Prevalence of high tumor mutational burden (TMB-H) and microsatellite instability-high (MSI-H) status in neuroendocrine neoplasms.

Abstract #2625
Poster #280

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INTRODUCTION

- Neuroendocrine neoplasms (NENs) encompass a rare group of tumors arising in nearly any organ site.
- Patients with advanced-stage NENs have limited treatment options.
- Molecular profiling is not routinely performed in NENs.
- Given tissue-agnostic FDA approvals for immunotherapy in biomarker-selected solid tumors, we sought to assess the frequency of tumor mutational burden-high (TMB-H) and microsatellite instability high (MSI-H) in NENs overall and by organ site.

METHODS

- De-identified records retrospectively analyzed from the clinical Tempus database of NENs
  - Tissue sequenced with the Tempus xT assay (DNA-seq of 595-648 genes at 500x coverage)
  - Pathologic diagnosis abstracted from pathology reports
- Inclusion criteria:
  - Primary cancer arose in the lungs, GI tract (esophagus, stomach, small bowel, colon, rectum), pancreas, or prostate
  - Histologic diagnoses classified as:
    - NENs, including high grade or low/intermediate grade
    - Non-NENs (predominantly adenocarcinoma, squamous cell carcinoma)
- Molecular Features
  - TMB-H was defined as > = 10 mutations/megabase.
  - MSI-H was calculated as previously published (PMID: 31570899).
- Primary comparisons included NENs vs. Non-NENs & within NENs, low/int grade vs. high grade. Statistical comparisons were limited to groups of 10 or larger.

ACKNOWLEDGMENTS

Acknowledgements: We thank Vanessa M. Nepomuceno and the Scientific Communications for visualization and poster review.
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SUMMARY

- In this real-world NEN cohort, the **actionable molecular alterations** of TMB-H (13%) and MSI-H (0.9%) as assessed by the Tempus xT assay were observed.
  - Majority of TMB-H NENs were not driven by MSI-H status.
  - TMB-H prevalence (low/int grade 6.2%, high grade 16.5%) varied by organ site, predominantly driven by NENs of lung origin.
- Taken together, the data suggest that **molecular profiling** (regardless of grade) may **help identify** a small but meaningful subset of patients with GI, pancreas, lung or prostate NENs who **may benefit** from immunotherapy.
- The identification of **MSI-H NENs has important implications** related to germline testing.

RESULTS

Table 1. Baseline Patient and Tumor Characteristics

Characteristic	Non-Neuroendocrine Neoplasm Controls (pooled) N = 26,523 N(%)	Neuroendocrine Neoplasms (pooled) N = 1,477 N(%)	p-value[†]
Gender			<0.001
Male	15,859 (60%)	757 (51%)	
Female	10,595 (40%)	717 (49%)	
Age at Diagnosis, median (IQR)	65 (57, 73)	64 (57, 71)	0.003
Race*			0.003
Known	15,795 (56.4%)	933 (63.2%)	
White	12,376 (78%)^	774 (83%)^	
Black or African American	2,084 (13%)^	103 (11%)^	
Asian	612 (3.9%)^	19 (2.0%)^	
Other	723 (4.6%)^	37 (4.0%)^	
Unknown	10,728 (43.6%)	544 (36.8%)	
Ethnicity			0.012
Known	8,987 (32.1%)	432 (29.2%)	
Not Hispanic or Latino	7,900 (88%)^	397 (92%)^	
Hispanic or Latino	1,087 (12%)^	35 (8.1%)^	
Unknown	17,536 (67.9%)	1,045 (70.8%)	
Smoking status			<0.001
Known	20,293 (72.5%)	1,164 (78.8%)	
Never	7,132 (35%)^	345 (30%)^	
History of smoking	13,161 (65%)^	819 (70%)^	
Unknown	6,230 (27.5%)	313 (21.2%)	
Site of Primary Cancer			<0.001
GI	10,093 (38%)	224 (15%)	
Lung	9,736 (37%)	951 (64%)	
Pancreas	3,889 (15%)	220 (15%)	
Prostate	2,805 (11%)	82 (5.6%)	

[†] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test, Self-reported, ^represents total of "known" cohort*

Table 2. Neuroendocrine Neoplasm Grade

Grade	GI, N = 224	Lung, N = 951[†]	Pancreatic, N = 220	Prostate, N = 82
Low/Int Grade	142 (63%)	198 (21%)	171 (78%)	26 (32%)
High Grade	82 (37%)	749 (79%)	49 (22%)	56 (68%)
Unknown	0	4	0	0

[†] High grade lung included N=138 large cell neuroendocrine carcinoma and N=559 small cell neuroendocrine carcinoma.

