

Genomic Profiling Distinguishes Gastroenteropancreatic Poorly Differentiated Neuroendocrine Carcinomas (GEP-NEC) from Small Cell Lung Carcinoma (SCLC)

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Background: Optimal therapy for GEP-NEC is not clear. Traditionally treated like SCLC, overall prognosis is poor and new therapies are needed. We examined genomic alterations (GA) in GEP-NEC of different sites compared to SCLC.

Methods: Sequential GEP-NEC cases from a database [Foundation Medicine] of tumors submitted for genomic profiling analyzed after digital pathology images reviewed by two different pathologists. Group 1: 274 cases with "some" component of morphologically apparent NEC -123 pancreas (P), 92 colorectal (CR), and 59 "other GI" sites; Group 2: 159 cases passing an independent, stricter pathology review (>50% NEC with small or large cell histology)- 91 P, 51 CR, and 17 "other GI". Hybridization-captured libraries of up to 315 cancer-related genes, plus select introns were sequenced (FoundationOne). All classes of GA identified in 192 cancer-related genes shared across 2 different assay versions. "Actionable" alterations were assessed. 593 SCLC cases used for comparison.

Results: There were 9 genes with alterations in >15% of tumors in any group (Group 1). Only TP53 crossed the 15% threshold in every group: MEN1 and DAXX >15% specific to P, APC and KRAS specific to CR, and CCNE1 >15% specific to "other GI". Every GEP-NEC group had a lower rate of alteration for TP53 and RB1 than SCLC. Analysis of Group 2 GEP-NEC showed similar findings ("Other GI" excluded due to small N). Pooled P and CR NEC with small cell histology (N=142) showed significantly different GA compared to SCLC. 37% of Group 2 GEP-NEC harbored potentially "actionable" GA.

Conclusion: Findings indicate underlying drivers of GEP-NEC may depend on site of origin and distinguish GEP-NEC from SCLC. Presence of potentially actionable GA in GEP-NEC suggest additional therapeutic targets. Lack of access to medical record/original tissue precludes correlation of GA with outcome or proliferation index; additional samples required to more fully explore large v small cell subtypes.