Abstract 4155

Comparative Analysis of the Targetable Landscape in KRAS-Mutant and Wild-Type Pancreatic Adenocarcinoma

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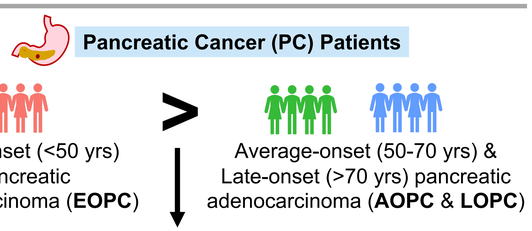
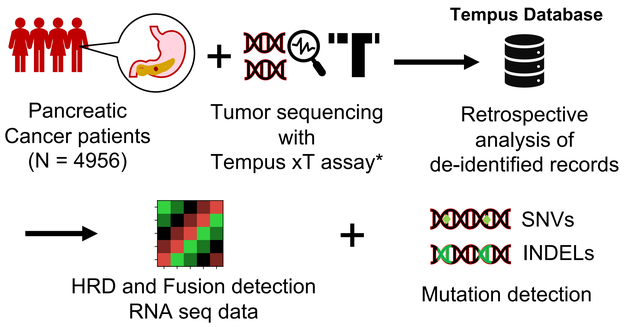
INTRODUCTION



- We investigated the prevalence of fusions, mutations, and homologous recombination deficiency (HRD) in *KRAS*^{WT} vs *KRAS*^{mut} PC to identify potential therapeutic targets
- We compare EOPC to non-EOPC to better characterize molecular differences in targetable alterations.

METHODS



*Tempus xT solid tumor assay - DNA-seq of 595-648 genes at 500x coverage; whole-exome capture RNA-seq

Cohort Overview

Characteristic	Overall, N=4956	EOPC, N=382	AOPC, N=2703	LOPC, N=1871
Gender, n (%)				
Male	2630 (53%)	225 (59%)	1425 (53%)	980 (52%)
Female	2317 (47%)	157 (41%)	1272 (47%)	888 (48%)
Unknown	9	0	6	3
Race, n (%)				
White	2398 (83%)	166 (76%)	1305 (83%)	927 (85%)
Black/African-American	280 (9.7%)	27 (12%)	162 (10%)	91 (8.3%)
Asian	96 (3.3%)	12 (5.5%)	50 (3.2%)	34 (3.1%)
Unknown	2074	164	1133	777
Age, Median (IQR)				
Years	67 (59, 73)	46 (42, 48)	63 (58, 66)	75 (73, 79)
***Stage, n (%)**				
Stage 1/2/3	865 (22%)	47 (15%)	481 (22%)	337 (23%)
Stage 4	3087 (78%)	276 (85%)	1711 (78%)	1100 (77%)
Unknown	1004	59	511	434
***KRAS Status, n (%)**				
KRAS^{WT}	1042 (21%)	116 (30%)	603 (22%)	323 (17%)

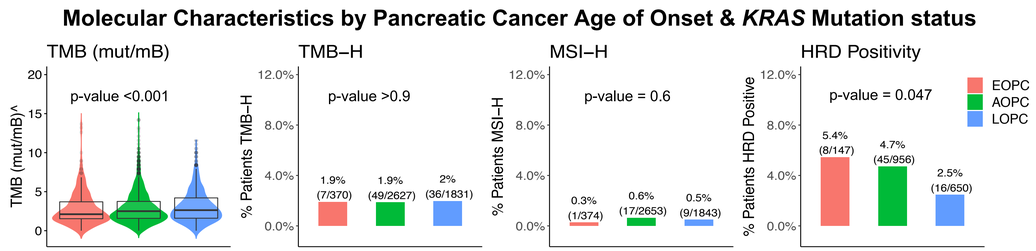
*Indicates significance by onset following Pearson's Chi-squared test, Fisher's exact test, or Wilcoxon rank-sum test; Age reflects data at diagnosis; Stage reflects data available closest to biopsy collection. Percentages were calculated from total known. IQR – Interquartile Range

Table 1. EOPC significantly differed from non-EOPC by stage and *KRAS* status (p<0.05).

SUMMARY

- **Oncogenic rearrangements, HRD, and TMB-H/MSI-H are more prevalent in *KRAS*^{WT} Pancreatic Cancer as compared to *KRAS*^{mut}.**
- EOPCs are more likely to be KRAS^{WT}, exhibit HRD phenotype and are more likely to have germline alterations in BRCA1/2
- These molecular analyses may provide additional therapeutic options for PC patients, warranting increased comprehensive genomic and transcriptomic profiling for this population.

RESULTS



TMB (mut/mB)=Tumor Mutational Burden (mutations/megabase), TMB-H=TMB High (>=10 mut/mB), MSI-H=microsatellite instability high, HRD Positivity=Homologous Recombination Deficiency Positivity, ^ indicates TMB truncated at 15 mut/mB, significance determined following Pearson's Chi-squared, Fisher's Exact, Wilcoxon rank sum, or Kruskal-Wallis rank sum tests.

