

Not all treated KRAS-mutant pancreatic adenocarcinomas are equal: KRAS G12D show the poorest survival.

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Background

KRAS is an oncogenic driver in pancreatic ductal adenocarcinoma (PDAC) with mutations identified in > 90% of cases. G12D is the most frequent variant, followed by G12V and G12R. We recently reported on the prognostic impact of distinct *KRAS* mutations. The current study utilized a large clinical and genomic database, to further explore and characterize the prognostic and molecular differences between *KRAS* variants, focusing on *KRAS* G12D and G12R.

Methods

PDAC samples were tested using whole transcriptome sequencing (WTS; Illumina NovaSeq) and NextGen DNA sequencing (NextSeq, 592 Genes and NovaSEQ, WES) at Caris Life Sciences (Phoenix, AZ). Transcriptomic signatures including MPAS (MAPK activation score), T-cell inflamed score and tumor microenvironment (TME) characterization were calculated on WTS data. Significance was determined by X² and Fisher-Exact and p-value was adjusted for multiple comparisons (q). Real-world overall survival (rwOS) obtained from insurance claims data was calculated from tissue collection to last contact (comparison done by Kaplan-Meier test).

Patient Demographics

	G12R	G12V	G12C	G12D
Count (N)	621	1294	74	1766
Median Age (range)	68.0 (37 - >89)	67.0 (29 - >89)	66.0 (38 - 85)	67.0 (23 - >89)
Male	48.6% (302/621)	52.8% (683/1294)	60.8% (45/74)	54.5% (962/1766)
Female	51.4% (319/621)	47.2% (611/1294)	39.2% (29/74)	45.5% (804/1766)

Table 1: patient demographics





Results

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25

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%15

10

Figure 1 – Immune Checkpoint marker prevalence for *KRAS* variants in PDAC

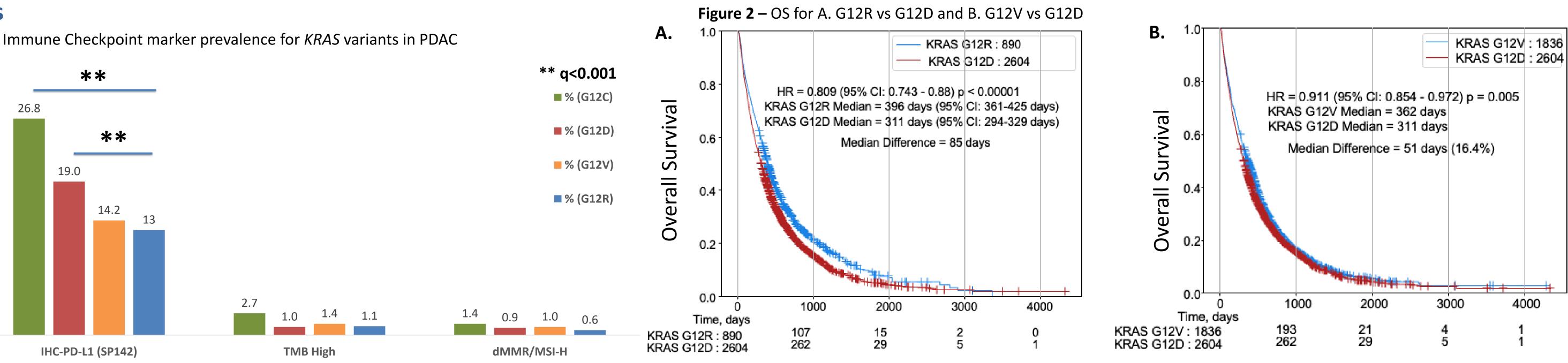
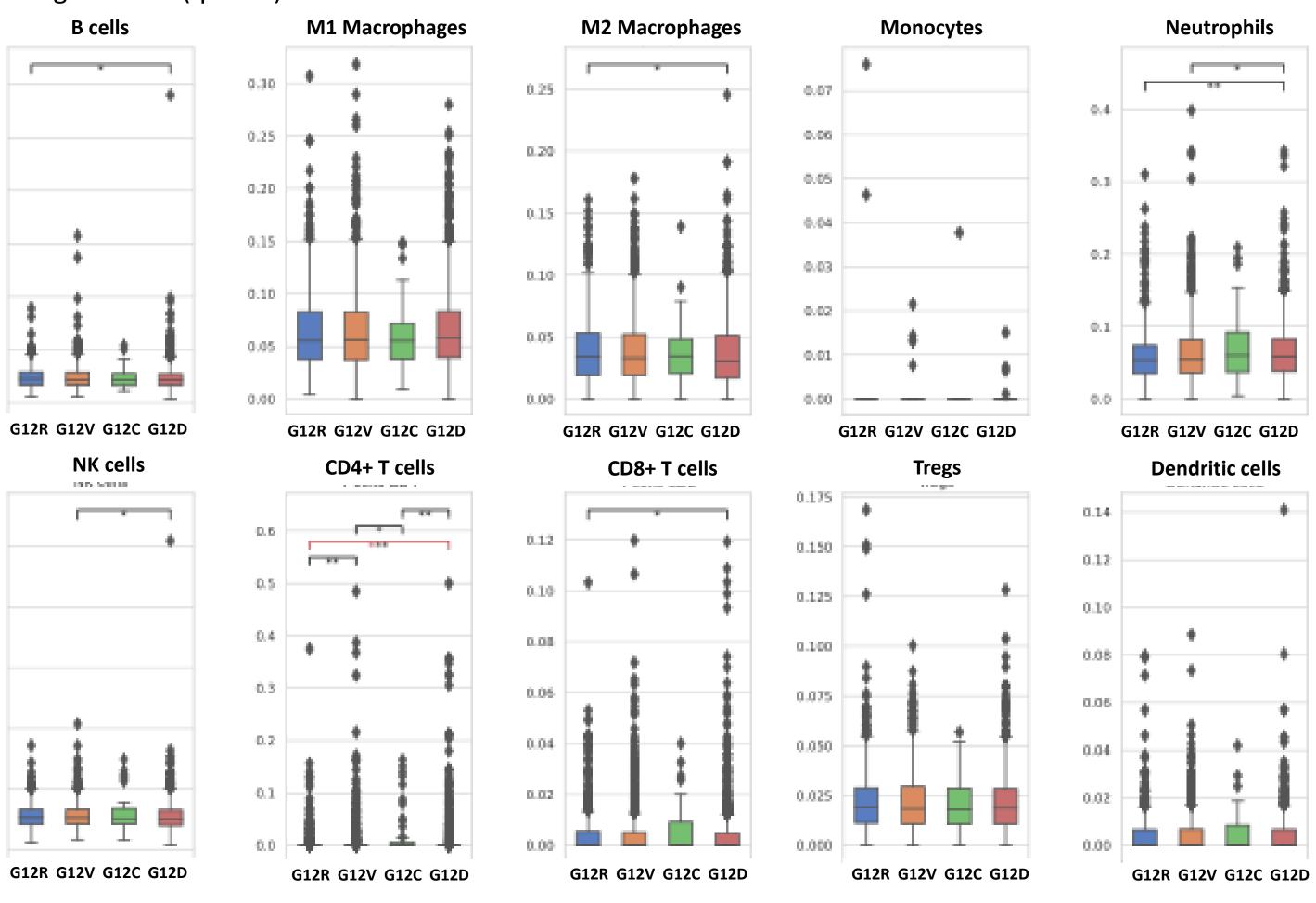
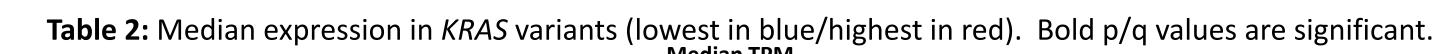


