Comprehensive analysis of KRAS variants in patients (pts) with pancreatic cancer
Clinical/molecular correlations and real-world outcomes across standard therapies

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Background

Molecular profiling in pancreatic adenocarcinoma (PDAC) has gained traction and we recently demonstrated that targeting actionable alterations can improve patient (pt) outcomes[1,2] using the Perthera Platform's real-world evidence database[4]. Unfortunately, most (~75%) PDAC genomic profiles do not have any actionable targets[1] due to a KRAS mutation frequency of 80-90%. The spectrum of KRAS isoforms vary considerably between tumor types, but the predictive and prognostic implications for specific KRAS variants in PDAC are largely unknown. Further subtyping of PDAC, particularly those with KRAS mutations and without actionable findings, may provide novel insights into optimal treatment sequencing for individual patients. Here, we categorized PDAC tumors by specific KRAS variants and performed exploratory analyses to understand their implications for prognosis or response to standard frontline therapies (Tx) in PDAC.

Acknowledgements

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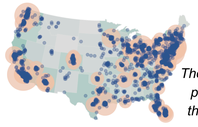
Conflicts of Interest
Perthera is a privately-held precision oncology company that captures molecular testing data and real-world outcomes

References

1. Pishvaian, et al, *Lancet Oncology*, 2020; PMID: 32135080
2. Pishvaian, et al, *JCO Precision Oncology*, 2019
3. AACR GENIE, *Cancer Discovery*, 2017
4. Madhavan et al., JAMIA Open, 2019; PMID: 32025647

Pancreatic Cancer Cohort



The Perthera Registry's Real-World Outcomes & Multi-Omic Database
Thousands enrolled via partnering physicians/institutions including the Know Your Tumor® program

Patients with Advanced PDAC & NGS Testing Results (n = 1060)

Molecularly-Defined Subgroups
- DDR Deficient*** (16%)
- KRAS G12D (33%)
- KRAS G12V (23%)
- KRAS G12R (11%)
- KRAS G12C (1%)
- KRAS Q61 (4%)
- RAS Other (1%)
- RAS Wild Type (10%)

Enrichment Analysis Benchmark

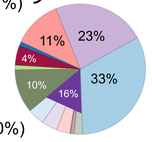
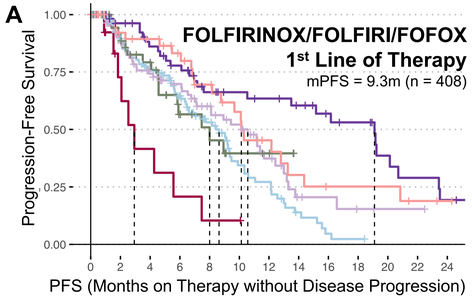
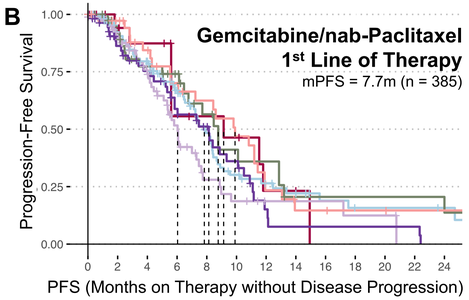


Figure 1: Pts with advanced pancreatic cancer (PDAC) and molecular profiles were analyzed based on specific RAS mutations (or DDR status) for OS/PFS analyses.
***Pts with mutations in DNA damage response (DDR) genes (e.g. BRCA1/2, PALB2, ATM/ATR, etc) were reassigned to the DDR subgroup (see pie chart) due to known implications for platinum-sensitivity[2]

PFS on 1st Line Therapies by RAS Mutational Subgroup



Molecularly-Defined PDAC Subgroup	1st Line PFS median [95% CI]	Enrichment p-value (HR)
DDR Deficient (61)	**19.1m** [13.5-23.4]	0.00023 (0.44)
KRAS G12D (143)	**8.6m** [6.6-9.5]	0.017 (1.51)
KRAS G12V (95)	10.6m [7.1-13.0]	0.42 (0.86)
KRAS G12R (51)	10.1m [8.8-20.8]	0.055 (0.63)
KRAS G12C (4)	10.3m [N/A]	0.91 (0.90)
KRAS Q61 (16)	**2.9m** [2.1-N/R]	0.00053 (3.36)
RAS Other (6)	N/A	N/A
RAS Wild Type (42)	8m [5.8-N/R]	0.80 (1.07)