Figure 1. Across onset groups, median TMB (mut/mB) increased with increasing age at onset (median 2.31 vs. 2.50 vs. 2.63) while the prevalence of HRD positivity decreased. Amongst onset groups combined, median TMB was higher in *KRAS*^{mut} vs. *KRAS*^{WT} (median 2.63 vs. 2.08); however, the prevalence of TMB-H was lower in *KRAS*^{Mut}. *KRAS*^{Mut} also demonstrated lower prevalence of MSI-H and HRD positivity compared to *KRAS*^{WT}

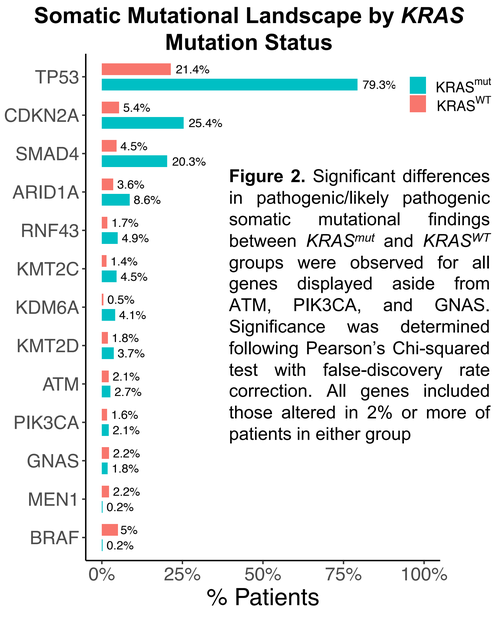
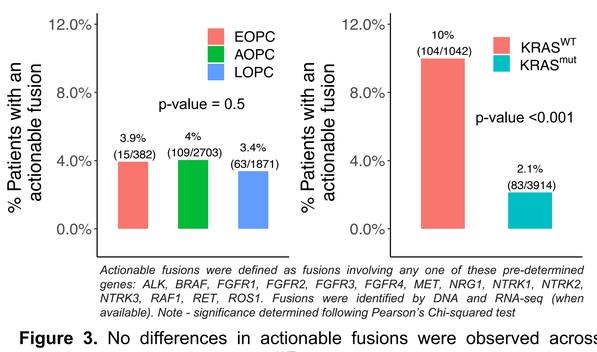


Figure 2. Significant differences in pathogenic/likely pathogenic somatic mutational findings between *KRAS*^{mut} and *KRAS*^{WT} groups were observed for all genes displayed aside from ATM, PIK3CA, and GNAS. Significance was determined following Pearson's Chi-squared test with false-discovery rate correction. All genes included those altered in 2% or more of patients in either group



Actionable fusions were defined as fusions involving any one of these pre-determined genes: ALK, BRAF, FGFR1, FGFR2, FGFR3, FGFR4, MET, NRG1, NTRK1, NTRK2, NTRK3, RAF1, RET, ROS1. Fusions were identified by DNA and RNA-seq (when available). Note - significance determined following Pearson's Chi-squared test

Figure 3. No differences in actionable fusions were observed across onset groups; however, *KRAS*^{WT} patients demonstrated significantly more actionable fusions detected than *KRAS*^{mut} patients (10% vs. 2%)

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Germline Mutational Landscape by PC Onset

Characteristic	EOPC N = 245[1]	AOPC N = 1,757[1]	LOPC N = 1,195[1]
BRCA2	11 (4.5%)	29 (1.7%)	10 (0.8%)
BRCA1	5 (2.0%)	7 (0.4%)	5 (0.4%)
MUTYH	4 (1.6%)	27 (1.5%)	24 (2.0%)
ATM	4 (1.6%)	24 (1.4%)	18 (1.5%)
PALB2	3 (1.2%)	6 (0.3%)	3 (0.3%)

[1] n (%)

Table 2. Amongst a subset of the cohort whose samples underwent tumor/normal (T/N) matched sequencing (N=3197), differences across groups were observed in incidental germline findings. Notably, prevalence of BRCA1 and BRCA2 alterations decreased with increasing age at onset. Note: no formal comparisons were made due to small numbers.

Prevalence of Actionable Fusion Genes

	Overall N = 4956[1]	*KRAS*^{WT} N = 1042[1]	*KRAS*^{mut} N = 3914[1]
NRG1	91 (1.8%)	31 (3%)	60 (1.5%)
BRAF	21 (0.4%)	21 (2%)	0 (0%)
FGFR2	12 (0.2%)	10 (1%)	2(<0.1%)
NTRK3	10 (0.2%)	6 (0.6%)	4 (0.1%)
RAF1	7 (0.1%)	4 (0.4%)	3 (<0.1%)
FGFR1	6 (0.1%)	4 (0.4%)	2 (<0.1%)
RET	6 (0.1%)	6 (0.6%)	0 (0%)
NTRK1	5 (0.1%)	5 (0.5%)	0 (0%)
FGFR3	3 (<0.1%)	1 (<0.1%)	2 (<0.1%)
MET	2 (<0.1%)	2 (0.2%)	0 (0%)
NTRK2	2 (<0.1%)	0 (0%)	2 (<0.1%)
ALK	1 (<0.1%)	0 (0%)	1 (<0.1%)
FGFR4	1 (<0.1%)	0 (0%)	1 (<0.1%)

[1] *n (%)*

Table 3. Across all onset groups and KRAS status, the most prevalent actionable fusion genes detected were NRG1 (N=91) and BRAF (N=21) (irrespective of gene partners).

Prevalence of Most Common Actionable Fusion Gene Pairs

	Overall N = 4,956[1]	*KRAS*^{WT} N = 1042[1]	*KRAS*^{mut} N = 3914[1]
LDAH-NRG1	81 (1.6%)	26 (2.5%)	55 (1.4%)
SND1-BRAF	6 (0.1%)	6 (0.6%)	0 (0%)
BRAF-CCNY	3 (<0.1%)	3 (0.3%)	0 (0%)
ETV6-NTRK3	3 (<0.1%)	3 (0.3%)	0 (0%)
NTRK3-EML4	3 (<0.1%)	2 (0.2%)	1 (<0.1%)

[1] *n (%), Table is restricted to gene pairs with at least 3 patients*

Table 4. Across all onset groups and KRAS status, the most prevalent gene pairs comprising at least one of the actionable fusion genes were LDAH-NRG1 (N=81) and SND1-BRAF (N=6).