





NANETS

NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

ABSTRACT COMPENDIUM

2026 MULTIDISCIPLINARY NET MEDICAL SYMPOSIUM





B-1

Expression patterns of novel genomic markers in pulmonary versus extra-pulmonary small cell neuroend

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BACKGROUND

Extrapulmonary Neuroendocrine Carcinomas (EP-NECs) are a heterogeneous group of rare tumors with poor clinical outcomes. These patients have limited treatment options and they follow SCLC treatment. Although DLL3, SEZ6, and HEPACAM2 are novel markers for SCLC with several ongoing targeted therapy trials, there is not enough data to understand their role in EP-NECs.

METHODS

The Tempus Lens Platform was used to query the de-identified Tempus multimodal database to analyze a cohort of patients with a histological diagnosis of SCLC or extrapulmonary NEC with xT (DNA; 648 genes) xR (RNA; whole transcriptome) testing, and tumor purity of at least 30%. RNA-seq data were normalized and quantified as transcripts per million (TPM). Expression levels of DLL3, SEZ6, HEPACAM2, TACSTD2 (TROP2), BCL2L11, BBC3, BID, BCL2 (BH3), and CD276 (B7H3) were compared across subgroups of EP-NEC and SCLC patients. Wilcoxon rank-sum test was used for 2-groups; and Kruskal-Wallis test for 3+ groups comparisons and Spearman correlations for marker co-expression. Analyses were two-sided, with statistical significance evaluated at the 0.05 alpha level.

RESULTS

2242 SCLC vs 965 EP-NEC were compared. SCLC samples had significantly higher expression of DLL3, SEZ-6, HEPACAM2, and BCL2, while EP-NEC had higher TACSTD2,

BBC3, BID and CD276 expression (p <0.001). Among EP-NEC subgroups, small cell EP-NEC (EP-SC-NEC) had significantly higher DLL3, SEZ-6, HEPACAM2, and BCL2 expression and lower BID expression compared to large cell EP-NEC (EP-LC-NEC) (p <0.001). There were also differences among EP-NEC primary tumors, with higher SEZ-6 and HEPACAM2 but lower TACSTD2 and BID expression in gastrointestinal (GI), genitourinary (GU), breast, and gynecological (Gyn) EP-NEC compared to head and neck (H&N) EP-NEC. BCL2 expression was higher in breast and Gyn EP-NEC, while CD276 was higher in GU and H&N EP-NEC.

CONCLUSIONS

Although SCLC and EP-SC-NEC share profound histological and morphological similarities, our results highlight significant molecular variation between both groups. These unique genomic traits should inform clinical development of novel therapies and could impact therapeutic decisions for EP-NEC according to their morphological, cellular, and site of origin subtypes.

ABSTRACT ID #36597

B-2

Identification of a recurrent fusion oncogene as a potential therapeutic target in pancreatic neuroendocrine tumors

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BACKGROUND

Pancreatic neuroendocrine tumors (pNETs) are an understudied cancer type with few effective treatment options. The development of new treatment strategies has been limited by a lack of molecular targets, a challenge that stems at least in part from an incomplete understanding of the genetic drivers of this disease. Applying complementary molecular profiling approaches to a cohort of NET liver metastases, we identified a recurrent somatic gene fusion, *PSIP1::TBL1X*. The chimeric protein combines the N-terminal chromatin binding region of PSIP1 with the full coding sequence of TBL1X, an oncogenic transcriptional regulator and the target of the clinical-stage inhibitor tegavivint. Tegavivint is currently being tested in phase 1 and 1/2 trials across multiple solid tumor types, pointing to a potential therapeutic strategy for this molecular subtype.

METHODS

PSIP1::TBL1X was identified by optical genome mapping and confirmed by PacBio long-read RNA sequencing, amplification of the fusion junction from cDNA, and a novel dual-color dual-fusion FISH assay. Fusion prevalence was assessed across a cohort of primary and metastatic pNET specimens. To evaluate oncogenic function, the fusion was stably expressed in pNET cell lines via lentiviral transduction. Protein interactions were assessed by co-immunoprecipitation and western blotting.

RESULTS

PSIP1::TBL1X was identified in 11% of metastatic pNET specimens and was absent from a cohort of primary resection specimens. Three transcript variants were identified, joining *PSIP1* exon 4, 6, or 9 to *TBL1X* exon 4, which contains the start of the *TBL1X* coding sequence. Because the PSIP1::TBL1X protein retains the TBL1X domain targeted by tegavivint, the fusion represents a potential target for this agent in fusion-positive pNETs. The functional consequences of *PSIP1::TBL1X* expression and tegavivint response are

being evaluated in pNET cell lines to better understand the mechanisms of fusion-driven oncogenesis and the potential for therapeutic targeting in fusion-positive pNETs.

CONCLUSIONS

Discovered by integrating complementary molecular profiling technologies, *PSIP1::TBL1X* defines a novel molecular subtype of metastatic pNET. Because TBL1X is the target of the clinical-stage inhibitor tegavivint, this subtype may be amenable to a targeted therapeutic approach. These findings demonstrate that sensitive structural variant detection can uncover clinically actionable targets missed by conventional sequencing, expanding treatment options for patients with neuroendocrine neoplasms.

ABSTRACT ID #36575

B-3

Epigenetic MTAP Loss Expands the Therapeutic Window of PRMT5 Inhibition in Gastroenteropancreatic Neuroendocrine Tumors

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BACKGROUND

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), particularly small bowel NETs (sbNETs) and pancreatic NETs (pNETs), are increasingly diagnosed yet remain biologically underdefined and therapeutically challenging in patients with advanced disease. Their low mutational burden and immune-excluded biology limit current targeted and immunotherapy options. One emerging vulnerability centers on MTAP, the rate-limiting enzyme of the methionine salvage pathway. MTAP loss leads to methylthioadenosine (MTA) accumulation, partial PRMT5 suppression, and dependence on MAT2A-mediated S-adenosylmethionine availability, supporting PRMT5/MAT2A inhibition as a synthetic-lethal strategy in MTAP-deficient cancers. MTAP loss in most cancers arises from 9p21.3 co-deletion with CDKN2A, whereas well-differentiated GEP-NETs, particularly sbNETs, silence MTAP epigenetically while retaining an intact genomic locus. We investigated whether epigenetic MTAP loss is common in GEP-NETs and serves as a biomarker for therapeutic vulnerability.

METHODS

We assembled two GEP-NET cohorts (17 sbNETs, 20 pNETs; primary and metastatic) and assessed MTAP protein by IHC with paired copy number analysis of the MTAP locus. Mechanistic studies used QGP1 and NECT2 cell lines and patient-derived organoid models, including doxycycline (Dox)-inducible genetically modified PDOs (GM-PDOs) recapitulating features of parental G1/G2 tumors in the Dox-off state. MTAP protein was measured by western blot, and epigenetic regulation was tested with decitabine. The MTAP-PRMT5 axis was functionally assessed by MTA accumulation and global symmetric dimethylarginine (SDMA) level, a pharmacodynamic readout of PRMT5 activity. CRISPR-mediated MTAP knockout models tested causal sensitivity to PRMT5/MAT2A inhibitors.

RESULTS

Near-complete MTAP protein loss by IHC occurred in 13 of 17 sbNETs (76.5%) and 5 of 20 primary pNETs (25.0%). Copy number analysis showed retention of the MTAP locus in sbNET tumors with MTAP protein loss and their matched PDOs, indicating that MTAP loss is predominantly epigenetic rather than genomic. MTAP protein was similarly reduced across GM-PDOs and GEP-NET cell lines relative to MTAP-proficient controls despite an intact locus, and decitabine restored MTAP expression in both models, supporting epigenetic regulation. CRISPR-mediated MTAP knockout recapitulated the metabolic and signaling consequences of MTAP loss, increasing MTA accumulation, reducing global SDMA levels, and sensitizing GM-PDO and cell-line models to PRMT5/MAT2A inhibition.

CONCLUSIONS

These findings identify epigenetic MTAP loss as a frequent, functionally meaningful event in GEP-NETs, especially sbNETs. Despite an intact locus, epigenetic MTAP loss drives the MTA accumulation, PRMT5 suppression, and inhibitor sensitivity classically associated with genomic MTAP deletion, extending the MTAP-PRMT5 synthetic-lethal strategy beyond genomically deleted cancers to epigenetically silenced NETs and informing biomarker-driven therapy in other tumors with epigenetic MTAP loss.

ABSTRACT ID #36509

B-4

Validation of PAM expression in PNETs using Targeted Spatial Proteomics

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BACKGROUND

Pancreatic neuroendocrine tumors (PNETs) arise from pancreatic islets and are the second most common pancreatic cancer. Three clinical biomarkers, Synaptophysin (SYP), somatostatin receptor 2 (SSTR2), and Chromogranin-A (CGA), are currently used for diagnostic or theragnostic purposes. Due to the high degree of heterogeneity of marker expression across tumors, these current biomarkers do not adequately predict clinical outcomes, demonstrating the need for novel biomarker discovery. The protein Peptidylglycine α-amidating monooxygenase (PAM) is classically expressed in healthy neuroendocrine cells, and its expression has been shown to positively correlate with recurrence-free survival in NETs. However, its expression on a single-cell level is still uncharacterized in PNETs. In this pilot study, we examined how PNET biomarker positivity correlates with PAM expression using targeted spatial proteomics. Given its neuroendocrine functions, we hypothesize that PAM expression will be elevated in tumor cells positive for SYP and SSTR2.

METHODS

Our study screened for resected, sporadic, non-functional, grade 1/2 PNETS. This pilot analysis consists of twelve formalin-fixed paraffin-embedded tumor cores from eight patients, which were assembled into a tissue microarray (TMA). This TMA underwent multiplex immunofluorescence using the COMET platform, allowing for the simultaneous staining of all 12 samples for known PNET biomarkers (SYP, SSTR2, and CGA) as well as PAM. Image analysis was performed using a custom pipeline in Visiopharm and data analysis was performed in R. Tumor cells were defined by positive fluorescent signal for at least one of the three biomarkers: SYP, SSTR2, and CGA. Marker expression was measured as mean fluorescent intensity.

RESULTS

We performed a targeted proteomic analysis of PNETs at single-cell resolution in a pilot cohort of twelve specimens. We uncovered a remarkable degree of tumor heterogeneity in the expression of the 3 known PNET biomarkers (SYP, SSTR2, CGA) across patients. Samples had an average of 35,762 cells (range: 15,291-50,556) which on average contained 78.8% tumor cells (range: 49.5%-98.2%). PAM expression was compared between SSTR2(+)/SSTR2(-) and SYP(+)/SYP(-) tumor cell groups. PAM was found to have higher expression in both SSTR+ (1.35-fold; p=0.002) and SYP+ (1.9-fold; p=0.005) PNET cells.

CONCLUSIONS

We found that PAM expression is significantly elevated in PNET cells with higher SSTR2 or SYP expression using proteomic analysis at single cell resolution. Due to its inherent neuroendocrine properties, PAM is a potential marker of PNET differentiation. Future studies with expanded cohort size will expand upon defining tumor types to better understand the role of PAM, and if certain tumor subtypes predict clinical outcomes.

ABSTRACT ID #36570

B-5

Development of patients-derived NET organoids

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BACKGROUND

Neuroendocrine tumors (NETs) are clinically and biologically heterogeneous neoplasms with limited representative cell lines. Patient-derived organoids (PDOs) are three-dimensional cell culture models that recapitulate the molecular characteristics of the original tumors. In this study, we aimed to establish PDO from patients with well-differentiated NETs.

METHODS

Patients with a diagnosis of gastrointestinal NETs undergoing surgical resection as part of standard clinical care were prospectively enrolled. Tumor specimens were collected and minced into approximately 1 mm^3 fragments, then embedded in Matrigel and seeded in 24-well plates in culture media containing 30% of Wnt3a conditioned media and 10% R-Spondin-1 conditioned media supplemented with growth factors; hEGF, hFGF, huIGF-1. PDO growth was monitored every 48 hours by light microscopy, and images were acquired.

