KRAS G12C-mutated pancreatic cancer: clinical outcomes based on chemotherapeutic regimen.

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Background

Frontline treatment for advanced pancreatic ductal adenocarcinoma (PDAC) has been either 5-fluorouracil, oxaliplatin and irinotecan (FOLFIRINOX) or gemcitabine and nab-paclitaxel (GP) for the past decade[1-2]. While the NAPOLI-3 trial, utilizing liposomal irinotecan, highlighted the superiority of a triplet regimen over GP, the question remains whether certain subgroups may derive particular benefit from GP[3]. Pre-clinical data in lung cancer suggest that *KRAS* G12C may facilitate enhanced DNA adduct removal after platinum chemotherapy and confer resistance to this drug class[4]. While multiple *KRAS* G12C inhibitors have shown early promise in PDAC, multi-agent chemotherapy remains the frontline standard and will likely remain an important therapeutic tool. This study aimed to investigate clinical outcomes after platinum and non-platinum-based chemotherapy in patients with advanced *KRAS* G12C-mutated PDAC relative to other *KRAS* variants.

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). Significance was determined by X^2 and Fisher-Exact and p adjusted for multiple comparisons (q). Real-world overall survival (rwOS) was obtained from insurance claims data and calculated from first of treatment to last contact with comparison done by Kaplan-Meier test.

Table 1: patient demographics

	G12R	*G12V*	*G12C*	*G12D*
Count (N)	621	1294	74	1766
Median Age (range) [N]	68.0 (37 - >89) [621]	67.0 (29 - >89) [1294]	66.0 (38 - 85) [74]	67.0 (23 - >89) [1766]
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 – Median OS comparison for patients treated with FOLFIRINOX vs Gemcitabine/nab-paclitaxel (GP) by *KRAS* variant.

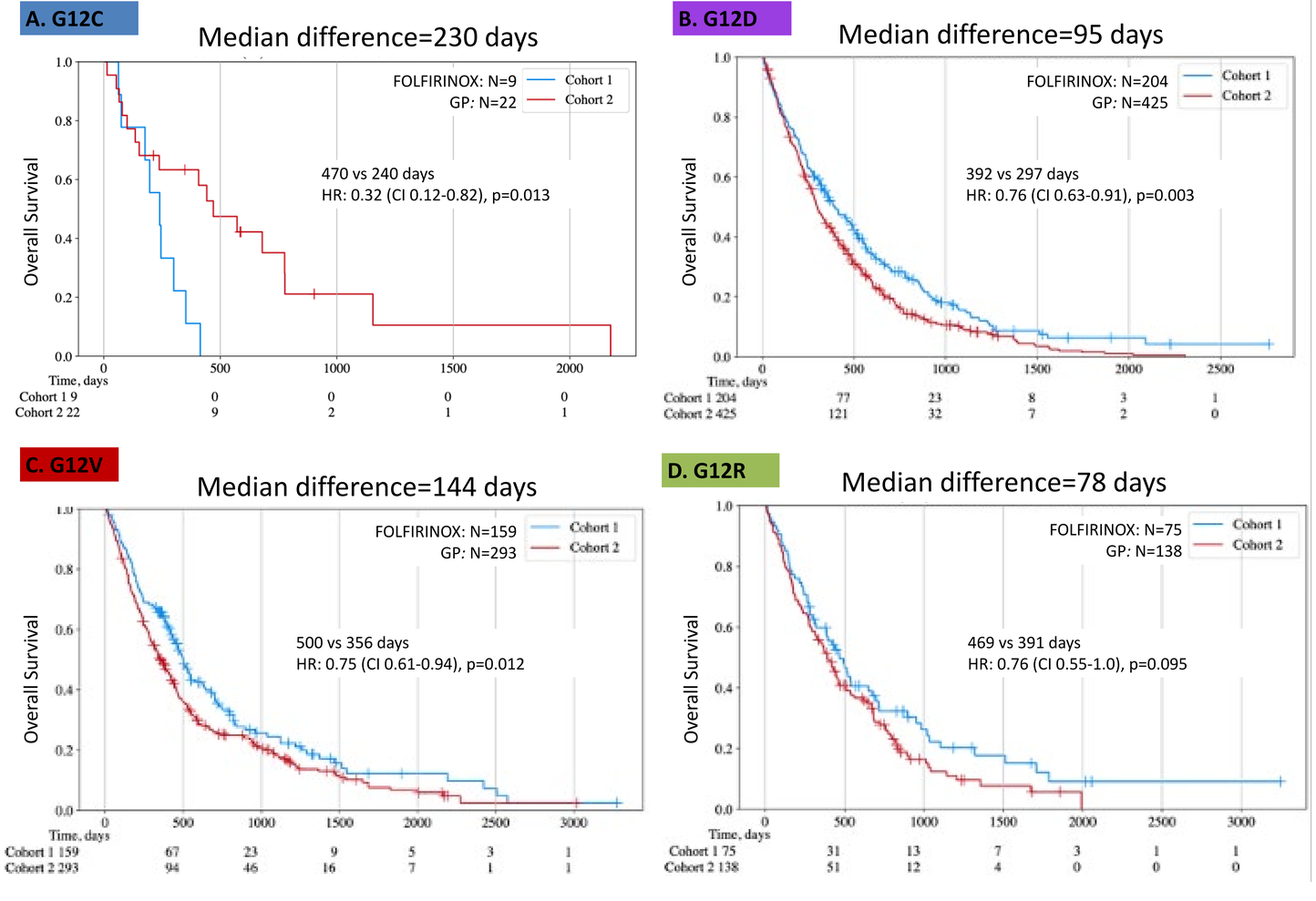
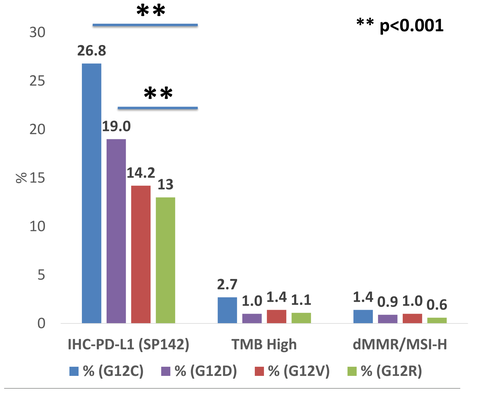


Figure 2 – Immune Checkpoint marker prevalence for *KRAS* variants in PDAC



Conclusions

- In patients with advanced PDAC and a G12C mutation, median overall survival appears significantly longer in those treated with GP compared to FOLFIRINOX.
- The opposite trend was seen in patients with other *KRAS* variants including G12D, G12V, and G12R, consistent with the recently presented NAPOLI-3 trial.
- PDL1 staining was also highest in the *KRAS* G12C cohort.
- While this is the largest reported analysis of outcomes to frontline chemotherapy in *KRAS* G12C-mutated PDAC, the sample size is small and needs validation in additional datasets.

References

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