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Molecular Profiling Defines Subsets of Neuroendocrine Tumors (NETs) with Aggressive Disease: A Fox Chase Cancer Center (FCCC) Study

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Background: The rarity of NETs limits clinical trial accrual to develop new therapies. A better understanding of underlying biology is critical to development of and assignment of patients (pts) to clinical trials.

Methods: Patients with NETs at FCCC were enrolled onto a prospective IRB approved protocol that utilized an NGS platform to detect somatic mutations (SM) in 50 cancer-related genes on archived tissue. Genes tested included *ABL1,AKT1,ALK,APC,ATM,BRAF,CDH1,CDKN2A,CSF1R,CTNNB1, EGFR,ERBB2,ERBB4,EZH2,FBXW7,FGFR1,FGFR2,FGFR3,FLT3,G NA11,GNAQ,GNAS,NF1A,HRAS,IDH1,IDH2,JAK2,JAK3,KDR,KIT, KRAS,MET,MLH1,MPL,NOTCH1,NPM1,NRAS,PDGFRA,PIK3CA, PTEN,PTPN11,RB1,RET,SMAD4,SMARCB1SMO,SRC,STK11,TP53* and *VHL.*

Results: Sixty-six pts (median age 59, males 53%) were enrolled from 10/2013-02/2015. Gene profiling results were available on fifty-nine patients [21(36%) high grade neuroendocrine carcinoma with Ki 67 >20% (HG), 11(19%) pancreatic NETs (PNET), and 27(45%) carcinoid]. Twenty-seven (45%) pts were found to have SMs and 32 (55%) did not, with 5(10%) pts' tumors having >1 SMs (3 HG and 2 PNETs). Incidence of SM was 77% (16/21) in HG NETs, 38% (4/11) in PNETs and 23% (6/24) in carcinoids. Most common SMs in HG NETs were TP53 (30%), BRAF (18%), KRAS (12%) and PIK3CA/PTEN (15%) [Table 1]. Low grade (LG) NETs (Ki67$\leq$ 2%) of small intestine origin didn't harbor any mutations. Among the low-intermediate grade (LIG) NETs (Ki67$\leq$20%), incidence of SMs was higher in pts with progressive disease in the 6 months preceding enrollment than

those with stable disease [7/18 (33%) vs 2/20 (10%), *p=0.01*].

Table 1. Mutation distribution by site and grade

Site	High Grade (Ki67>20%)		Intermediate Grade (Ki67 2-20%)		Low grade (Ki67≤2%)	
	n/N	Mutation	n/N	Mutation	n/N	Mutation
Small Intestine	1/2	TP3	2/7	CTNNB1 PIK3CA	0/13	None
Colon	6/7	KRAS,TP53 BRAF, PIK3CA, Wnt, APC, RB1	1/2	KRAS	0/2	None
Pancreas	2/3	TP53, PIK3CA	4/10	KRAS, TP53, IDH-1, RB1	1/1	ATM
Unknown Other	7/8	PTEN, BRAF, APC, IDH1, TP53,CTNNB1, FBXW7	1/2	TP53	1/2	KRAS
Total	16/21 (77%)		7/20 (34%)		2/18 (11%)	

Conclusion: SMs are seen frequently in HG-NETs but are rare in LG-NETs. TP53, KRAS, BRAF and PIK3CA/PTEN mutations are common in HG carcinomas and PNETs. Higher mutational load in LIG-NETs is associated with higher chance of progressive disease on prior regimen which may affect future treatment. These findings provide a basis to develop new targeted therapy trials for NETs. Analysis of relationship of SM to clinical outcome based on treatment received is ongoing to assess their prognostic /therapeutic implications.