RESULTS

A total of four patient samples were collected from primary and metastatic sites, and PDO cultures were established. The following samples were collected: patient 1, a liver metastasis from a small bowel NET, grade 2; patient 2, a liver metastasis from a small bowel NET grade 1; patient 3, two liver metastases from a pancreatic, grade 1 NET; patient 4, a primary pancreatic NET, grade 3. All liver metastasis–derived samples demonstrated successful PDO growth, independent of primary tumor site or grade. Notably, patient 3-derived organoids from pancreatic primary liver metastases exhibited the most rapid growth. In contrast, PDO establishment from the primary pancreatic lesion was unsuccessful, and extensive tissue necrosis was observed in the specimen.

CONCLUSIONS

We successfully established PDO from liver metastases of patients with neuroendocrine tumors originating from the small bowel and pancreas, spanning grades 1 to 3. This

model represents a promising platform for preclinical drug testing and for studying NET biology.

ABSTRACT ID #36653

B-6

Integrated Bulk and Single-Cell Transcriptomics Identify Liver-Adaptive Tumor States in Metastatic siNET

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BACKGROUND

Liver metastasis is a major determinant of poor outcome in small-intestinal neuroendocrine tumors

(siNETs), yet mechanisms enabling metastatic adaptation remain unclear. Whether siNET liver

metastases simply reflect neuroendocrine (NE) tumor cells growing in hepatic tissue or include tumorassociated

cells with liver-adaptive transcriptional programs remains unknown. We hypothesized that

siNET liver metastases contain compartmentalized tumor states, including remodeled NE cells and liveradaptive

hepatocyte (hep)-like cells.

METHODS

Public bulk RNA-seq from GSE98894 was analyzed by differential expression and pathway enrichment

across primary and liver-metastatic siNETs. To validate these findings at single-cell resolution, we

analyzed five matched primary/metastatic siNET pairs using in-house scRNA-seq integrated with

Seurat/Harmony. Cell states were annotated using curated NE, hepatic, epithelial, stromal, and immune

markers. NE and hep-like clusters were analyzed by marker expression, module scoring, differential

expression, enrichment analysis, and Slingshot trajectory inference. Unresolved cells were refined into

expanded NE and hep-like compartments. Patient-aware pseudobulk differential expression,

inferCNV/CNV-like burden scoring, and DecontX ambient RNA correction assessed remodeling, tumor

association, and liver RNA contamination. A single-cell-derived NE/liver-adaptive/epithelial signature

was evaluated in 72 bulk siNET samples from GSE98894.

RESULTS

Bulk RNA-seq showed that siNET liver metastases upregulated liver/metabolic programs compared with

primary tumors. Single-cell clustering revealed distinct NE and hep-like populations within the metastatic

niche. NE clusters retained CHGA, CHGB, SYP, INSM1, PCSK1, and TPH1, whereas hep-like clusters

were enriched for TTR, APOA1, ALB, and fibrinogen genes. Pseudotime suggested remodeling across

primary- and metastasis-associated NE and hep-like states. Patient-aware pseudobulk identified 264

significant genes between metastatic and primary expanded NE cells and 139 between metastatic

expanded hep-like and metastatic expanded NE cells. Expanded hep-like and NE compartments showed

comparable inferCNV-derived CNV-like burden, higher than other cells, supporting tumor association of

a subset of hep-like cells. DecontX correction did not abolish the liver-adaptive program. In bulk

validation, the liver-adaptive score distinguished liver metastases from primary siNETs (FDR=7.85e-9;

AUC=0.922), and a hybrid score was also enriched in metastasis (FDR=8.72e-4; AUC=0.748).

CONCLUSIONS

Integrated bulk and single-cell transcriptomics support a model in which siNET liver metastases contain

remodeled NE compartments and a candidate tumor-associated liver-adaptive hep-like state. Defining

these compartment-specific states may nominate metastasis-associated programs for future therapeutic

targeting. Tissue-level validation is warranted to confirm NE, liver-adaptive, and epithelial marker coexpression

in metastatic tumor cells.

ABSTRACT ID #36555

B-7

Initial Cellular Characterization and Therapeutic Targeting of the Alternative Lengthening of Telomeres Phenotype in PNETs: Role of Telomeric Replication Stress

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BACKGROUND

A small subset of cancers (~10%) utilize a telomerase-independent telomere maintenance mechanism termed, Alternative Lengthening of Telomeres (ALT), which is present in ~40% of PNETs. Clinical studies have shown that ALT positivity in PNET patients correlates with both worse prognosis and clinical outcome. ALT+ cells have heightened levels of telomeric replication stress (stalling of the replication fork), which is believed to act as both a trigger and catalyst for ALT activity. ALT+ cancers are reliant on sustained replication stress-induced telomere damage to promote telomere elongation. Yet, replication stress and telomere damage levels must be kept within strict thresholds, and a fine balance must be struck to maintain cellular viability in ALT+ cancers. Importantly, relatively little is known regarding ALT in PNETs. With replication stress-induced DNA damage and its subsequent repair playing important roles in actively driving ALT, we are focused on selectively targeting key players and pathways pertinent to funneling the cause and effect of replication stress through the ALT phenotype in PNETs, for therapeutic benefit.

METHODS

Our overarching research goal is to selectively increase replication stress levels in ALT+ PNETs past a viable threshold. It was previously shown in ALT+ sarcoma cells that loss of FANCM, a DNA repair protein that limits replication stress, results in a “hyper-ALT” phenotype leading to massive replication stress-dependent cell death. As proof of concept for targeting ALT in PNETs, targeting FANCM, in our hands, involved inducible shRNA-mediated high-level knockdown of FANCM in ALT- (QGP-1) and ALT+ (NT18-P) PNET cell lines using a Dox-inducible lentiviral shRNA system. Cell viability was determined through clonogenic assays. Western blot analysis was performed to confirm FANCM knockdown and to quantify potential changes in replication stress levels.

RESULTS

Clonogenic assay results confirmed that targeting of FANCM, using our Dox-inducible lentiviral shRNA system, selectively decreased cell viability in the ALT+ PNET cell line, NT18-P. Western blot analysis confirmed high-level knockdown of FANCM in both PNET cell lines, with significantly higher levels of replication stress markers found in the ALT+ cell line.

CONCLUSIONS

ALT+ PNET cells are selectively sensitive to FANCM loss, with corresponding higher levels of replication stress and reduced cell viability. Ongoing studies are currently focused on targeting regulators of the ALT phenotype and replication stress management using small molecule inhibitors. With limited treatments for patients with advanced PNETs available, specifically targeting the ALT phenotype may offer innovative treatment regimens for nearly half of all PNET patients.

ABSTRACT ID #36611

B-9

Unmasking High-Grade (HG) Neuroendocrine Carcinoma (NEC) biology through transcriptomic profiling in lung and bladder cancer

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BACKGROUND

High grade neuroendocrine carcinomas (HGNECs), including small-cell (SC) and large-cell (LCNEC), are aggressive malignancies frequently misclassified due to subtle morphology and inconsistent use of neuroendocrine (NE) immunohistochemistry in routine pathology workflows. Whether transcriptomically defined tumors with HGNEC-like biology have inferior outcomes when treated conventionally is unknown. Leveraging a large real-world dataset, this study aims to identify biologically equivalent HGNEC to improve upon morphology-based classification.

METHODS

49,144 lung cancer and 13,087 bladder cancer specimens underwent DNA and RNA sequencing at Caris Life Sciences. Using a previously reported framework, we developed a weighted, z-scored based HGNEC activity score (HAS) from 10,137 pathologically defined HG- and LG- NEC specimens and applied it to characterize NSCLC and bladder cancer samples (lacking pathologist assigned HGNEC diagnosis) further stratified by histology. Overall survival (OS) was obtained from insurance claims data and calculated from specimen biopsy to last contact using Kaplan-Meier and Cox proportional hazards estimates. Where applicable, P values were adjusted for multiple hypothesis testing using the Benjamini–Hochberg method, with $q < 0.05$ considered statistically significant.

RESULTS

To identify a high-confidence HGNEC-like subpopulation, a HAS threshold (z-score>=3) was applied for NSCLC, classifying 0.2% squamous (sq) and 2.3% non-squamous (nsq) as HGNEC-like, consequently our analysis is focused in nsq. Patient demographics including age, gender, race, ethnicity and smoking history, were similarly matched between the HGNEC-like and non-HGNEC-like nsq-NSCLC. HGNEC-like neoplasms were associated

with poor OS (HR:1.18, 95% CI:1.07–1.31, p<0.001). In bladder cancers, applying a HAS cutoff of **1.5** identified 4.0% of papillary variant urothelial carcinomas (PUC) as HGNEC-like and were associated with significantly poorer overall survival (HR, 1.39; 95% CI, 1.01–1.92; p=0.045).For nsq-NSCLC, HGNEC-like neoplasms were enriched for mutations in *TP53*, *PTEN*, *RUNX1*, *MTOR* and *RB1* (OR: 1.7-14.1), as well as amplifications in *MYC* and *CCNE* (OR: 2.2–3.5). These neoplasms were also predominantly PDL1 negative (64 vs 47%) with significantly lower odds of *KRAS* and *EGFR* mutations (OR: 0.4–0.5, all p-adj<0.05). Consistent with a highly proliferative phenotype, nsq-NSCLC HGNEC-like neoplasms were enriched for replication rates (3.0-fold) and cell-cycle scores (1.5-fold, all p-adj<0.05). Similar molecular features were observed in HGNEC-like PUC, including increased odds of *TP53* and *RB1* mutations (OR: 1.7–10.0), *MYC* amplification (OR: 2.5), elevated replication rates (1.3-fold), and higher cell-cycle scores (1.5-fold, all adjusted p<0.05.Finally, HGNEC-like neoplasms demonstrated significantly increased transcriptomic expression of clinically actionable NE targets, including *DLL3* (10-fold), *SEZ6* (3.7-fold), *SEZ6L* (10-fold), and *SSTR2* (10-fold) in nsq-NSCLC, as well as *DLL3* (5-fold) and *SEZ6* (2.6-fold) in PUC (all p-adj<0.05).

CONCLUSIONS

We identify a transcriptomically defined subset of NSCLC and PUC with HGNEC-like biology, inferior survival and potential therapeutic targets. These observations support using transcriptomics to complement morphology-based classification in a multimodal approach to inform clinical trial design and identify NEC-targeted therapies in lung and bladder cancer.

ABSTRACT ID #36596

B-10

Tumor Microenvironment Remodeling Mediates Resistance to 177Lu-DOTATATE in Metastatic Well-Differentiated Neuroendocrine Tumors

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE improves progression-free survival in advanced neuroendocrine tumors (NETs), yet responses remain highly variable. The tumor microenvironment (TME) may be a key determinant of PRRT response. We characterized immune changes within the TME to elucidate immunomodulatory effects and identify potential combination strategies.

METHODS

Tumor tissues were obtained from two patient cohorts treated at UChicago Medicine: one undergoing surgical debulking after PRRT, with lesions classified as non-progressing or progressing, and a second undergoing paired pre- and post-PRRT debulking. Samples included small bowel NET (SBNET) and pancreatic NET (PNET) primary tumors and liver metastases (58 lesions, 13 patients). Six-plex multiplex immunofluorescence (CD4, CD8, CD68, FoxP3, PD-L1, CD31) quantified immune features at single-cell resolution. Tumor-intrinsic features (Ki-67, SSTR2, CA9, γH2AX, and CD31) were assessed by immunohistochemistry. Clinical-grade genomic profiling was performed using the OncoPlus next-generation sequencing panel for all patients. Bulk RNA sequencing with immune deconvolution was performed on 23 liver metastases.

