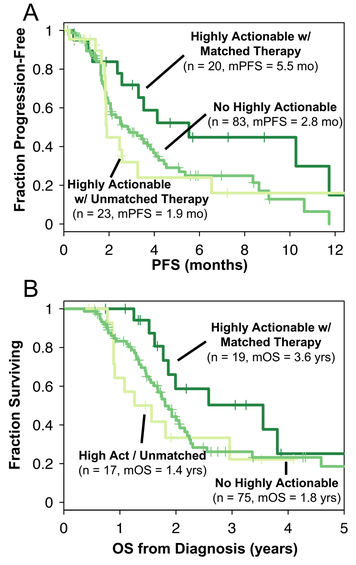


Figure 5: Survival in patients based on actionability and matched therapy. PFS **(A)** and OS **(B)** in patients with highly actionable genomic alterations on matched therapy, on unmatched therapy, and those with no highly actionable alterations.

	n	HR	95% CI	P-value
Actionability				
No H.A. alterations	83	1.0		
≥1 H.A. alteration	43	0.68	0.49 – 0.94	**0.02**
Matched therapy				
H.A., unmatched therapy	23	1.0		
H.A., matched therapy	20	0.55	0.30 – 1.0	**0.05**

Table 2: Statistical comparison. PFS for the Kaplan-Meier curves in Figure 5A was compared using inverse propensity score-weighted Cox proportional hazards models. OS differences were found to be not statistically significant (data not shown). H.A. = highly actionable.

Conclusions

- Implementation of multi-omic profiling for pancreatic cancer has been successful independent of type of practice (academic vs. community).
- Moderately and highly actionable findings have been reported in approximately half of all cases, demonstrating that molecular targets are frequently present in tumors of the pancreas.
- Preliminary outcomes analysis indicates that patients with highly actionable alterations who receive matched therapy have significantly longer PFS than patients who do not receive matched therapy, although this effect has not yet been observed for OS.

Citations/Acknowledgments

(1) Pishvaian et al. 2018 Under review

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