Molecularly-Defined PDAC Subgroup	1st Line PFS median [95% CI]	Enrichment p-value (HR)
DDR Deficient (60)	8.1m [5.8-10.5]	0.39 (1.18)
KRAS G12D (132)	7.8m [7.1-8.7]	0.32 (0.84)
KRAS G12V (87)	**6.0m** [5.3-7.6]	0.034 (1.5)
KRAS G12R (39)	9.9m [7.2-11.9]	0.32 (0.8)
KRAS G12C (4)	9.4m [5.4-N/R]	0.87 (0.89)
KRAS Q61 (24)	9.1m [5.6-N/R]	0.60 (0.84)
RAS Other (3)	N/A	N/A
RAS Wild Type (43)	8.8m [6.8-13.2]	0.41 (0.83)

Figure 3: Enrichment analyses comparing PFS on 1st line Tx across RAS subgroups. Notable differences between each group and the benchmark subgroups (G12D/V/R) are highlighted (via univariate Cox regression).

Results & Discussion

Novel Insight: Could KRAS Q61 possibly represent a novel predictive biomarker for differential response to SOC in PDAC?
- The KRAS Q61 subgroup had shorter PFS on 5FU-based Tx compared to KRAS G12D/V/R-mutated PDAC (**Figure 3A**)
- No difference was seen for the KRAS Q61 subgroup who received 1st line gemcitabine/nab-paclitaxel (**Figure 3B**)
- KRAS Q61 trend for OS was similar to G12D but not significant for enrichment vs G12D/V/R-mutated PDAC (**Figure 4**)
- Pertinent Caveat: No difference observed in 2nd line where 5FU/nal-Irinotecan is more common (data not shown)

As expected, the DDR deficient subgroup performed exceptionally well on 5FU-based regimens (**Figure 3A**)
- DDR mutations were excluded from RAS variant-specific subgroupings for this known reason[2]
- Majority received FOLFIRINOX or FOLFOX in the frontline setting (DDR is predictive for response to platinums[2])

Only modest OS/PFS differences were observed between the 3 most common KRAS variant subgroups (**Figures 3 & 4**)
- KRAS G12D was enriched for slightly shorter PFS on 5FU-based therapy compared to KRAS G12V/R-mutated PDAC
  - KRAS G12D also had slightly shorter OS compared to KRAS G12V/R-mutated PDAC (predictive or prognostic?)
- KRAS G12V was enriched for slightly shorter PFS on Gemcitabine/nab-P compared to KRAS G12D/R-mutated PDAC

Additional data are needed to assess the predictive/prognostic implications of uncommon RAS variant subgroups
- KRAS G12C is surprisingly rare (**Figure 2**) in PDAC (1.2% of RAS mutations) limiting our ability to assess OS/PFS trends
- KRAS Q61R/H is found in 5.8% of all PDAC (7% of RAS mutations) and more abundant than G12C in many GI subtypes
- Most other KRAS/NRAS/HRAS mutations are rare in PDAC but other drivers can influence the MAPK pathway in PDAC[1]

KRAS wild type & DDR deficient subgroups had longer OS compared to patients with KRAS G12D/V/R-mutatated PDAC
- DDR alterations are predictive markers of response to PARPi/platinums (NOT prognostic in the absence of platinums[2])
- Many patients within the RAS wild type subgroup received targeted therapies[1] for other drivers (e.g. NTRK/ROS1/BRAF)

Co-occurrence and mutual exclusivisity analyses were performed on each RAS mutational subgroup
- KRAS G12R-mutated tumors were often found alongside mutations in STK11/PIK3CA; however, KRAS G12R was mutually exclusive with ARID1A mutations (all 3 impact PI3K/AKT/mTOR signaling, relevant for previous studies)
- KRAS Q61 & RAS Other were both enriched for co-occurrence with SF3B1 mutations (dysregulates RNA processing)