RESULTS

Progressing tumors exhibited elevated CD8$^+$ T-cell infiltration compared with non-progressing tumors in post-PRRT lesions (275.8 vs. 101.3 cells/mm^2; p=0.020), with increased PD-L1 positivity on CD68$^+$ macrophages (0.93% vs. 0.18%; p=0.0047) and on other tumor compartments (0.90% vs. 0.10%; p=0.0085). Spatially, macrophages were

closer to $CD8^+$ T cells in progressing tumors (35.0 vs. 100.8 µm; p=0.0045). Progressing tumors had lower SSTR2 expression in post-PRRT lesions (p=0.0068). CD31 IHC cross-validated mIF endothelial density (p=0.001), positively correlated with macrophage infiltration (p=0.0003), and inversely correlated with $CD8^+$ T-cell density (p=0.001). Transcriptomic profiling identified subtype-specific resistance programs: PNETs were enriched for ECM-receptor interaction (FDR=1.9×10^{-4}) and PI3K-Akt signaling (FDR=4.7×10^{-4}), while SBNETs were enriched for epithelial-mesenchymal transition (FDR=7.1×10^{-9}) and TNFα-NFκB signaling (FDR=0.013). Immune deconvolution confirmed enrichment of fibroblasts, plasma cells, neutrophils, and non-classical monocytes with depletion of endothelial and dendritic cell populations. Tumor mutational burden showed no relation to the derived TME metrics, while mutation-detected SBNETs showed higher endothelial density than mutation-negative SBNETs (275.4 vs. 198.0 cells/mm^2; p=0.029).

CONCLUSIONS

PRRT resistance might operate through a two-hit mechanism: $CD8^+$ T cell infiltrates suppressed by PD-L1-mediated checkpoint engagement, compounded by reduced SSTR2 mediated drug delivery. Tumor vascularity independently drives immunosuppressive macrophage recruitment and T cell exclusion across this cohort. These findings support further pre-clinical investigation of PD-1/PD-L1 checkpoint inhibitor and anti-VEGF combinations with PRRT in patients with progressive NETs.

ABSTRACT ID #36556

B-11

Loss of nuclear Menin alters lipid homeostasis in pancreatic neuroendocrine tumor cells

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BACKGROUND

Background: Reduced expression of nuclear Menin encoded by the *MEN1* gene is a common feature in *MEN1*-mutated and *MEN1*-unaffected pancreatic neuroendocrine tumors (PanNETs). Prior studies have largely relied on genetic knockdown approaches to modulate Menin expression levels, however the impact of recent Menin inhibitors (MIs) on subcellular Menin expression and its tumor suppressor function are less understood. Here, we launch an original investigation to define the downstream consequence of MI-mediated Menin regulation in the pathogenesis of PanNETs.

METHODS

Methods: We evaluated the impact of three MIs, MI-503, MI-3454, and Ziftomenib, on Menin protein expression in an established human PanNET cell line (BON-1). Nuclear-to-cytoplasmic shuttling of Menin in response to small molecule inhibition was evaluated by western blot and immunofluorescent staining. Bulk RNA sequencing (RNA-seq) was performed to identify differentially expressed pathways resulting from loss of nuclear Menin. The functional consequence of Menin loss was evaluated using an MTT assay, crystal violet staining, and BrdU incorporation in the presence and absence of statin-mediated cholesterol inhibition. Lastly, surgically resected PanNETs were evaluated for dysregulated lipid homeostasis using quantitative PCR, western blot, and immunohistochemical staining.

RESULTS

Results: Menin inhibition using MI-503, MI-3454, and ziftomenib led to a decrease in Menin total protein expression in BON-1 cells. At the subcellular level, MIs induced nuclear export of Menin in a dose-dependent manner. Low-dose treatment with MI-3454 and ziftomenib increased cell proliferation, whereas treatment with MI-503 elicited the opposite effect. Menin inhibition strongly upregulated the expression of genes mapped to cholesterol biosynthesis, including *HMGCS1, HMGCR, ACAT2, SQLE, IDI1, LSS,* and *FDFT1* and this was consistent with decreased expression of the lipid efflux transporter *ABCG1*. Treatment of BON-1 cells with atorvastin led to a dose-dependent reduction in cell proliferation, suggesting a potential role for dysregulated lipid homeostasis in driving tumor cell growth.

CONCLUSIONS

Conclusions: These studies raise a potential role for altered lipid homeostasis downstream of nuclear Menin loss. Future work will focus on dissecting the mechanism and clinical relevance of targeting this pathway in expanded PanNET models.

ABSTRACT ID #36614

B-12

Allosteric ClpP agonist JZP3507 (formerly ONC206) alters mitochondrial metabolism, stress response and chromatin accessibility to elicit apoptosis in pheochromocytoma

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BACKGROUND

JZP3507 (formerly ONC206), a second generation imipridone, is a caseinolytic protease P (ClpP) agonist and dopamine receptor D2/3 (DRD2/3) antagonist with nanomolar potency. Dordaviprone demonstrated responses in patients with pheochromocytoma-paraganglioma (PCPG). We characterized the mechanism of action, in vitro efficacy, response determinants and acquired resistance for JZP3507 in PC.

METHODS

ClpP was expressed in E. coli and purified by His-tag affinity for biochemical assays. PC (hPheo1, PC12, MPC10) and fibroblast (HFF-1, MRC-5) cells were commercially sourced. Cell viability (CellTiter-Glo, CyQuant), apoptosis (Caspase Glo, annexin V) assays, seahorse analysis, and multi-omics were conducted in PC cells treated with vehicle/JZP3507. Resistant hPheo1 cells were generated by passaging with increasing JZP3507 concentrations.

RESULTS

Co-crystallization with ClpP revealed an allosteric ligand interaction with distinctions in the JZP3507-ClpP resolved crystal structure relative to the dordaviprone-bound or apo complexes. JZP3507 was a more potent agonist than dordaviprone in cell-free human ClpP casein/peptide assays. Adrenal gland tumors emerged as most sensitive when JZP3507 cytotoxicity was assessed in a panel of 432 human cancer cell lines. JZP3507 induced dose- and time-dependent apoptosis in PC but not fibroblast cells. JZP3507 demonstrated stronger cell viability inhibition and/or apoptosis induction in PC lines relative to dordaviprone, temozolomide, sunitinib, and belzutifan at equivalent and/or therapeutically relevant concentrations. In hPheo1 cells, CRISPR-mediated SDHB or FH knockout and DRD2 overexpression did not impact JZP3507 sensitivity while ClpP knockout impaired JZP3507 sensitivity. Proteomics indicated inhibition of mitochondrial metabolism by JZP3507, including OXPHOS/TCA cycle while metabolomics revealed elevated α-ketoglutaric acid, 2-hydroxyglutaric acid and reduced succinic acid, fumaric acid in a ClpP-dependent manner. Consistent with epigenetic regulation by metabolites,

ATACseq revealed JZP3507 altered chromatin accessibility while RNAseq demonstrated upregulated stress response, apoptosis and downregulated metabolism-related pathways. Western blot confirmed JZP3507 downregulated mitochondrial proteins, neuroendocrine markers and upregulated stress response. JZP3507 reduced chromogranin A secretion by ELISA in hPheo1 cells that underwent neuroendocrine differentiation. PCR and western blot of acquired resistant cells revealed ClpP silencing in some resistant lines, confirmed by ATACseq. Whole exome sequencing revealed diverse ClpP missense and/or termination mutations. Seahorse analysis showed JZP3507 inhibited mitochondrially derived ATP in parental but not acquired resistant lines. Overexpression of ClpP missense mutations in wt cells conferred resistance while overexpression of wt ClpP restored JZP3507 sensitivity in acquired resistant lines.

CONCLUSIONS

JZP3507 is a potent novel agent that is superior to SOC and dordaviprone in PC. ClpP mediates response and acquired resistance to JZP3507 in PC.

ABSTRACT ID #36607

B-13

Cardiac Arrhythmogenic Sensitivity in a Rat Model of Neuroendocrine Tumor Metastasis

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BACKGROUND

Neuroendocrine tumor (NET) metastasis poses a significant risk to cardiovascular health. Patients with NET metastases exhibit hemodynamic instability, characterized by tachycardia, syncope, and cardiac arrythmias. These events may be attributed to the vasoactive hormones secreted by NETs, but the specific physiologic mechanisms are not known. Therefore, accurate animal models are needed to investigate the impact of NETs on cardiovascular function.

Our NET mouse model with identifiable liver metastases demonstrates baseline electrocardiographic (ECG) abnormalities, lower thresholds for epinephrine-induced arrhythmias, and altered vascular function. Building on these findings, this pilot study sought to develop a novel rat model of NET liver metastasis to evaluate mechanisms underlying altered hemodynamic responsiveness. We hypothesized that similar to our mouse model, this rat model would exhibit liver NET metastases and a sensitized risk for cardiac arrhythmic events.

METHODS

Anesthetized (3-5% isoflurane in 100% O_2) male NIH-nude rats received intrasplenic injections of 5-15x10^6 BON-1 NET cells (BON-1, n=4) or Dulbecco's Phosphate Buffered Saline (VEH, n=2) and monitored for 14 weeks. Resting 10-minute ECG tracings were recorded every two weeks to assess for ECG irregularities. At the14-week timepoint, intraperitoneal injections of epinephrine (0.01-2mg/kg) were given to induce cardiac arrhythmias in all NIH-nude rats (n=6) and an additional cohort of age-matched male Sprague Dawley rats (SD, n=3). The VEH and SD rats were combined into the control (CON) group. Cardiac arrhythmias were identified as abnormal deviations in the P wave, QRS complex, and/or T waves relative to normal sinus rhythm. Liver samples from BON-1 and VEH rats were sectioned and assessed for tumor presence by hematoxylin & eosin (H&E) staining. Percent occurrence of arrhythmias were compared by Chi-squared test, with significance set at $p<0.05$.

RESULTS

Liver tumor metastases were present in all BON-1 rats, and absent in VEH rats. Spontaneous baseline cardiac arrhythmias were not present in VEH or BON-1 rats during tumor development. However, the overall occurrence of epinephrine-induced arrhythmias was higher in BON-1 (60%) compared to CON (29%, $p<0.01$). Lower doses of epinephrine (0.01-0.1mg/kg) triggered arrhythmias in 75% of BON-1 rats ($p=0.18$). CON rats developed comparable arrhythmias starting at 0.2mg/kg epinephrine.

CONCLUSIONS

These data confirm the successful development of a NET rat model characterized by the presence of liver NET metastases and a sensitized induced arrhythmia threshold. This model parallels key cardiac abnormalities observed in our NET mouse model, providing a viable rodent model to investigate the influence of NET metastasis on cardiovascular function.

ABSTRACT ID #36410

B-14

BH3-mimetics synergise with systemic therapies to induce apoptosis in patient-derived neuroendocrine tumour organoids

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BACKGROUND

Neuroendocrine tumours (NETs) are growing rapidly in prevalence, yet current systemic treatments result predominantly in prolonged disease stabilisation, necessitating novel approaches to induce objective tumour regression and prevent recalcitrant disease. Single-cell transcriptomic profiling of NET patients demonstrated expression of the BCL2 family of apoptosis inhibitors—comprising BCL-2, BCL-w, BCL-xL, and MCL-1—which may contribute to cancer cell persistence following treatment. We hypothesised that BH3-mimetics, drugs targeting the BCL2 family, may induce cell death in NETs and represent an effective therapy, either alone or in combination with existing standard-of-care (SOC).

METHODS

NET patient-derived organoids (PDOs) were established from fresh, surplus surgical specimens, cultured for 3–4 weeks in hydrogel-coated 384-well plates, and treated with combinations of BH3-mimetics and SOC agents. Treatment response was assessed by confocal imaging using fluorescent, non-toxic dyes to measure metabolic activity and Annexin V to detect apoptosis. Further characterisation by Western blotting and RNA-seq were also conducted to validate the pro-apoptotic mechanisms of BH3-mimetics in NET cells.

RESULTS

We have established PDOs from primary (small intestine, pancreas, colon) and metastatic (lymph node, liver) low-grade, well-differentiated NETs with >90% success, and validated their expression of neuroendocrine markers and key apoptosis regulators at both RNA and protein levels. Inhibition of all anti-apoptotic BCL2 proteins with a combination of BH3-mimetics resulted in prominent cell death alongside upregulation of apoptosis markers Annexin V, cleaved Caspase-3, and cleaved PARP, indicating an active apoptotic machinery in NETs. The drug-specific modulation of different BCL2 proteins was also confirmed, suggesting that the observed cell death is an on-target effect of BH3-mimetics. Next, treatment with BH3-mimetics specific to single BCL2 proteins identified MCL-1 to be essential, but not sufficient, for NET survival. Finally, we found Pelcitoclax—a well-tolerated BH3-mimetic in clinical studies—to effectively induce cell death when combined with current NET SOCs, while the single treatments exhibited a significantly lower effect. A strong synergistic effect was observed when Pelcitoclax was combined with Cabozantinib or Sunitinib, and to a lesser extent with Everolimus, while no synergy was observed with Octreotide.

