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 NextSeq DNA sequencing (NextSeq, SQ2 Genes, and NovoSeq, WES) at Caris Life Sciences (Phoenix, AZ). Transcriptomic signatures including MMP9 (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

Table 1: patient demographics

<table>
<thead>
<tr>
<th>Variant</th>
<th>G12D</th>
<th>G12V</th>
<th>G12C</th>
<th>G12R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count (%)</td>
<td>621</td>
<td>1294</td>
<td>74</td>
<td>1716</td>
</tr>
<tr>
<td>Median Age (range)</td>
<td>68 (17–89)</td>
<td>67 (29–89)</td>
<td>68 (16–80)</td>
<td>67 (23–98)</td>
</tr>
<tr>
<td>Male</td>
<td>48.8% (302/612)</td>
<td>52.8% (683/1294)</td>
<td>86.8% (65/74)</td>
<td>54.5% (938/1716)</td>
</tr>
<tr>
<td>Female</td>
<td>51.2% (319/621)</td>
<td>47.2% (612/1294)</td>
<td>13.2% (29/74)</td>
<td>45.5% (788/1716)</td>
</tr>
</tbody>
</table>

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.