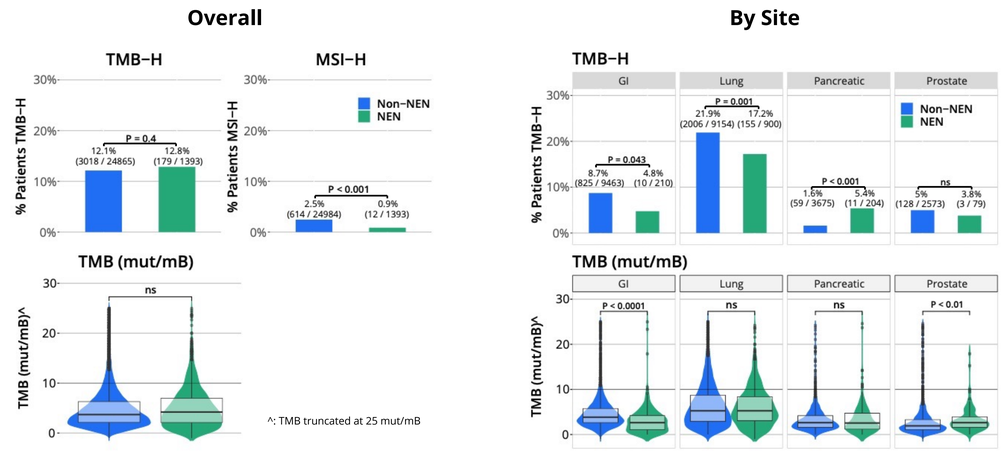

Figure 1. TMB-H and MSI-H Status of NENs vs. Non-NENs Overall and by Organ Site.

- MSI-H status was observed in 0.9% (N = 12) of NENs overall (0.9% high grade & 0.8% low/int grade), including in 0.4% (N = 4) lung, 1.4% (N = 3) pancreas, 1.9% (N = 4) GI, and 1.2% (N = 1) prostate.
- Of MSI-H cases, 96% (N=56/586) of non-NEN controls and 83% (N=10/12) of NENs were also TMB-H.
- Of TMB-H cases, 19% (N=566/3018) of non-NEN controls and 5.7% (N=10/179) of NENs were also MSI-H.

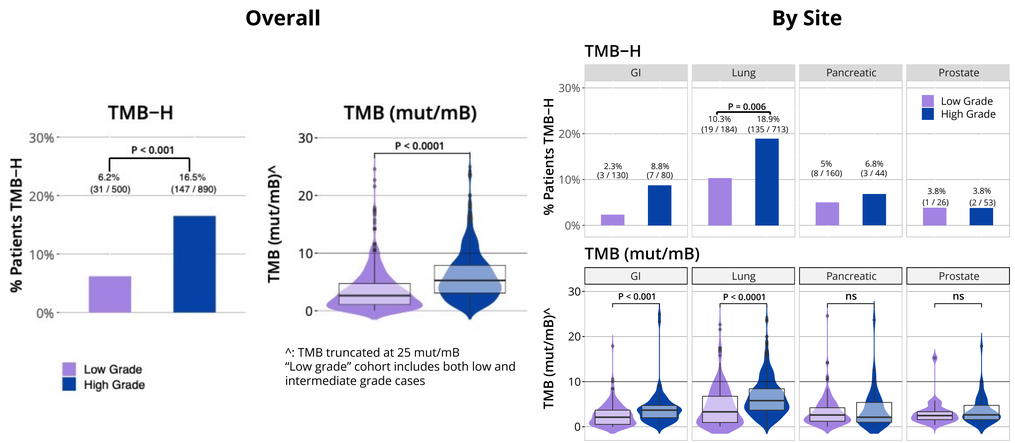

Figure 2. TMB-H Status of High Grade vs. Low/Int Grade NENs Overall and by Organ Site.

- Most patients with TMB-H lung NENs had a current or prior smoking history (94%, N = 119).
- TMB-H was most common in NENs arising in the lungs (17%, N = 155), followed by the pancreas (5.4%, N = 11), GI tract (4.8%, N = 10), and prostate (3.8%, N = 3).
- TMB-H comparisons of high vs. vs. low/int grade NENs by organ site (except lung) limited by sample size.