CONCLUSIONS

This study demonstrates that the apoptotic machinery of well-differentiated neuroendocrine tumours is active and that their survival depends on the activity of BCL2 family proteins. Inhibition of these proteins by BH3-mimetics combined with SOC effectively induces cell death in patient-derived preclinical models. Overall, our data warrant investigating BH3-mimetics with SOC in patients with NETs as a novel therapeutic approach.

ABSTRACT ID #36601

B-15

Tumor microenvironment features in extrapulmonary neuroendocrine carcinomas for predicting response to immunotherapy and platinum-based therapy

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BACKGROUND

Extrapulmonary neuroendocrine carcinomas (EP-NECs) are rare, aggressive, and poorly understood tumors that lack reliable biomarkers. Moreover, standard Ki-67 immunohistochemistry (IHC) does not always predict therapeutic response. To address this gap, we analyzed the tumor microenvironment (TME) transcriptome of EP-NEC to uncover markers of response to immunotherapy and platinum-based chemotherapy.

METHODS

The BostonGene (BG) Tumor Portrait® test was used to analyze 15 EP-NEC samples. Their signature scores were computed using modified ssGSEA and median-scaled relative to the BG NEC reference cohort. Each sample was then classified using the KNeighborsClassifier algorithm as immune-enriched, fibrotic; immune-enriched, non-fibrotic; fibrotic; or immune desert.

RESULTS

Three TME subtypes were identified: immune-enriched, non-fibrotic (n = 3), fibrotic (n = 8), and immune desert (n = 4). The immune-enriched TME was associated with favorable response to immunotherapy, while the immune desert TME was linked to disease progression (Fisher's p = 0.03). The partial response group showed at least a twofold higher concentration of CD4 and CD8 T-cells than the stable and progressive disease groups. No association was found between TME subtype and response to first-line therapy carboplatin/etoposide ± atezolizumab, while RNA-seq-derived MKI67 expression

showed a stronger correlation in stratifying response to platinum-based chemotherapy than Ki-67 IHC.

CONCLUSIONS

Transcriptomic profiling of the TME for EP-NEC revealed an immune-active TME corresponding to a greater likelihood of response to immunotherapy. Expandable to other cancer types, our approach can enhance patient stratification, treatment response prediction, trial design, and biomarker discovery.

ABSTRACT ID #36640

C-1

Efficacy and Safety of Cabozantinib in Advanced Neuroendocrine Tumors By Hormone Functional Status: Subgroup Analysis of Phase 3 CABINET Trial

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BACKGROUND

In the CABINET trial (Alliance A021602), cabozantinib (CABO) significantly prolonged progression-free survival (PFS) compared to placebo (PB) in patients (pts) with advanced, previously treated extrapancreatic NET (epNET) or pancreatic NET (pNET) (Chan et al., NEJM, 2025). Here we report outcomes according to functional status based on hormone secretion.

METHODS

Pts with progressive, locally advanced or metastatic epNET or pNET were randomized 2:1 in separate cohorts to receive CABO 60 mg daily vs PB. Pts with functional NET due to hormone secretion and non-functional NET were included. In this post hoc analysis, we analyzed PFS by blinded independent central review and adverse events (AEs) for pts receiving CABO vs PB according to functional status. Cox regression models were used with stratification on primary tumor site (epNET vs pNET). Subset analyses were conducted in pts with functional and non-functional tumors. Due to small numbers, results for those with unknown functional status are not included.

RESULTS

Among 298 pts enrolled in both cohorts, 74 had functional NET (CABO, n=47; PB, n=27); 179 had non-functional NET (CABO, n=123; PB, n= 56); 45 had unknown functional status (CABO, n=28; PB, n=17). For functional NET, primary tumor sites were GI tract (n=50; 68%), pancreas (n=15; 20%), unknown (n=4; 5%), lung (n=3; 4%), thymus (n=2; 3%). Secreted hormones that were reported included serotonin (55%), somatostatin (18%), gastrin (16%), glucagon (4%), insulin (4%), ACTH (1%), VIP (1%). For non-functional NET, primary tumor sites were pancreas (n=75; 42%), GI tract (n=42; 23%), lung (n=30; 17%), unknown (n=17; 9%), thymus (n=8; 4%), other (n=7; 4%). Concurrent SSA was received by 91% and 53% of pts with functional and non-functional NET, respectively. In both subgroups, CABO was associated with improved PFS compared to PB (functional NET: stratified hazard ratio [sHR], 0.40; 95% confidence interval [CI]: 0.20-0.82, P= 0.012; non-functional NET: sHR, 0.26; 95% CI: 0.17-0.41, P<0.001). The most frequent grade 3/4 AEs attributed to CABO vs PB in pts with functional NET included hypertension (21% vs 11%), diarrhea (9% vs 11%), and fatigue (2% vs 15%); in pts with non-functional NET, grade 3/4 AEs included hypertension (21% vs 4%) and fatigue (18% vs 4%).

CONCLUSIONS

Subset analyses of the CABINET trial suggest that CABO is effective in pts with functional or non-functional epNET or pNET. Efficacy and safety results for pts with functional or non-functional NET treated with CABO are consistent with results for the entire trial.

Support: U10CA180821, U10CA180882; U10CA180820 (ECOG-ACRIN); U10CA180868 (NRG Oncology); U10CA180888 (SWOG); 5U24CA180803 (IROC); Exelixis; NCT03375320.

ABSTRACT ID #36579

C-2

Cabozantinib in high grade neuroendocrine neoplasms.

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BACKGROUND

High grade neuroendocrine neoplasms (HG-NENs) are commonly treated with chemotherapy but progression is common and salvage options are limited in efficacy. Cabozantinib (CABO), a multikinase inhibitor (VEGFR, MET, TYRO3, AXL, and MER) was approved by the FDA for treatment of well differentiated (WD) NENs of both pancreatic and extrapancreatic origins. However, its efficacy in the whole spectrum of HG-NEN patients has not been prospectively explored.

METHODS

This was a single institution, Phase II study. Key inclusion/exclusion criteria were NENs of any origin except SCLC, high grade by Ki-67 of > 20%, ECOG of < = 1, appropriate CBC, no history of bleeding or active cardiac disease. CABO was given orally starting at 60 mg po daily in 3-week cycles. The primary endpoint of this study was overall response rate (ORR). Secondary endpoints included progression free survival (PFS) and overall survival (OS). A Simon optimal 2-stage design tested the null hypothesis that the true ORR is < = 1% at the type I error rate of 5%, resulting in projected enrollment of up to 32 total patients. Toxicities were graded according to CTCAE v5.0 and response was evaluated according to RECIST v1.

RESULTS

All patients have been accrued, with 4/32 patients still on treatment. Median age was 62 years, male:female ratio was 1.46. Origin of tumor was GI (68.8%), thoracic (6.3%), prostate (6.3%) cervical (6.3%) head/neck (3.1%) and unknown (9.4%). Median Ki-67 was 55%, 11 patients had Ki-67 > 70%. Histology was WD-HG (40%) and PDD (60%). Two patients had mixed PDD/other components (MiNEN). Median PFS in evaluable patients was 4.01 months [95% CI 2.66 to 9.30] and mOS was 9.97 mo [95% CI 6.73 to 20.96]. Three patients so far (9.3%) have had partial response as best response (PDD-colon, WD-pancreas and PDD-cervical) while 19/32 (59.4%) patients have had stable disease as best response so far

(disease control rate 68.8%). Five (15.6%) patients have received more than 10 treatment cycles. The three longest treated patients had WD-pancreas (23 and 17 cycles) and PDD-unknown (12 cycles). One patient post resection of a metastatic site is currently without evidence of disease. Three patients withdrew because of toxicities (shortness of breath, GI bleeding, thromboembolism). Twenty-six patients have expired.

CONCLUSIONS

CABO monotherapy showed efficacy in some HG-NEN patients including PDD with no unexpected side effects. Supported by Exelixis and a Siteman investment program grant. Clinical trial information NCT04412629.

ABSTRACT ID #36628

C-3

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

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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.

ABSTRACT ID #36571

C-4

DOTATATE PET/CT at Diagnosis Is Associated With Decreased Mortality in Gastroenteropancreatic Well-Differentiated Neuroendocrine Tumors: A Propensity-Matched Retrospective Cohort Study

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BACKGROUND

Advanced functional imaging with Copper-64 or Gallium-68 DOTATATE PET/CT has become integral to the evaluation of well-differentiated gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs), but it remains unclear whether it is associated with significant survival benefit.

METHODS

A retrospective cohort study using the TriNetX US Collaborative Network (2018–2023) identified adults with well-differentiated neuroendocrine neoplasms of the stomach, small intestine, pancreas, or large intestine/appendix/rectum. Patients undergoing DOTATATE PET/CT within 6 months were compared with those without imaging. One-to-one nearest-neighbor propensity score matching was performed using demographics and major comorbidities. Kaplan-Meier and Cox models estimated hazard ratios (HRs) with 95% CI.

RESULTS

Among 13,632 patients, 1,960 (14.4%) underwent DOTATATE PET/CT within 6 months. After matching, cohorts included stomach (192 vs 192), small intestine (1,207 vs 1,207), pancreas (179 vs 179), and large intestine/appendix/rectum (380 vs 380). DOTATATE use was associated with significantly increased 5-year survival rate in pancreatic primaries (72.2% vs 60.9%, HR 0.50, p=0.001) and large intestinal/appendiceal/rectal primaries (80.9% vs 77.4%, HR 0.68, p=0.037). Small intestinal tumors demonstrated lower mortality at 1 year (HR 0.48, 95% CI 0.32–0.71; p<0.001) and 3 years (HR 0.76, 95% CI 0.59–0.97; p=0.028), without difference at 5 years. No significant differences were observed in gastric primaries.

CONCLUSIONS

DOTATATE PET/CT within 6 months of diagnosis was strongly associated with improved 5-year survival rate in pancreatic and large intestine/appendix/rectum well-differentiated neuroendocrine neoplasms. This association may reflect improved survival among patients treated at multidisciplinary centers with access to neuroendocrine-specific imaging, although further investigation is needed to clarify this relationship.

ABSTRACT ID #36631

C-5

Bowel Obstruction in Patients with Neuroendocrine Tumor (NET) Treated With ^{177}Lu-DOTATATE: A Comparative Cohort and Time-to-Event Analysis

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BACKGROUND

Previous studies have suggested that peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE may increase the risk of bowel obstruction (BO). This may particularly happen in patients with mesenteric or peritoneal disease, possibly due to radiation-induced inflammation and exacerbation of desmoplastic fibrosis. However, most studies lacked non-PRRT control groups, limiting the ability to distinguish PRRT effects from the natural history of advanced disease or known risks of BO from prior bowel surgery. We compared BO rates between patients with NET who received PRRT and those who did not, and identified independent risk factors using multivariate and time-to-event analyses.

METHODS

We conducted an Institutional Review Board-approved retrospective cohort study of 492 patients with NET, including 211 treated with PRRT and 281 without PRRT. BO occurrence, timing relative to PRRT, and clinical covariates (including pre-treatment bowel resection, peritoneal carcinomatosis, liver metastases, and primary tumor site) were analyzed. BO events were cross-referenced with PRRT dosing dates to identify episodes occurring within 3 months of treatment. Multivariate logistic regression evaluated factors associated with BO. Because the PRRT cohort had longer follow-up (median 9.1 vs 6.7 years, $p<0.001$), sensitivity analyses included incidence rate comparisons, Kaplan–Meier estimation, and Cox proportional hazards modeling.

