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Mutational analysis of cfDNA to identify predictive biomarkers in previously untreated patients with metastatic pancreatic cancer receiving the GSK-3 inhibitor elraglusib (9-ING-41) in combination with gemcitabine/nab-paclitaxel in the 1801 phase 2 study.

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Background: Glycogen Synthase Kinase-3beta has been well-credentialed as a therapeutic target in patients with advanced cancer including pancreatic cancer. Elraglusib (9-ING-41), a novel best-in-class GSK-3 inhibitor, is being developed in combination with gemcitabine/nab-paclitaxel (GnP) as first-line therapy for patients with metastatic pancreatic cancer (mPDAC). Using liquid biopsy samples from an ongoing randomized phase 2 trial (1801 Part 3B; NCT03678883), we examined whether gene mutations in cfDNA correlated with clinical outcomes in mPDAC patients treated with GnP or elraglusib/GnP. **Methods:** Pre-dose plasma samples were obtained from 37 (GnP arm) and 89 (elraglusib/GnP arm) mPDAC patients previously untreated for advanced disease. Mutational analysis of cfDNA extracted from plasma samples was performed by Tempus (Chicago, IL) using the xF+ platform. The Tempus xF+ assay is an NGS cfDNA liquid biopsy tumor profiling assay for identifying genomic alterations in 523 genes. Tempus xF+ reports were used for analysis of gene mutations. **Results:** In 126 pancreatic cancer patients, frequently mutated genes ($>10\%$) consisted of KRAS (93/126, 74%), TP53 (79/126, 63%), CDKN2A (26/126, 21%), DNMT3A (25/126, 20%), NOTCH1/2 (25/126, 20%), and MLL3 (23/126, 18%). Gain-of-function mutations in KRAS, and loss-of-function mutations of TP53, and CDKN2A genes were associated with worse overall survival (OS) in patients treated with elraglusib/GnP ($P < 0.05$) but not in GnP-treated patients. Multivariate analysis of frequently mutated genes showed that patients with double (KRAS+TP53) and triple (KRAS+TP53+CDKN2A) mutations had significantly worse OS only in the elraglusib/GnP arm. The presence of DNMT3A, NOTCH1/2 or MLL3 gene mutations did not correlate with any clinical outcomes. **Conclusions:** Our preliminary analysis of gene mutations in liquid biopsy samples obtained from patients in the ongoing 1801 Part 3B phase 2 trial identified potential predictive biomarkers of clinical outcome in mPDAC patients treated with combination of elraglusib/GnP. Clinical trial information: NCT03678883. Research Sponsor: None.