B-22

Genomic Profiling of Extrapulmonary High-Grade Neuroendocrine Carcinomas (EP-NEC) Reveals "Actionable" Mutations

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BACKGROUND: Optimal therapy for EP-NEC is unknown; new therapeutic strategies are urgently needed. Our previous analysis of EP-NEC cases from the Foundation One (FO) database suggested that over 1/3 of patients with GEP-NEC harbor potentially "actionable" genomic alterations (GA). The analysis suffered from lack of access to original tumor samples for pathology review and a liberal definition of actionability. In light of this shortcoming, we performed a more interpretable analysis of genomic alterations in EP-NECs in patients evaluated at UCSF.

METHODS: We performed a retrospective chart review of 56 G3 EP-NEC patients under routine care whose tumor biopsies were reviewed by a UCSF pathologist and analyzed for GA using a CLIA-approved platform. This included 36 cases sequenced with the in-house UCSF500 assay and 20 cases by FO as part of routine care. Actionability was defined based on OncoKB levels of evidence.

RESULTS: The 56 cases included 20 colorectal (36%), 14 pancreas (25%), 6 other GI (11%) and 16 other (29%). 30 (54%) patients were male. Average diagnosis age was 58.5 years. Average Ki-67 was 71%. Seven genes were altered in >15% of tumors in any primary site; only TP53 and RB1 crossed the 15% threshold in every group. Assessment of GA found actionable mutations (FDA-recognized biomarkers) in 8 (14%) patients (Table 1). Other variants (including TSC1, PTEN, RET, HRAS, PTCH1, CDK4 and AKT2) were identified with potential therapeutic implications for approved therapies in 6 (11%) more patients (for a total 25%

with potentially “actionable” mutations). MSI status was available for 25 patients (45%), of which 1 was MSI-H (4%).

CONCLUSION: GA analysis in this cohort of pathologically-confirmed EP-NEC revealed several patients with potentially actionable mutations. Given the need for novel treatment strategies for refractory disease, our results suggest a role for commercial platforms in identifying potential therapeutic targets in patients with G3 EP-NEC.

Table 1:

Patient Mutations with FDA-Recognized Biomarkers Predictive of Response to Approved Drug in Another Indication

Primary	Patient	Actionable Mutations
Colorectal	ID 1	MSI-H
	ID 2	BRAF V600E
	ID 3	ERBB2 amplification
	ID 4	BRAF V600E
	ID 5	BRCA1 & BRCA2 deletions
Pancreas	ID 6	ERBB2 amplification
	ID 7	BRAF V600E
Stomach	ID 8	ERBB2 amplification