RESULTS

Crude BO rates were higher in the PRRT group (30.3% [64/211] vs 22.1% [62/281]; OR 1.54, 95% CI 1.02–2.31, p=0.047). However, PRRT patients had significantly more advanced disease, including higher rates of peritoneal carcinomatosis (31.8% vs 13.9%), liver metastases (100% vs 61.2%), and stage IV disease (92.9% vs 72.2%). Among PRRT patients with BO, 89.1% (57/64) had events before PRRT initiation. Only 5 patients (2.4%) developed BO within 3 months of treatment, while the remaining post-PRRT events occurred a median of 15 months later. On multivariate logistic regression, PRRT was not an independent predictor of BO (OR 1.02, 95% CI 0.49–2.11, p=0.97), whereas prior bowel

resection (OR 7.14, p<0.001) and peritoneal carcinomatosis (OR 4.17, p<0.001) were significant. Similarly, Cox regression confirmed PRRT was not associated with increased BO risk (HR 1.28, 95% CI 0.80–2.04, p=0.30), while bowel resection (HR 5.27, p<0.001) and peritoneal carcinomatosis (HR 2.51, p<0.001) remained independent predictors.

CONCLUSIONS

After multivariable adjustment, PRRT was not an independent risk factor for BO. Prior bowel resection and peritoneal carcinomatosis are the dominant predictors for BO in NET. Previously reported PRRT–BO associations may reflect confounding by indication rather than a direct treatment effect.

ABSTRACT ID #36637

C-6

Hematologic Effects of Splenectomy in Patients with Pancreatic Neuroendocrine Tumors who Receive ^{177}Lu-DOTATATE PRRT

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) can cause hematologic toxicity, but its longitudinal pattern and the impact of prior splenectomy remain poorly defined. In pancreatic neuroendocrine tumors (pNET), distal pancreatectomy with splenectomy is common and usually leads to elevated baseline platelet and leukocyte counts. We characterized PRRT-associated hematologic changes and evaluated how splenectomy modifies absolute and proportional cytopenias, using non-PRRT treated patients as controls.

METHODS

We retrospectively analyzed 227 patients with pNET across four groups: PRRT with splenectomy (n=30), PRRT without splenectomy (n=54), non-PRRT treated with splenectomy (n=55), and non-PRRT treated without splenectomy (n=88). Approximately 55,000 serial hemoglobin, platelet, WBC, MCV, and RDW values were modeled longitudinally. Outcomes included per-patient percent change from baseline, worst CTCAE grade, and multivariable logistic regression of any-grade cytopenia adjusted for baseline count and follow-up duration.

RESULTS

Groups were similar in age, sex, and race. Within treatment arms, splenectomy was not associated with disease characteristics; PRRT patients had higher-grade tumors and more metastatic disease. Splenectomy was associated with higher baseline platelets (median 280 vs 194×10^9/L; p<0.001) and WBC (7.6 vs 5.3×10^9/L; p<0.001). After PRRT, platelets and WBC declined to a 6–12-month nadir with partial recovery. Proportional platelet decline was identical with and without splenectomy (−28.5% vs −28.6%; p=0.55), as was WBC decline. Hemoglobin decreased progressively by approximately 1 g/dL over 1–2 years, with parallel MCV increase (~3–4 fL) and stable RDW, consistent with a macrocytic pattern. Non-PRRT-treated patients were frequently anemic (~94%) but lacked progressive decline or count nadirs. By CTCAE thresholds, splenectomized PRRT patients had fewer cytopenias, including leukopenia (41% vs 78%; p=0.001). For thrombocytopenia, this effect was largely baseline driven, although three splenectomized patients developed

late grade ≥3 thrombocytopenia up to 7 years post-PRRT despite normal counts at treatment. Splenectomy remained independently protective against leukopenia after adjustment (OR 0.31; p=0.009), but was not associated with anemia-related outcomes. Splenectomized PRRT patients had longer overall survival (57.6 vs 30.5 months; p=0.022), likely reflecting selection for resectable disease; splenectomy was not associated with survival in non-PRRT patients.

CONCLUSIONS

PRRT produces a reproducible hematologic signature in pNET: reversible thrombocytopenia and leukopenia with progressive macrocytic anemia, a pattern absent in non–PRRT-treated controls. Splenectomy does not attenuate proportional marrow suppression but reduces absolute-threshold cytopenias through higher baseline hematologic reserve, with additional baseline-independent protection against leukopenia. Absolute CTCAE grading may therefore underestimate PRRT marrow effects in splenectomized patients, suggesting relative-decline monitoring warrants prospective evaluation.

ABSTRACT ID #36639

C-7

Characterizing Long-Term Hematologic Toxicity After ^{177}Lu-DOTATATE: A Real-World Analysis of Patients with Gastrointestinal Neuroendocrine Tumors

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BACKGROUND

Lutetium-177 (^177Lu)-DOTATATE peptide receptor radionuclide therapy (PRRT) is an important treatment for well-differentiated, advanced, somatostatin receptor–positive gastrointestinal neuroendocrine tumors (GI-NETs). Although generally well tolerated, hematologic toxicity remains clinically relevant, and long-term data beyond one year are limited. We performed a comprehensive assessment of incidence, severity, longitudinal trends, and correlates of hematologic toxicity following ^177Lu-DOTATATE.

METHODS

We performed an observational retrospective analysis of adults (≥18 years) with histologically confirmed GI-NETs who received ≥1 cycle of ^177Lu-DOTATATE between 2017 and 2024 and had baseline laboratory data within 30 days before treatment. Patients were excluded for known hematologic malignancy, concurrent cytotoxic chemotherapy during PRRT, or inadequate follow-up for toxicity grading, defined as no laboratory follow-up through one year. Hemoglobin, white blood cell and platelet counts were monitored at baseline and approximately 3, 6, 12, and 24 months. Toxicity was graded by CTCAE v6.0. Treatment delays, interruption/discontinuation, supportive interventions, and development of MDS were recorded. Descriptive statistics were used; exploratory associations were evaluated using Fisher's exact test.

RESULTS

Sixty-three treatment-course records were analyzed. Hematologic toxicity was common but mostly low grade. Grade ≥2 anemia occurred in 19/63 (30.2%), including Grade ≥3 anemia in 7/63 (11.1%). Anemia peaked at approximately 12 months, when Grade ≥2 anemia was observed in 13/62 (21.0%), improving to 6/47 (12.8%) at 24 months. Thrombocytopenia was the most clinically relevant toxicity. Grade ≥2 thrombocytopenia occurred in 9/63 (14.3%), including Grade ≥3 thrombocytopenia in 5/63 (7.9%). Clinically significant thrombocytopenia peaked at 6 months (6/63, 9.5%), decreasing to 4/62 (6.5%) at 12 months and 2/47 (4.3%) at 24 months. The strongest association was treatment

exposure: patients receiving >4 treatments had higher composite Grade ≥2 anemia/thrombocytopenia than those receiving four treatments (8/14, 57.1% vs 9/46, 19.6%; p≈0.015), and higher Grade ≥3 toxicity (5/14, 35.7% vs 2/46, 4.3%; p≈0.006). Tumor grade and metastatic burden showed no clear association. Five patients (7.9%) required treatment delay, interruption, or discontinuation; four (6.3%) required transfusion support and/or hospitalization. Three patients (4.8%) developed therapy-related MDS; two occurred after 8 treatments at approximately 9 and 15 months, and one after 3 treatments at approximately 12 months. Two additional patients had persistent multilineage cytopenias with macrocytosis concerning for MDS without confirmatory marrow evaluation.

CONCLUSIONS

Hematologic toxicity after ^{177}Lu-DOTATATE was frequent and predominantly low-grade, though Grade ≥3 cytopenias and MDS occurred in a clinically meaningful minority. Higher treatment exposure and repeat PRRT were associated with more severe cytopenias, supporting careful patient selection and closer monitoring during extended or repeat therapy. Delayed, persistent cytopenias warrant long-term follow-up and marrow evaluation when clinically indicated.

ABSTRACT ID #36563

C-8

Patterns of Metastases and Outcomes in Patients with Pancreatic Neuroendocrine Tumors

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BACKGROUND

Half of patients with pancreatic neuroendocrine tumors (PNETs) present with distant metastases, with a median overall survival (OS) of 25 months. Some patients will also develop metastases after surgical resection. This study seeks to evaluate the anatomic distribution of metastases in PNET patients having operations at a tertiary center, determine how many patients develop metastases in follow-up, and to compare OS between patients with no metastases (M0), those presenting with metastases (M1 initial), and for those developing metastases later (M1 late).

METHODS

Patients with PNETs who underwent surgical intervention (primary/nodal resections with/without metastatic cytoreduction) between 2000-2023 were identified from a single-institutional prospective database. Demographics, disease characteristics, treatments, and outcomes were abstracted. Primary endpoints were the rate of M0 to M1 progression and risk factors for progression. Secondary endpoint was OS (assessed from first surgery) which was estimated by Kaplan-Meier Method and compared by Log Rank Test.

RESULTS

208 patients met inclusion criteria. 85 (40.9%) patients presented with metastases (M1 Initial), most commonly in the liver (95.3%), bone (25.9%), and retroperitoneal nodes (23.5%). Presence of nodal metastases and elevated preoperative pancreastatin were associated with increased odds of M1 at presentation on multivariable analysis. 24/123 (19.5%) of patients presenting with M0 disease developed metastases at a median of 40 months (M1 Late; 95% CI: 25 – 77 mos.). The most common sites of metastases in the M1 Late group were the liver (91.7%), retroperitoneal nodes (37.5%) and bone (16.7%). About 30% of both M1 Initial and M1 Late patients had extra-abdominal sites of metastases. Nodal metastases and Grade 3 disease were associated with increased odds of progressing from M0 to M1 on multivariable analysis. Patients with M0 disease had better

OS than both M1 Initial (not reached vs 103 mos., p<0.01) and M1 Late (150 mos., p=0.02). M1 Late had better OS than M1 Initial patients (p=0.05).

CONCLUSIONS

Metastases were seen in 41% of PNET patients at presentation, and another 20% developed metastases at a median of 40 months. OS was highest in patients with M0 disease, and those presenting later with metastases had significantly improved OS relative to those presenting initially with metastases. Improved outcomes in M1 Late vs M1 Initial patients may be due to earlier detection of metastases, lower disease burdens, and use of additional therapies. These results demonstrate the patterns and prognosis of metastases in surgically managed patients with PNETs and highlight the importance of long-term surveillance.

ABSTRACT ID #36589

C-9

Emergency versus elective resection for small intestine neuroendocrine tumors: a population-based analysis of short-term post-operative outcomes.

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BACKGROUND

There is much debate over whether small bowel neuroendocrine tumors should be resected when asymptomatic. Delaying surgery runs the risk of the need for emergency intervention. The consequences of emergency surgery remain uncertain compared with elective surgery. We described the use of emergency surgery and compared post-operative outcomes between emergency and elective surgery for resection for siNETs.

METHODS

We conducted a population-level retrospective cohort study of adults (≥18 years) undergoing small bowel resection for siNETs (2000–2024), using linked administrative health data. The incidence rate ratio of emergency surgery over years was computed. The primary outcome for comparison was 90-day major morbidity; secondary outcomes were 90-day mortality and prolonged length of stay (LOS; ≥75th percentile days). Multivariable logistic regression models 1) identified factors independently associated with receipt of emergency surgery and 2) estimated the association between emergency surgery and each outcome, adjusting for age, sex, comorbidity, metastatic status, hospital and surgeon procedure volume, and year. Sensitivity analyses incorporated elevated 24-hour urinary 5-hydroxyindoleacetic acid (u5-HIAA) for those with these data available.

