Circulating DNA is a marker of aggressivity in Pancreatic Ductal Adenocarcinoma.

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Purpose
Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with no definite cure available. In patients, levels of circulating DNA are associated with a poor prognosis. Previous studies have demonstrated that the *in vitro* and *in vivo* inhibition of PI3Kα, a class I PI3K isoform, prevents the onset of PDAC’s most frequent oncogenic driver, mutated Kras. We sought to identify circulating/cell-free DNA (cfDNA) as a marker of aggressive metastatic disease in preclinical *in situ* pancreatic cancer models, and to demonstrate that the inhibition of PI3Kα in such context of high levels of cfDNA could be beneficial for patients’ outcome.

Experimental Design
We conducted *in vivo* studies using a murine model of progressive PDAC to determine the effects of p110α isoform-specific inhibition in established tumors. One of the major obstacles when treating PDAC is its late detection. To establish the optimal time for starting the treatment using the specific p110α inhibitor (BYL-719), we established a diagnostic protocol. The protocol couples high-resolution ultrasound imaging with the quantitative analysis of cfDNA. In order to increase the specificity of the cfDNA assay, we performed next generation sequencing (NGS) to assess the integrity of the cfDNA.

Results
We found that the quantification and integrity of cfDNA correlates with the severity of the disease and is a prognostic marker in PDAC. Inhibiting p110α tended to delay the development of ascites, tumor growth, metatasis formation and cfDNA concentration. Proliferation of tumoral cells was drastically decreased.

Conclusion
Our studies highlight the potential of cfDNA as a biomarker and its feasibility to be included as part of the diagnosis of PDAC. Regarding PI3Kα inhibition, we observed that it delays the rapid progression of PDAC and metastatic burden.

References
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