# C-3

## Stage-Independent Prognostic Value of TP53 and DAXX/ATRX in Pancreatic Malignant Carcinoid and Neuroendocrine Carcinoma

*Aasiya Islam[1], Rasa Zarnegar[1], Thomas J. Fahey III[1], Brendan M. Finnerty[1]*

*[1]Department of Surgery, Weill Cornell Medicine*

### BACKGROUND

Malignant carcinoid tumors and neuroendocrine carcinomas (NEC) represent distinct histologic subtypes of pancreatic neuroendocrine tumors (pNETs) with markedly different prognoses, yet current risk stratification relies on histology and stage alone. DAXX/ATRX and TP53/RB1 are largely mutually exclusive driver pathways, with DAXX/ATRX classically associated with well-differentiated disease and TP53/RB1 with NEC. Despite the availability of routine tumor sequencing, molecular profile is not currently incorporated into clinical decision-making. Whether tumors carrying mutations atypical for their histologic class behave according to histology or genotype remains unknown.

### METHODS

Patients with malignant carcinoid tumor (n=157) and NEC (n=63) were identified from the publicly available MSK-CHORD cohort via cBioPortal using ICD-O Histology Description codes and confirmed PANET OncoTree code designation. TP53, RB1, DAXX, ATRX, and MEN1 mutation status was obtained from MSK-IMPACT sequencing and merged with clinical annotations at the patient level. Genes were also tested as combined pathway variables (DAXX/ATRX; TP53/RB1). Kaplan-Meier survival analysis and univariate Cox regression evaluated overall survival (OS) by mutational status. Significant genes were advanced to multivariable Cox proportional hazards models adjusting for stage and age, with covariate selection constrained by events-per-variable within each histologic cohort.

### RESULTS

The prevalent mutations were MEN1 (carcinoid 40.1%, NEC 58.7%), DAXX/ATRX combined (carcinoid 37.6%, NEC 46.0%), and TP53 (carcinoid 9.6%, NEC 11.1%). RB1 mutation was rare (carcinoid 0.6%, NEC 4.8%). MEN1 was the predominant mutation in both subtypes but did not predict OS on Kaplan-Meier, univariate Cox, or multivariable analysis. Among carcinoid tumors, TP53 mutation (n=15) was independently associated with worse OS after adjustment for stage IV disease and age (HR 2.81, 95% CI 1.31–6.00, p=0.01). Stage IV disease remained the dominant predictor in this model (HR 8.52, 95% CI 3.99–18.20, p<0.005). Among NEC patients, DAXX/ATRX alteration (n=29) was independently associated with improved OS after adjustment for stage (HR 0.38, 95% CI 0.16–0.91,

p=0.03). Reciprocal pathway alterations including DAXX/ATRX alteration in carcinoid and TP53/RB1 alteration in NEC were not significant predictors of OS.

## CONCLUSIONS

Mutations characteristic of the opposing histologic subtype, such as TP53 in carcinoid and DAXX/ATRX in NEC, were independently associated with discordant survival outcomes after stage adjustment, suggesting genotype may provide prognostic information not captured by histology alone. These findings support a potential role for molecular profiling as a complementary prognostic tool alongside conventional clinicopathologic factors by identifying molecularly discordant subgroups. Independent validation in larger cohorts is needed.

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