RESULTS

Among 2,218 patients (median age 64 years old), 750 (33.8%) underwent emergency surgery. This proportion declined from 58.5% in 2000 to 26% in 2024 (incidence rate ratio 0.96/year, 95%CI 0.95–0.97). Advancing age, high comorbidity burden, and lower socioeconomic status were independently associated with higher odds of emergency surgery, while female sex, metastases at diagnosis, rural residence, care at an academic hospital, and higher surgeon volume were independently associated with lower odds of

emergency surgery. 90-day major morbidity was more than twice as frequent after emergency surgery (31.2% vs 14.8%; p<0.001), as was 90-day mortality (6.3% vs 1.8%); 64.4% of all deaths followed emergency surgery. Median LOS was longer after emergency surgery (8 vs 6 days; p<0.001), and prolonged LOS (≥ 75th percentile of 9 days) more common (39.6% vs 15.3%; p<0.001). After adjustment, emergency surgery was independently associated with higher odds of 90-day major morbidity (OR 2.21, 95%CI 1.76–2.78) and prolonged LOS (OR 2.80, 95%CI 2.24–3.50). Results were not altered when adjusting for elevated u5-HIAA.

CONCLUSIONS

Though less common over the last two decades, emergency small bowel resection for siNETs was independently associated with over double the odds of 90-day major morbidity and prolonged LOS, compared to elective resection. These findings support care strategies designed to avoid emergency surgery for siNETs when appropriate.

ABSTRACT ID #36553

C-10

Patient-reported symptom burden after surgery for entero-pancreatic neuroendocrine tumors: a population-level analysis.

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BACKGROUND

Patients with entero-pancreatic neuroendocrine neoplasms (EP-NENs) have unique supportive care needs. Patient-reported evidence on the post-operative experience after EP-NET surgery is limited. We described patient-reported symptom patterns and identify factors associated with moderate-to-severe symptom burden in the 6 months following surgery for EP-NENs.

METHODS

We conducted a population-level retrospective cohort study of adults (≥18 years old) undergoing resection for EP-NENs. Patient-reported symptom burden was captured with prospectively collected Edmonton Symptom Assessment System (ESAS) scores. Monthly prevalence of moderate-to-severe symptoms (ESAS ≥4) over 6 months after surgery was computed. Multivariable modified Poisson regression identified factors associated with reporting moderate-to-severe symptoms. Generalized linear mixed models estimated symptom score trajectories over time.

RESULTS

Among 1,327 patients completing at least one ESAS assessment, 3,078 scores were recorded over 6 months after surgery. The most commonly reported moderate-to-severe symptoms over that time period were tiredness (32%–41%), lack of wellbeing (30%–37%), and anxiety (21%–28%). Overall prevalence of moderate-to-severe symptoms was relatively stable, with clinically significant changes observed only for anxiety, which decreased by 12% within the first post-operative month, and lack of appetite, which rose initially before declining by month 3. Average total-ESAS score improved by approximately 5 points over 6 months after all EP-NENs surgeries, from an average of 21.4 before surgery to 14.6 at month 4. Pancreatectomy was associated with an initial rise in moderate-to-severe symptom reporting followed by progressive decline by month 3. Small bowel resection

and hepatectomy had clinically stable symptom trajectories overall. Symptom burden did not differ by 24-hour urinary 5-hydroxyindoleacetic acid elevation. Female sex was associated with higher risk of reporting moderate-to-severe anxiety, nausea, lack of appetite, tiredness, and poor wellbeing. Advancing age was independently associated with lower risk of reporting moderate-to-severe anxiety, depression, drowsiness, nausea, and tiredness.

CONCLUSIONS

Patients undergoing surgery for EP-NENs report a mostly stable burden of moderate-to-severe symptoms over 6 months after surgery, with procedure-specific trajectories and patient-level predictors that can guide counseling, expectations setting, recovery care pathways, and proactive symptom management.

ABSTRACT ID #36425

C-11

Normal Organ Dosimetry to Guide Safe Re-treatment PRRT

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BACKGROUND

Re-treatment PRRT has become more common in routine clinical practice, but it remains unclear how many additional cycles are safe to deliver. At our institution, we use dosimetry to help guide this decision. Here, we present dosimetry results for management of re-treatment PRRT.

METHODS

11 well-differentiated NET patients received 4-timepoint dosimetry at 4-, 24-, 48-, and 72-hours post-administration, with their first (N = 9) or second (N = 2) cycle of re-treatment PRRT. Dosimetry was performed with MIM Software. Single-cycle dose was extrapolated over the total number of prior cycles to calculate the cumulative organ dose. The organ dose limits used were 30 Gy to the liver, 17.5 Gy to the lungs, and 2 Gy to the bone marrow. Kidney dose limits were based on biologically effective dose (BED) rather than absorbed dose, using 29 Gy for patients with comorbidities and 38 Gy for those without. The limiting organ was defined as the one which most restricted the number of cycles, assuming standard prescribed activity per cycle.

RESULTS

Of the 11 dosimetry patients studied, the kidneys were the limiting organ for 8 patients, while bone marrow was the limiting organ for 2 patients. One patient did not have any dose limitations. The following table displays the results (9 patients shown due to 10-row limit).

Patient	# of Re-treatment Cycles (200 mCi) Permitted by Kidney Dosimetry	# of Re-treatment Cycles (200 mCi) Permitted by Bone Marrow Dosimetry	Limiting Organ	# of Re-treatment cycles administered
1	3	0	Bone Marrow	2
2	2	3	Kidneys	1
3	1	2	Kidneys	4
4	1	2	Kidneys	3 cycles at 200 mCi, 1 cycle at 100 mCi during first treatment
5	4	4	Kidneys	4
6	1	1	Kidneys	2
7	4	4	Kidneys	4

8	0	0	Kidneys	4
9	4	4	-	4

Kidney absorbed dose was always equally or more limiting than BED, which emphasizes the importance of comparing renal BED and absorbed dose. Dosimetry information is always used in context with the overall clinical picture, not as an absolute limit, demonstrated by bone marrow dose where complete blood counts are used to monitor myelotoxicity rather than relying on bone marrow dose alone.

CONCLUSIONS

This work shows how dosimetry can help guide the number of re-treatment PRRT cycles that can safely be administered. There are several limitations/assumptions in this process, and additional patient numbers and correlation with toxicity is ongoing work.

ABSTRACT ID #36645

C-12

Clinical Outcomes and Toxicity Profile of Cabozantinib in Advanced Neuroendocrine Tumors: A Multi-Center Real World Analysis

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BACKGROUND

Cabozantinib is a multi-kinase inhibitor that has recently emerged as a standard treatment option for progressive neuroendocrine tumors (NETs) following the phase III CABINET trial. However, real-world outcomes across heterogeneous patient populations remain limited.

METHODS

We conducted a retrospective multi-institutional cohort study using IRB-approved institutional NET registries. Eligible patients had advanced NETs treated with cabozantinib in routine clinical practice between 2018 and 2026. Endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and time-to-treatment discontinuation (TTD). Survival outcomes were estimated using the Kaplan-Meier method and compared using log-rank testing. ORR comparisons were performed using Fisher's exact test. Adverse events were graded according to CTCAE criteria.

RESULTS

Fifty-two patients were included; 27 (51.9%) were male and most had preserved performance status (ECOG 0–1; 43/49, 87.8%). Most had heavily pretreated disease, with ≥3 prior systemic therapy lines in 36/52 (69.2%). Among 48 patients with available histologic grade, most had grade 2 disease (58.3%), followed by grade 3 (22.9%) and grade 1 (18.8%). Starting doses were 40 mg in 70.0%, 60 mg in 24.0%, and 20 mg in 6.0%. Among 37 evaluable patients, ORR was 13.5% and DCR was 73.0%, including partial response in 13.5% and stable disease in 59.5%. Median PFS was 9.1 months (95% CI, 6.9–11.3), median OS was 14.5 months (95% CI, 10.4–23.3), and median TTD was 8.4 months (95% CI, 5.0–15.8). Exploratory subgroup analyses showed no statistically significant differences in ORR or

PFS by primary site, grade, age, or sex. ORR was numerically higher in pancreatic versus extra-pancreatic NETs (25.0% vs 5.9%, p=0.17) and in grade 3 versus grade 1/2 tumors (30.0% vs 8.0%, p=0.13). Treatment-related AEs were predominantly grade 1–2 (44/52, 84.6%). The most common AEs were fatigue (26.9%), palmar-plantar erythrodysesthesia (26.9%), diarrhea (11.5%), nausea/vomiting (11.5%), and thromboembolic events (11.5%). Grade ≥3 AEs occurred in 8/52 (15.4%), most commonly thromboembolic events (5.8%), hypertension (3.8%), and thrombocytopenia (3.8%).

CONCLUSIONS

In this multi-institutional real-world analysis, cabozantinib demonstrated clinically meaningful antitumor activity in a heavily pretreated NET population. Clinical benefit was observed across tumor grades, primary sites, age groups, and sexes, supporting the broad applicability of cabozantinib in routine practice. Toxicities were largely low grade, likely reflecting frequent use of reduced starting doses, and outcomes remained favorable despite this approach. These findings support cabozantinib as an effective later-line therapy and warrant prospective evaluation of dose-optimized strategies to improve tolerability without compromising efficacy.

ABSTRACT ID #36599

C-13

Phase I Study of Fulvestrant in Combination with 177Lu-DOTATATE for Advanced Pancreatic Neuroendocrine Tumors

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-DOTATATE prolongs progression-free survival (PFS) in patients with advanced well-differentiated pancreatic neuroendocrine tumors (pNETs) expressing somatostatin receptors, but further improvement in efficacy is needed. Preclinical data has shown that estrogen receptor alpha (*ESR1*) inhibition with Fulvestrant, an *ESR1* antagonist, radiosensitizes pNET cells. We conducted a study to evaluate the safety and preliminary efficacy of Fulvestrant in combination with ^{177}Lu-DOTATATE for advanced metastatic pNETs (NCT06663072).

METHODS

This is an investigator-initiated phase I study of Fulvestrant in combination with ^{177}Lu-DOTATATE for patients with well-differentiated pNETs. A total of 19 patients (pts) will be enrolled in Stage 1 (safety run-in, 6 pts) and Stage 2 (dose-expansion, 13 pts). PRRT with ^{177}Lu-DOTATATE was administered at 7.4 GBq (200 mCi) IV every 8 weeks for a total of 4 cycles. Fulvestrant was administered at 500mg IM on Cycle 1 days 1, 15, and 29, then every 4 weeks thereafter, for a total of 9 doses. The primary endpoint is to assess the safety and preliminary efficacy of Fulvestrant in combination with ^{177}Lu-DOTATATE for advanced pNETs based on objective response rate (ORR) assessed by RECIST v1.1. Post-therapy ^{68}Ga-DOTATATE PET/CT scans were performed following completion of cycle 4, and PET responses were assessed by PERCIST v1.0. Tumor volumes and associated statistics were quantified from PET images using MIM Software version 7.4.4.

RESULTS

At the time of data cutoff, 6 patients were enrolled in Stage 1 (safety run-in). Four patients completed all 4 cycles, and two patients completed cycle 2 only. All patients received Fulvestrant and ^{177}Lu-DOTATATE per protocol. There were no serious adverse events (SAEs) or AEs that led to dose reduction/interruption or treatment discontinuation. All reported adverse events (AEs) were Grade 1 or 2 with the majority (97%, 116/119) being Grade 1. Most common AEs were nausea, vomiting, diarrhea, fatigue, flushing, and

leukopenia. No patients experienced grade ≥3 AEs. ORR was 50% with partial response (PR) in 50% (3/6) and stable disease in 50% (3/6) of patients. Partial metabolic response (PMR) was observed in 100% (4/4) of PET response evaluable patients, with a mean tumor volume reduction of -56.5% (range -38.6%, -92.8%).

CONCLUSIONS

Fulvestrant in combination with ^{177}Lu-DOTATATE is safe and shows preliminary efficacy in advanced PNET patients with an ORR of 50%. Enrollment is currently underway in Stage 2 (dose-expansion) of our study.

ABSTRACT ID #36490

C-14

Retreatment With 177Lu-DOTATATE in Well-Differentiated Neuroendocrine Tumors: Interim Analysis of a Multicenter Registry

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BACKGROUND

177Lu-DOTATATE is an established peptide receptor radionuclide therapy (PRRT) for somatostatin receptor (SSTR)-positive, well-differentiated neuroendocrine tumors (WDNETs). In patients with clinical benefit from an initial course of 177Lu-DOTATATE, retreatment (rePRRT) is increasingly utilized at disease progression; however, data guiding patient selection remain limited. We present an interim analysis of rePRRT outcomes from a multicenter US registry.