RAS Mutation Breakdown by Cancer Type

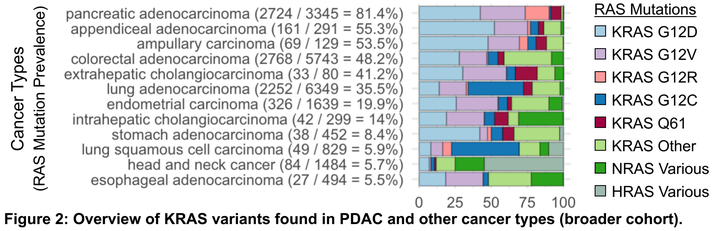


Figure 2: Overview of KRAS variants found in PDAC and other cancer types (broader cohort).
- Prevalence was calculated using data from AACR GENIE[3] & Perthera's real-world registry[4]
- KRAS G12D (43%) and G12V (31%) are the two most common isoforms found in RAS-mutated PDAC
- KRAS G12R is more common in PDAC (17% of RAS mutations) than in lung cancers (1-6%)
- KRAS G12C is surprisingly rare in PDAC (1.2% of RAS mutations) relative to lung cancers (38-47%)
- KRAS Q61H/R is found in 5.8% of all PDAC (7% of RAS mutations) similar to other GI cancer types
- Most other KRAS/NRAS/HRAS mutations are rare in PDAC despite a RAS mutation rate above 80%

Baseline Characteristics

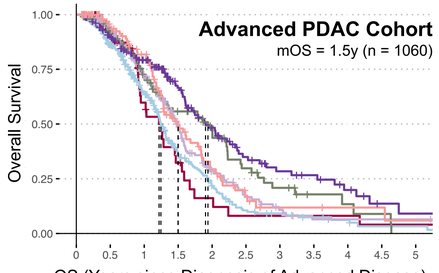
Molecularly-Defined PDAC Subgroup	Age (median [IQR])	Sex (% Female)	Background (% White)
DDR Deficient (175)	62 [55-61]	47%	77%
KRAS G12D (358)	63 [56-62]	47%	84%
KRAS G12V (250)	64 [57-63]	50%	81%
KRAS G12R (120)	63 [57-63]	55%	76%
KRAS Q61 (49)	64 [55-63]	43%	74%
RAS Wild Type (108)	61 [54-60]	46%	91%

Questions? @Perthera or hope@perthera.com

Conclusions & Further Questions

1. Perthera's real-world clinical/molecular datasets may provide novel insights into biomarkers that predict response to standard of care (or lack thereof).
2. Prospective validation may be warranted to optimize treatment sequencing for KRAS Q61 mutations (found in 6% of all PDAC cases).
3. Multivariate analyses are underway to delineate the predictive vs prognostic role of specific KRAS mutations across all lines of therapy.
4. Treatment-specific differences in outcomes motivate the need for a better understanding of tumor biology to support future clinical trial design
5. As expected, DDR-mutated tumors were the most prominent group to benefit from 5FU-based therapy (DDR is predictive for platinum response[2]).
6. Perthera previously demonstrated a 1-year OS benefit for molecularly-matched Tx[1] which likely explains the favorable OS trends for DDR-mutated (independent of RAS status) and RAS wild type tumors (not prognostic)
7. Perthera's outcomes collection efforts for molecularly-profiled patients may begin to support directing specific therapies to certain mutational subgroups

OS in the Advanced Setting by RAS Mutational Subgroup



Molecularly-Defined PDAC Subgroup (n)	Advanced OS median [95% CI]	Enrichment p-value (HR)
DDR Deficient (175)	**1.9y** [1.6-2.4]	0.0000064 (0.58)
KRAS G12D (358)	**1.2y** [1.2-1.3]	0.0035 (1.34)
KRAS G12V (250)	1.5y [1.4-1.6]	0.073 (0.82)
KRAS G12R (120)	1.5y [1.3-1.8]	0.12 (0.81)
KRAS G12C (12)	0.8y [0.5-N/R]	0.99 (0.99)
KRAS Q61 (49)	1.2y [0.9-1.6]	0.45 (1.16)
RAS Other (12)	1.3y [1.3-N/R]	0.88 (1.08)
RAS Wild Type (108)	**1.9y** [1.3-2.2]	0.011 (0.70)

Figure 4: Enrichment OS analyses from advanced diagnosis across RAS subgroups. Differences against the benchmark (G12D/V/R) were noted but do not necessarily suggest prognostic associations[1,2] (see Discussion).