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

Bach Ardalan[1], Aaron Ciner[2], Yasmine Baca[3], Sourat Darabi[4], Anup Kasi[5], Emil Lou[6], Jose Ignacio Azqueta[1], Joanne Xiu[3], Chadi Nabhan[3], Anthony F. Shields[7], Andrew Aguirre[8], Harshabad Singh[8], Rachna T. Shroff[9], Michael J. Pishvaian[10], Sanjay Goel[11]

1. Sylvester Comprehensive Cancer Center, Miami, FL; 2. University of Maryland, Baltimore, MD; 3. Caris Life Sciences, Phoenix, AZ; 4. Hoag Memor Hosp, Newport Beach, CA; 5. University of Kansas Cancer Center, Westwood, KS; 6. Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN; 7. Barbara Ann Karmanos Cancer Institute, Detroit, MI; 8. Dana-Farber Cancer Institute, Boston, MA; 9. University of Arizona Cancer Center, Tucson, AZ; 10. Johns Hopkins University School of Medicine, Washington, DC; 11. Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

CARIS® PRECISION ONCOLOGY ALLIANCE

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 X^2 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

Table 1: 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)

Results

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

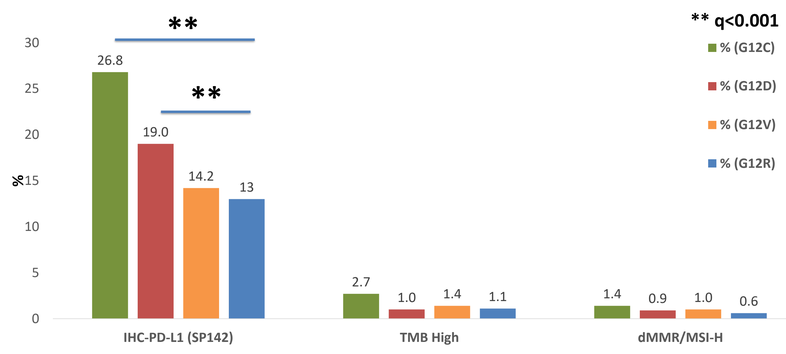

Figure 2 – OS for A. G12R vs G12D and B. G12V vs G12D

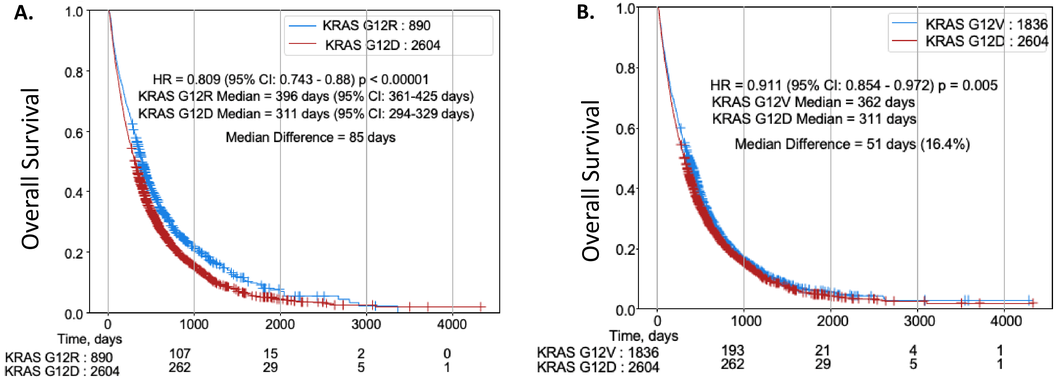

Figure 3 – Tumor immune microenvironment (Quantiseq). Black bars show trends (p<0.05) and red bars show significance (q<0.05).

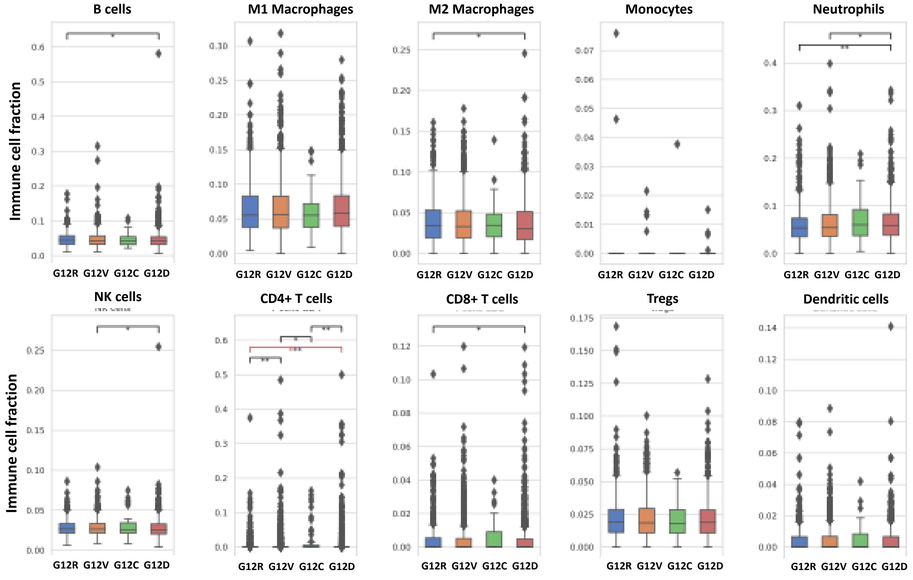

Table 2: Median expression in *KRAS* variants (lowest in blue/highest in red). Bold p/q values are significant.

		Median TPM									
	Gene	G12R	G12V	G12C	G12D	Pairwise p-value (G12R vs G12V)	Pairwise p-value (G12R vs G12C)	Pairwise p-value (G12R vs G12D)	Pairwise q-value (G12R vs G12V)	Pairwise q-value (G12R vs G12C)	Pairwise q-value (G12R vs G12D)
IO related	***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
Glutamine metabolism	***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**
Signature	***T cell inflamed***	-27.5	-11	-17	-4	0.07	0.37	**0.02**	0.39	0.37	0.32
	MPAS	0.24	0.40	0.39	0.48	0.47	0.90	**0.04**	0.74	0.90	0.32

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.

ASCO . June 2023