METHODS

We analyzed data from 543 patients with WDNETs; 98 (18%) underwent rePRRT. Patient demographics, tumor characteristics, toxicity, radiographic response (by clinical report), PFS (time from rePRRT initiation to progression/death) were evaluated.

RESULTS

Median age 56 years. Tumor grade: 1 (n=29, 30%), 2 (n=51, 52%), 3 (n=10, 10%), unknown n=8, 8%). Primary site of origin: pancreas (n=40, 41%), small bowel (n=28, 29%), bronchial (n=6, 6%), rectal (n=5, 5%), gastric (n=2, 2%), other (n=7, 7%), unknown (n=10, 10%). Patients received a mean of 2.4 rePRRT cycles (1 cycle, n=25; 2 cycles, n=31; 3 cycles, n=15; 4 cycles, n=27).

47/98 patients (48%) experienced a TRAE during rePRRT, most commonly hematologic toxicities (n=39, 83%; grade >3 in one patient (1%)). Sixteen patients (16%) experienced leukopenia (15 grade 1/2; 1 grade 3), 17 patients (17%) experienced grade 1/2 anemia, 24 patients (24%) experienced grade 1/2 thrombocytopenia. One patient developed therapy-related MDS (3 initial PRRT followed by 2 rePRRT; total cumulative activity 996.7 mCi); this patient presented with new onset leukocytosis, prompting further workup. MDS developed 4.6 months after last rePRRT dose.

In the 77 patients with radiographic response data, best response to rePRRT was: CR (2 patients, 3%), PR (19 patients, 25%), SD (45 patients, 58%), PD (11 patients, 14%); disease

control rate (86%). Median re-PRRT PFS was 14.2 months (95% CI 13.0-21.1 months). Median PFS after initial PRRT was 25.5 months (95% CI 21.8-31.4 months). Stratification by initial PRRT median PFS demonstrated a significant difference in rePRRT outcomes: patients with initial PFS >25.5 months achieved a median rePRRT PFS of 22.2 months (95% CI 13.4-29.0 months), compared with 13.1 months (95% CI 10.7 - 16.0 months) for those with initial PFS ≤25.5 months (p=0.005).

CONCLUSIONS

In this interim analysis of the largest US multicenter rePRRT cohort reported to date (n=98), rePRRT demonstrated a disease control rate of 86% with a favorable safety profile (grade >3 TRAEs 1%). PFS after initial 177Lu-DOTATATE was significantly associated with rePRRT PFS, suggesting that first-line treatment duration may be a clinically useful predictor for rePRRT patient selection.

ABSTRACT ID #36552

C-15

Therapy-Related Myeloid Neoplasms After Radioligand Therapy in Neuroendocrine Tumors: A Multicenter Real-World Analysis

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BACKGROUND

Therapy-related myeloid neoplasms (t-MNs), including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), represent an uncommon but serious long-term hematological toxicity associated with radioligand therapy (RLT). Real-world data on the incidence of t-MNs and associated risk factors following RLT in are limited. We sought to investigate the incidence and risk factors of t-MN in patients with NETs treated with 177Lu-Dotatate.

METHODS

We conducted a multicenter retrospective cohort study using the TriNetX research network. Adult patients with NETs who received 177Lu-dotatate were identified, with first administration defined as the index date. The primary outcome was development of t-MNs (incident MDS or AML) with a 12-month latency period after target treatment. Incidence was calculated and Cox proportional hazards models were used to evaluate associations between baseline covariates and t-MN risk. Covariates included age, sex, race, primary tumor site (small bowel, colon, pancreas, lung), liver and bone metastases, prior alkylating chemotherapy (temozolomide exposure), chronic kidney disease (CKD), and nicotine or alcohol dependence. Treatment pathways were assessed for 177Lu-Dotatate re-treatment and temozolomide duration.

RESULTS

A total of 1,811 patients met the inclusion criteria. Mean age at index was 65.4 ± 10.9 years; 977 (54.0%) were male, and 1,503 (83.0%) were White. Median follow-up duration was 20.5 months. Following 177Lu-Dotatate, 37 of 1,807 patients (2.05%) developed MDS, and 15 of 1,804 patients (0.83%) developed AML, with an overall incidence of t-MNs 2.88% (52/1,804). At baseline, mean age (67.1 ± 9.3 vs 65.4 ± 11.0 years, p=0.27) and sex (males 42.0% vs 54.2%, p=0.14) were comparable between

patients who did and did not develop t-MNs. On multivariable Cox proportional analysis, higher age at index (HR 1.03; 95% CI 1.01–1.07; p=0.048) and baseline CKD (HR 2.69; 95% CI 1.32–5.49; p=0.006) were independently associated with increased risk of t-MNs. Sex, race, primary tumor site, presence of liver or bone metastases, alkylating chemotherapy exposure, and nicotine or alcohol dependence were not significantly associated with t-MN risk. Evaluation of treatment pathways demonstrated similar 177Lu-Dotatate re-treatment rates (2.33% vs 2.77%, p=1.0), and comparable receipt of temozolomide for ≥12 months (18.6% vs 16.4%, p=0.66) between groups that did and did not develop t-MNs, respectively.

CONCLUSIONS

In this large real-world cohort of NET patients treated with 177Lu-dotatate, t-MNs were uncommon but clinically significant. Older age and CKD were associated with increased risk, whereas repeat 177Lu-Dotatate and alkylating chemotherapy exposure were not associated with increased t-MN incidence. These findings may inform risk stratification, patient counseling, and long-term hematologic surveillance following 177Lu-Dotatate.

ABSTRACT ID #36577

C-16

Diagnostic performance of 64Cu-SARTATE compared to 68Ga-DOTATATE in patients with known or suspected neuroendocrine tumors with focus on liver findings

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BACKGROUND

Diagnostic imaging is critical to theranostic management of neuroendocrine tumors (NETs). ^{64}Cu-SARTATE (SARTATE) may provide advantages over existing imaging agents due to its longer half-life and sarcophagine chelator, potentially improving accurate detection of additional disease in NETs.

METHODS

This multi-center Phase II study compared the diagnostic performance and safety of SARTATE (200 MBq) with ^{68}Ga-DOTATATE (DOTATATE) in gastroenteropancreatic (GEP)-NETs (NCT04438304). Participants with known/suspected GEP-NETs prospectively received SARTATE PET/CT at 4±1 hrs and 20±4 hrs post-injection. The SARTATE scans were compared with DOTATATE PET/CT scans obtained within 35 days prior to SARTATE administration by two independent blinded central readers. All abnormal lesions potentially related to GEP-NET and cannot be accounted for by a benign process were recorded. Discordant lesions (lesions only present on either DOTATATE or SARTATE scan) were subsequently evaluated by an independent assessor against a standard of truth (SOT; biopsy and/or follow-up conventional imaging). Per-lesion sensitivity for discordant lesions was calculated for both SARTATE and DOTATATE (defined as the proportion of true positive lesions / [true positive lesions + false negative lesions]; primary endpoint). Safety was assessed using standard clinical parameters.

RESULTS

Forty-five participants were enrolled and received SARTATE (41 known NETs, 4 suspected NETs), most with stage 3 or 4 disease. The mean number of lesions detected by SARTATE was 441 vs. 227 by DOTATATE. A total of 238 discordant lesions were identified in 34 subjects with scan pairs; 223 of these were detected by SARTATE alone and 15 by DOTATATE alone. For the 122 discordant lesions with evaluable SOT, the difference in sensitivity for SARTATE vs. DOTATATE was statistically significant (94.7% [95% CI 65.1, 99.5]

for SARTATE vs. 5.4% [95% CI 0.5, 34.9] for DOTATATE; p<0.001). The liver had the highest number of lesions detected by both tracers (352 lesions on SARTATE vs. 180 on DOTATATE) among all sites. Seven participants (15.6%) experienced 9 SARTATE-related adverse events; 8 were Grade 1 and 1 was Grade 2, with most resolving within 2 days.

CONCLUSIONS

SARTATE was safe and well-tolerated in patients with GEP-NETs. SARTATE lesion detection was numerically higher than DOTATATE, with the liver having the highest number of lesions identified. SARTATE detected additional true positive lesions compared to DOTATATE. The enhanced diagnostic performance offered by SARTATE, especially in key organs affected by GEP-NETs, may have important clinical implications to inform treatment decisions. A phase III study of SARTATE in GEP-NETs is being planned.

ABSTRACT ID #36508

C-18

[177Lu]Lu-edotreotide Effectiveness in Patients with Functional and Non-functional Gastrointestinal Neuroendocrine Tumors: A SwissNET Registry Analysis

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BACKGROUND

The SwissNET registry, launched in 2008, has prospectively collected data from patients with neuroendocrine tumors (NETs) in Switzerland who consent to participate. Recent clinical trials have demonstrated efficacy of [^{177}Lu]Lu-edotreotide in participants with gastroenteropancreatic NETs; however, real-world evidence (RWE) of [^{177}Lu]Lu-edotreotide effectiveness in clinical practice is limited. The objective of this analysis was to summarize [^{177}Lu]Lu-edotreotide effectiveness in patients with functional and nonfunctional gastrointestinal (GI)-NETs using data from the SwissNET registry.

METHODS

SwissNET participants with functional and nonfunctional GI-NETs were included in the efficacy analysis if they had received at least 2 cycles of [^{177}Lu]Lu-edotreotide in any line of therapy (on-site magistral preparation according to national Swiss laws). Baseline and tumor characteristics were summarized using descriptive statistics. Real-world median progression-free survival (rwPFS), median overall survival (OS), overall response rate (rwORR), and disease control rate (rwDCR) were calculated, and between-group comparisons for rwPFS and OS were carried out using a log-rank test.

RESULTS

102 patients with GI-NETs were analyzed; 49 had functional tumors (mean age: 62.2±13.1 years, female: 38.8%), 51 nonfunctional tumors (mean age: 63.1±12.4; female: 56.9%) and 2 unknown tumor functional status. Most participants had grade 1 or 2 GI-NETs; prior surgery was recorded in 59.2% and 76.5% of participants with functional and nonfunctional GI-NETs, respectively.

Participants received a median number of 4 (range: 2-8) cycles of [^{177}Lu]Lu-edotreotide.

Median rwPFS was 21.3 (95% confidence interval [CI]: 11.8-38.9) vs 21.7 (95%CI: 14.1-32.0) months in participants with functional and nonfunctional GI-NETs, respectively, and median OS was 50.8 (95%CI: 38.9-86.8) vs 63.6 (95%CI: 35.6-90.1) months (Table 1). rwORR was 17.4% vs 25.5% and rwDCR was 87.0% vs 80.9% in participants with functional and nonfunctional GI-NETs, respectively.

Table 1: RWE Outcomes in Patients with GI-NETs

Parameters	Functional GI-NETs (n=49)	Nonfunctional GI-NETs (n=51)	P-value
Median (95%CI) rwPFS, months	21.30 (11.80-38.90)	21.70 (14.10-32.00)	0.650
Median (95%CI) OS, months	50.80 (38.90-86.80)	63.60 (35.60-90.10)	0.387
Complete response, n (%)[a]	3 (6.5%)	3 (6.4%)	
Partial response, n (%)[a]	5 (10.9%)	9 (19.1%)	
Stable disease, n (%)[a]	32 (69.6%)	26 (55.3%)	
rwORR (95%CI), %	17.4% (7.8%-31.4%)	25.5% (13.9%-40.3%)	
rwDCR (95%CI)	87.0% (73.7%-95.1%)	80.9% (66.7%-90.9%)	

[a]percentages are based on number of participants with response assessment

CONCLUSIONS

[^{177}Lu]Lu-edotreotide showed similar rwPFS in participants with functional and nonfunctional GI-NETs, suggesting that treatment response is not influenced by tumor functional status.