Figure 3 – Tumor immune microenvironment (Quantiseq). Black bars show trends (p<0.05) and red bars show significance (q<0.05).









			Me	edian TPN	Λ						
						Pairwise p-	Pairwise p-	Pairwise p-	Pairwise q-	Pairwise q-	Pairwise q-
						value (G12R	value (G12R	value (G12R	value (G12R	value (G12R	value (G12R
	Gene	G12R	G12V	G12C	G12D	vs G12V)	vs G12C)	vs G12D)	vs G12V)	vs G12C)	vs G12D)
IO related Glutamine metabolism	LAG3	0.50	0.56	0.56	0.53	0.02	0.23	0.09	0.10	0.47	0.29
	CD274	3.15	3.47	3.97	3.81	0.02	0.04	<0.001	0.15	0.20	<0.01
	CD86	6.53	7.06	7.15	7.49	0.16	0.60	0.01	0.39	0.75	0.09
	CD80	3.93	4.39	4.13	4.79	0.07	0.48	<0.01	0.26	0.71	0.01
	PDCD1LG2	0.83	0.93	0.86	0.98	0.05	0.59	<0.01	0.21	0.75	0.02
	CTLA4	0.95	1.04	1.26	1.10	0.21	0.20	0.04	0.45	0.44	0.20
	IFNG	0.16	0.18	0.16	0.16	0.05	0.78	0.40	0.20	0.84	0.69
	HAVCR2	14.77	15.89	15.19	17.17	0.06	0.62	<0.01	0.22	0.76	0.04
	PDCD1	0.30	0.34	0.34	0.35	0.13	0.86	0.03	0.34	0.90	0.17
	IDO1	1.14	1.29	1.84	1.31	0.10	0.10	0.02	0.30	0.30	0.10
	GOT1	16.36	17.95	16.11	18.50	0.04	0.80	<0.01	0.18	0.87	0.02
	GOT2	8.75	9.84	10.11	10.14	<0.01	0.40	<0.001	0.03	0.56	<0.01
Glucose metabolism	SLC2A1	29.66	31.88	42.15	36.25	0.18	0.06	<0.001	0.45	0.29	<0.01
	LDHA	230.83	254.81	263.75	269.12	0.08	0.51	<0.001	0.30	0.69	<0.01
	RPE	34.29	37.35	34.56	38.63	0.01	0.95	<0.01	0.07	0.95	0.03
I2C G12D Signature	T cell inflamed	-27.5	-11	-17	-4	0.07	0.37	0.02	0.39	0.37	0.32
Signature	MPAS	0.24	0.40	0.39	0.48	0.47	0.90	0.04	0.74	0.90	0.32
	Glutamine metabolism	LAG3CD274CD86CD80PDCD1LG2CTLA4IFNGHAVCR2PDCD1ID01Glutamine metabolismGOT2SLC2A1Glucose metabolismLDHARPESignatureT cell inflamed	LAG3 0.50 CD274 3.15 CD86 6.53 CD80 3.93 PDCD1LG2 0.83 CTLA4 0.95 IFNG 0.16 HAVCR2 14.77 PDCD1 0.30 ID01 1.14 Glutamine metabolism GOT1 16.36 GOT2 8.75 Slc2A1 29.66 LDHA 230.83 RPE 34.29 Signature T cell inflamed -27.5	Gene G12R G12V LAG3 0.50 0.56 CD274 3.15 3.47 CD86 6.53 7.06 CD80 3.93 4.39 PDCD1LG2 0.83 0.93 CTLA4 0.95 1.04 IFNG 0.16 0.18 HAVCR2 14.77 15.89 PDCD1 0.30 0.34 IDO1 1.14 1.29 Glutamine metabolism GOT1 16.36 17.95 Glucose metabolism SLC2A1 29.66 31.88 LDHA 230.83 254.81 RPE 34.29 37.35 Signature T cell inflamed -27.5 -11 -11	Gene G12R G12V G12C LAG3 0.50 0.56 0.56 CD274 3.15 3.47 3.97 CD86 6.53 7.06 7.15 CD80 3.93 4.39 4.13 PDCD1LG2 0.83 0.93 0.86 CTLA4 0.95 1.04 1.26 IFNG 0.16 0.18 0.16 HAVCR2 14.77 15.89 15.19 PDCD1 0.30 0.34 0.34 IDO1 1.14 1.29 1.84 Glutamine metabolism GOT1 16.36 17.95 16.11 Glucose metabolism SLC2A1 29.66 31.88 42.15 RPE 34.29 37.35 34.56 RPE 34.29 37.35 34.56	LAG3 0.50 0.56 0.56 0.53 CD274 3.15 3.47 3.97 3.81 CD86 6.53 7.06 7.15 7.49 CD80 3.93 4.39 4.13 4.79 PDCD1LG2 0.83 0.93 0.86 0.98 CTLA4 0.95 1.04 1.26 1.10 IFNG 0.16 0.18 0.16 0.16 HAVCR2 14.77 15.89 15.19 17.17 PDCD1 0.30 0.34 0.34 0.35 IDO1 1.14 1.29 1.84 1.31 Glutamine metabolism GOT1 16.36 17.95 16.11 18.50 Glucose metabolism SLC2A1 29.66 31.88 42.15 36.25 IDHA 230.83 254.81 263.75 269.12 RPE 34.29 37.35 34.56 38.63	Gene G12R G12V G12C G12D Pairwise p-value (G12R LAG3 0.50 0.56 0.56 0.53 0.02 CD274 3.15 3.47 3.97 3.81 0.02 CD274 3.15 3.47 3.97 3.81 0.02 CD266 6.53 7.06 7.15 7.49 0.16 CD80 3.93 4.39 4.13 4.79 0.07 PDCD1LG2 0.83 0.93 0.86 0.98 0.05 CTLA4 0.95 1.04 1.26 1.10 0.21 IFNG 0.16 0.18 0.16 0.05 0.13 IDO1 1.14 1.29 1.84 1.31 0.10 Glutamine metabolism GOT2 8.75 9.84 10.11 10.14 <0.01 Glucose metabolism LDHA 230.83 254.81 263.75 269.12 0.08 RPE 34.29 37.35 34.56 38.63	International condition Gene G12R G12V G12C Pairwise p-value (G12R) vs G12C) Pairwise p-value (G12R) vs G12C) Value (G12R) vs G12C) Vs G12C)	Image: second	Image: log matrix Gene G12R G12V G12C G12D Pairwise p-value (G12R vs G12C) Pairwise p-value (G12R vs G12D) Pairwise p-value	Image: log related Gene G12R G12V G12C G12D Pairwise p-value (G12R Pairwise q-value (G12R Value (G12R Vs G12C) Vs G

Conclusions

- Patients with G12D mutations have significantly lower survival compared to G12R.
- Significant molecular differences were seen in MAPK pathway gene expression, markers of immune activation, and genes involved in glucose and glutamine metabolism.
- Metformin use appeared to impact survival in the KRAS G12R subgroup.
- We aim to further explore distinct vulnerabilities based on MAPK pathway activation and dysregulated metabolism.
- Based on this data, future studies should address the *KRAS* mutation status and explore distinct therapeutic vulnerabilities.

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