**B-24**

Activation of Alternative Lengthening of Telomeres (ALT) in Primary Pancreatic Neuroendocrine Tumors Serves as Both a Prognostic Biomarker and Potential Therapeutic Target

*Anthony Rizzo1; Jacqueline Brosnan-Cashman1; Mindy Graham1; Ralph Hruban1,1; Christopher Heaphy1*

1 Johns Hopkins University School of Medicine

**BACKGROUND:** A key hallmark of cancer is unlimited replicative capacity. While many tumors maintain telomere lengths by expressing the enzyme telomerase, a subset utilize a cancer-specific, telomerase-independent telomere maintenance mechanism, termed Alternative Lengthening of Telomeres (ALT). We have previously shown ALT is tightly linked to alterations in two chromatin remodeling proteins, ATRX and DAXX. This complex deposits histone variant H3.3 in heterochromatic regions of chromosomes containing highly repetitive elements, particularly pericentromeric regions and telomeres. Thus, due to telomere deprotection and alterations in chromatin dynamics, telomere maintenance in ALT-positive cancers is mediated through homology-directed DNA repair.

**METHODS:** ALT is assessed in archived tissue specimens by utilizing a robust telomere-specific fluorescence in situ hybridization assay. Presence or absence of nuclear protein expression for ATRX and DAXX is assessed by standard immunohistochemistry.

**RESULTS:** In a large Korean cohort (N=278) of surgically resected primary PanNETs, we observed that primary ALT-positive PanNETs were associated with reduced recurrence-free survival (Kim et al, Clinical Cancer Research, 2017). Specifically, ALT and ATRX/DAXX loss were significantly associated with higher WHO grade, larger tumor size, lymphovascular and perineural invasion, and
presence of lymph node and distant metastases. Subsequently, we recently demonstrated the feasibility of determining ALT and ATRX/DAXX status in fine needle aspirates, which may become increasingly important in the design of clinical trials (VandenBussche et al, Cancer Cytopathology, 2017). While directly targeting inactivating ATRX and DAXX mutations is difficult, ALT-positive cancer cells display unique molecular features, including extensive genome rearrangements, G2/M checkpoint defects, and altered double-strand break repair. We are currently evaluating the hypothesis that these common ALT-associated molecular characteristics may be exploited therapeutically.

**CONCLUSION:** Taken together, these results suggest that ALT may be used as a prognostic marker and intriguingly, eventually used to identify patients that could benefit from ALT-specific targeted therapies.