Mutant KRAS in Circulating Tumor DNA as a Biomarker in Pancreatic Cancer in Patients Treated with Neoadjuvant Chemotherapy

Dominic J. Vitello MD, Dhavan Shah MD, Amy Wells MS, Larissa Masnyk BA, Madison Cox BS, Lauren M. Janczewski MD MS, MD, John Abad MDZ3, 2, Kevin Dawravoo MD, Arlene D'Souza MD, Grace Suh MD, Robert Bayer MD, Massimo Cristofanilli MD, David Bentrom MD MS, Yinghe Liu MS, Hui Zhang PhD, Lucas Santana-Santos PhD, Lawrence J. Jennings MD PhD, Qiang Zhang MD PhD, Akhil Chawla MD

Introduction
Pancreatic ductal adenocarcinoma (PDAC) is currently the third leading cause of cancer-related death in the United States. Currently, carbohydrate antigen 19-9 (CA 19-9) is the only validated biomarker in use for PDAC. Given the need for deeper understanding in tumor biology, the limitations of CA 19-9, and ongoing investigations in other solid malignancies, circulating tumor DNA (ctDNA) has emerged as a PDAC biomarker candidate. Digital droplet PCR (ddPCR) is distinct from NGS in detection of ctDNA in that it is 1000 times more sensitive as well as less costly than NGS testing. Given our prior results, we sought to evaluate the detection and prognostic capability of mutant KRAS ctDNA in PDAC patients treated with neoadjuvant chemotherapy (NAC) as assessed by ddPCR.

Methods
Data source: Prospectively recruited cohort

Inclusion Criteria
- Newly diagnosed PDAC
- Patients with resectable disease
- Patients planned to undergo NAC

Exclusion Criteria
- Surgically unresectable
- Not a candidate for NAC
- Not undergoing curative-intent treatment
- 1 or fewer samples collected

Sample handling
- Peripheral blood samples collected at diagnosis, after NAC, and after resection
- Samples analyzed by ddPCR for mutant KRAS G12D, G12V, and G12R

Analysis
- Primary outcome was overall survival (OS)
- Kaplan-Meier with log-rank testing and multivariable Cox regression assessed survival differences
- KRAS mutations are detectable in ctDNA samples obtained in peripheral blood samples in patients with PDAC by ddPCR
- These mutations are detectable in PDAC patients treated with neoadjuvant chemotherapy (NAC)

Results

1. Genomic KRAS mutations are detectable in ctDNA in patients with PDAC by ddPCR
2. These mutations are detectable in patients with PDAC by ddPCR
3. The presence and copy number concentration of mutant KRAS G12V after resection was independently predictive of prognosis
4. Clearance was also associated with improved survival

Further study by our group using ddPCR in the detection of mutant KRAS ctDNA will include examination of recurrence and the association of oncologic outcomes with the quantitative information provided by ddPCR.

Conclusions

Acknowledgments

References