Genomic profiling of extrapulmonary high-grade neuroendocrine neoplasms reveals “actionable” mutations

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BACKGROUND

- Optimal therapy for extrapulmonary neuroendocrine carcinomas (EP-NEC) unclear – new therapeutic strategies urgently needed for refractory disease
- Previous analysis of EP-NEC cases in Foundation One database suggested >1/3 of patients with GEP-NEC harbor potentially “actionable” genomic alterations[1]
  - Analysis lacked access to original tumor samples for pathology review
  - Histopathology can be difficult to categorize
    - EP-NEC: Grade 3 (G3) poorly differentiated large and small cell NEC
    - Well differentiated G3 NET (neuroendocrine tumor)-pancreas
    - Ambiguous G3 morphology[2]
- As a follow-up study, we analyzed genomic alterations (identified as part of routine clinical care) in extrapulmonary G3 neuroendocrine neoplasms (EP-NENs) evaluated at UCSF

METHODS

- Performed retrospective chart review of 71 G3 EP-NEN cases evaluated at UCSF:
  - Histopathology review performed by UCSF pathologist
  - Genomic alterations assessed using CLIA-approved platform
    - 45 cases sequenced with UCSF500 assay[3]
    - 26 cases sequenced with Foundation One[4]
- “Actionability” defined based on OncoKB levels of evidence[5]
  - Main analysis focused on levels 1-2B

RESULTS

Table 1 – Characteristics of G3 NEN cohort by primary site

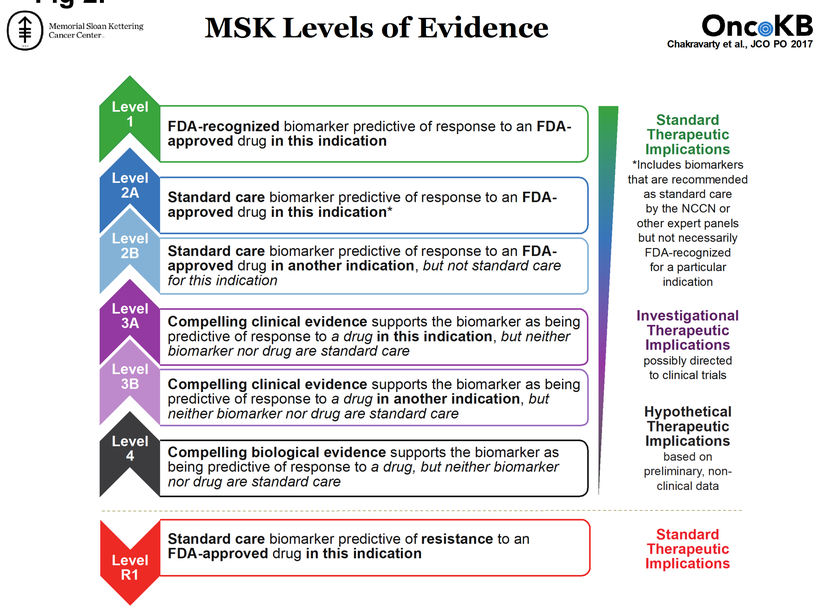
	Colorectal (N=19)	Pancreas (N=19)	Other (N=14)	Unknown (N=19)	Total (N=71)
Sidedness					
Left	12	-	-	-	-
Right	7	-	-	-	-
Sex					
Male	10	13	8	7	38
Female	9	6	6	12	33
All G3 NEN Ki67 (Median %)	77%	57%	82%	40%	60%
PD-NEC Ki67 (Median %)	80%	75%	87%	80%	80%
Age at Dx (Median Yrs)	58	57	63.5	55	58
Histologic Subtype					
G3 PD-NEC	15	4	12	9	40
G3 WD-NET	2	10	1	5	18
Ambiguous G3 NEN	2	5	1	5	13

- 71 cases included 19 colorectal (27%), 19 pancreas (27%), 14 other (20%), 19 unknown (27%)

Table 2 – Mutations predictive of response to FDA-approved therapies (in another indication) identified in 13 NEN cases (18%). PD-NEC in **BOLD**

			Level 1-2B	Biomarker with FDA-Approved Therapy in Another Indication
Patient ID	**Primary Site**	**Differentiation**	**Mutation(s)**	
1	Colorectal (Ascending colon)	G3 NET	BRCA1 & 2 deletion	
2	Pancreas	G3 NET	BRCA2 p.K1139fs	
3	**Unknown**	**PD-NEC**	**BRCA2 E1113***	
4	**Colorectal (Ascending colon)**	**PD-NEC**	**BRAF p.V600E**	
5	**Colorectal (Ascending colon)**	**PD-NEC**	**BRAF p.V600E**	
6	**Pancreas**	**PD-NEC**	**BRAF V600E**	
7	**Colorectal (Ascending colon)**	**PD-NEC**	**ERBB2 amplification**	
8	**Other GI (GE junction)**	**PD-NEC**	**ERBB2 amplification**	
9	Pancreas	Ambiguous	ERBB2 amplification	
10	Pancreas	Ambiguous	TSC1 Q55*	
11	**Colorectal (Ascending colon)**	**PD-NEC**	**MLH1 p.D485fs**	
12	Unknown	Ambiguous	CDK4 amplification	
13	Pancreas	Ambiguous	GPHN-RET fusion	

Fig 2.



CONCLUSIONS

- Genomic analysis of pathologically-confirmed EP-NENs reveals 18% with potentially “actionable” mutations
  - 7/40 (18%) PD-NEC cases also revealed actionable mutations, suggesting a role for targeted therapies (prospective studies needed).
- Need for novel treatment strategies for refractory disease
- Results suggest role for commercial platforms in identifying potential therapeutic targets in patients with G3 NEN

REFERENCES

[1] Bergsland et al., *NANETS* 2016
[2] Tang et al., *Clin Cancer Res*, 2016
[3] UCSF500 Cancer Gene Panel
[4] FoundationOne® Technical Information
[5] Chakravarty et al., *JCO PO* 2017