ABSTRACT ID #36342

C-19

Toward a Ki-67 -Informed Grading Framework for Metastatic Pulmonary Neuroendocrine Tumors

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BACKGROUND

Ki-67 is routinely reported in pulmonary neuroendocrine tumors (NETs) and widely used to estimate proliferative activity, yet it is not incorporated into current histopathologic grading, which relies on mitotic rate and necrosis. This gap is increasingly relevant as emerging data and recent WHO/ENETS discussions recognize a subset of well-differentiated pulmonary NETs with higher proliferative indices. However, clinically applicable Ki-67-based stratification, particularly in metastatic disease, remains undefined. We evaluated multiple Ki-67-based stratification approaches to inform the development of a clinically relevant grading framework in stage IV pulmonary NETs.

METHODS

We performed a retrospective cohort study of patients with stage IV well-differentiated pulmonary NETs treated at Moffitt Cancer Center (2008-2024). Clinicopathologic variables, including Ki-67 index, mitotic rate, metastatic sites, imaging findings, treatments, and survival outcomes, were collected. Ki-67 was analyzed using gastrointestinal NET-style strata (<3%, 3–20%, >20%), WHO/ENETS-informed lung NET strata (≤5%, 6–20%, >20%), and binary thresholds (5%, 10%, 15%, and 20%). Mitotic rate-based classification was evaluated as a comparator. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test, with Cox proportional hazards models used for multivariate analysis.

RESULTS

The cohort included 205 patients; Ki-67 was available in 169 (82.4%) and mitotic rate in 152 (74.1%). Median age at diagnosis was 62 years, and median OS was 68 months. Ki-67-based stratification demonstrated consistent prognostic value across multiple schemas, with separation driven by higher proliferative categories. Both gastrointestinal-style and WHO/ENETS-informed grouping significantly stratified OS (p=0.02), largely reflecting worse outcomes in tumors with Ki-67 >20% (median OS ~51 months) compared with lower-proliferation groups (~91-95 months). Binary thresholds of 5% and 10% did not significantly stratify OS (p>0.3), whereas 15% was the lowest threshold associated with a significant separation (median OS 95 vs 68 months, p=0.018). A 20% cutoff provided the strongest discrimination (p=0.006) and remained independently associated with worse

OS (HR 1.78, 95% CI 1.17-2.69; p=0.007). In contrast, conventional mitotic rate-based categories did not significantly stratify OS (log-rank p=0.404; Cox p=0.410).

CONCLUSIONS

Ki-67 offers reproducible, clinically meaningful prognostic stratification in metastatic well-differentiated pulmonary NETs and outperforms mitotic-rate–based grading in this cohort. Prognostic separation occurs at higher Ki-67 values, with 15% as the lowest significant binary cutoff and 20% providing the most robust discrimination and independent association with survival. These findings support integrating Ki-67 into a refined grading

ABSTRACT ID #36634

C-20

Outcomes of TARE as salvage liver-directed therapy in patients with poor response to first-line TAE/TACE for neuroendocrine liver metastases

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BACKGROUND

To assess the safety and efficacy of salvage transarterial radioembolization (TARE) in patients with neuroendocrine liver metastases (NELM) who fail liver-directed therapy (LDT) with bland (TAE) or chemoembolization (TACE).

METHODS

This single-center retrospective study identified 18 patients (10 male; median age 61 years [range, 36–82]) who failed TAE/TACE, with failure defined as hepatic progression within <12 months, and underwent subsequent TARE from 2011-2023. Demographic, clinical, treatment, and adverse event data were collected. Adverse events were graded per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and Society for Interventional Radiology (SIR) classification criteria. Hepatic progression-free survival (hPFS) and overall survival (OS) were estimated using Kaplan–Meier analysis and compared using log-rank test.

RESULTS

Primary tumors were pancreatic (61%), small bowel (11%), and other/unknown (29%). Tumors were grade 1 (6%), grade 2 (78%), grade 3 (6%), and unknown (10%). Liver-only disease was present in 44%, and liver-dominant disease in 56%. First-line LDT was TAE in 16% and TACE in 84%, with a median of two sessions. Median hPFS after TAE/TACE was 5.6 months (95% CI, 3.9–7.9). Patients underwent 31 TARE sessions (87% lobar), with a median delivered activity of 52.7 mCi. The median follow-up after salvage TARE was 22.6 months (range, 1.4–146.2 months). Median hPFS after TARE, assessed by RECIST criteria, was 13.8 months (95% CI, 5.8–59.1), significantly longer than after TAE/TACE (log-rank p=0.001; HR 0.20, 95% CI 0.07–0.52, p<0.001). Median OS after TARE was 17 months (95% CI, 5.8–31.7). Common acute adverse events (AEs) following salvage TARE were fatigue (78%), nausea or vomiting (61%), abdominal pain (50%), and constipation (39%), all of which were CTCAE grade 1/2. Mild hepatic encephalopathy occurred in one patient (6%). No patients met full criteria for radioembolization induced liver disease, however, one patient with

hyperbilirubinemia was treated as such. Chronic AEs were observed in 2 patients (11%). One patient developed grade 1 radioembolization-induced chronic hepatotoxicity (RECHT) with evidence of pseudocirrhosis and portal hypertension, without ascites, and mild liver function test abnormalities. Another patient developed probable grade 4 RECHT, with development of ascites 13 months after TARE. No procedure-related mortality was observed.

CONCLUSIONS

TARE is a safe and effective salvage therapy for patients with NELMs who progress after TAE/TACE, providing significantly longer hepatic progression-free survival with acceptable toxicity. These findings support early consideration and incorporation of TARE into a sequential embolization algorithm for NELMs, offering a viable salvage option for TAE/TACE non-responders.

ABSTRACT ID #36495

C-21

A Phase I Study of Safety, Immunogenicity, and Preliminary Clinical Activity of the Survivin Long Peptide Vaccine (SurVaxM) in Patients with Metastatic Neuroendocrine Neoplasm

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BACKGROUND

Survivin (BIRC5), an inhibitor-of-apoptosis protein, is overexpressed in neuroendocrine neoplasm (NENs) and is associated with higher tumor grade and inferior survival. SurVaxM (SVN53-67/M57-KLH) is a survivin-targeted long-peptide vaccine designed to induce both cellular and humoral antitumor immunity. We evaluated the safety, immunogenicity, and preliminary clinical activity of SurVaxM in patients with metastatic NENs.

METHODS

This open-label, single-arm phase I study (NCT03879694) enrolled patients with metastatic, survivin-positive NENs of any grade with RECIST 1.1 progression within 6 months before enrollment. Patients received SurVaxM emulsified in Montanide with GM-CSF every 2 weeks for four priming doses, followed by booster vaccinations every 3 months until disease progression or unacceptable toxicity. The primary endpoint was regimen-limiting toxicity (RLT). Secondary endpoints included safety, objective response, progression-free survival (PFS), and overall survival (OS). Exploratory analyses evaluated associations between vaccine-induced immune responses and clinical outcomes.

RESULTS

Between 2019 and 2025, 18 patients (G1, n=1; G2, n=8; G3, n=9) received at least one dose of SurVaxM and were included in the safety analysis. Fourteen patients were evaluable for efficacy, and 11 were evaluable for immune analyses. No RLT was observed. Treatment-related adverse events were exclusively grade 1 and included injection-site reactions (11.1%), bruising (11.1%), flu-like symptoms (5.6%), and bone pain (5.6%). Seven patients experienced serious adverse events, all attributed to disease progression or unrelated causes. Median PFS was 4.3 months (95% CI, 2.8-11.1), and median OS was 10.7 months

(95% CI, 7.4-not reached). Six of 14 evaluable patients achieved stable disease (42.9%; 95% CI, 17.7-71.1), while four patients (28.6%) remained progression-free for ≥6 months, including two patients with grade 3 NENs. Patients with prolonged disease control consistently demonstrated vaccine-induced immune responses, characterized by either robust anti-survivin IgG antibody titers (>1:5,000) or IFN-γ-producing $CD8^+$ T-cell responses. One patient achieved durable disease control for 3.5 years with a peak anti-survivin IgG titer of 1:25,400, was successfully retreated following antibody decline at progression, and remained progression-free for an additional 18 months.

CONCLUSIONS

This study demonstrated that SurVaxM has a favorable safety profile and is immunogenic in patients with metastatic NENs. Disease stabilization and prolonged PFS were observed in a subset of patients. These findings support further investigations of SurVaxM in combination regimens to better define clinical efficacy and relationship to immune activation.

ABSTRACT ID #36652

C-22

Preoperative Somatostatin Receptor-based Imaging Should be Routinely Performed in Neuroendocrine Tumors

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BACKGROUND

While contemporary gastroenteropancreatic neuroendocrine tumor (GEPNET) management guidelines recommend routine use of functional imaging preoperatively, there are little data highlighting trends in functional imaging adoption. This manuscript reviews 24 years of NET experience to identify changes in rates of preoperative functional imaging use, highlight performance differences between functional imaging types (somatostatin receptor positron emission tomography (SSTR PET) and Octreoscan) in small bowel (SBNET) and pancreas (PNET) NETs, and describe patters of preoperative metastatic spread in SBNETs and PNETs.

METHODS

A retrospective, single institution study was performed from 2000 to 2023 identifying patients with SBNETs and PNETs undergoing surgical resection and/or cytoreduction who underwent preoperative functional imaging. Primary endpoints were frequency of functional imaging use over time and location of metastases identified on preoperative imaging.

RESULTS

392 SBNET and 208 PNET patients had surgical treatment. 248 (63.3% of total) SBNET and 113 (54.3%) PNET patients received preoperative functional imaging. In SBNET patients, 158 had SSTR PET and 90 Octreoscans, and in PNET patients 47 had SSTR PET and 66 Octreoscans. While only 55.4% of patients with SBNETs or PNETs had functional imaging performed preoperatively between 2005 and 2009, the percentage increased to 73.5% between 2020 and 2023. There was a significant trend to increasing preoperative functional imaging use in SBNET patients (~2.5% per year, $p<0.01$), but not in PNETs

(p=0.82). 82.3% (204/248) of SBNET and 54.9% (62/113) of PNET patients had metastatic disease at presentation (p<0.01) with 28.2% and 17.7% presenting with extra-abdominal spread, respectively (p=0.03). SBNET patients had higher rates of metastases to the liver (72.6% vs 53.1%, p<0.01), peritoneum (13.3% vs 1.8%, p<0.01) and thoracic nodes (14.9% vs 4.4%, p<0.01) as compared to PNET patients. SSTR PET scans more frequently identified bone and retroperitoneal nodal metastases than Octreoscans in both SBNET and PNET patients. SSTR PET overtook Octreoscan as the preferred functional imaging modality in 2017-2018.

CONCLUSIONS

Preoperative functional imaging use increased significantly at our institution over the last 24 years in SBNET but not as much in PNET patients. Reasons for the lack of increase in PNETs may be due to higher incidence of false-positive results and reduced rates of distant metastases, although its use has increased over the last 2 years. Patients with SBNETs and PNETs frequently presented with metastatic disease and SSTR-based functional imaging was extremely helpful in identifying distant disease, for intra-operative planning, and making further management decisions.

ABSTRACT ID #36525

C-23

A Retrospective Review of Patients' Octreotide Administration During 177Lu-Dotatate Treatment

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BACKGROUND

Both the NETTER-1 and NETTER-2 trials demonstrated improved progression-free survival (PFS) for GEP-NET patients receiving ^{177}Lu-Dotatate with Octreotide LAR over Octreotide LAR monotherapy. In both studies, the Octreotide LAR or synthetic somatostatin analog (SSA) was administered 28 days before ^{177}Lu-Dotatate. Since then, many institutions and the Lutathera package insert continue to emphasize a 28-day SSA washout. This regimen relies heavily on adept interdepartmental coordination and high patient health literacy, and it remains unclear how meaningful and practical this washout is in everyday practice.

METHODS

Charts were evaluated from 20 GEP-NET patients who received ^{177}Lu-Dotatate at Oregon Health and Science University (OHSU) between 11/22/2023-6/10/2025. All patients had progressed on SSAs. At OHSU, SSAs are only administered during ^{177}Lu-Dotatate for patients with functional tumors. Documentation was reviewed to determine whether SSAs were continued during ^{177}Lu-Dotatate treatments, if there was 28-day washout, and whether patients had progressed at time of review.

RESULTS

Of the 20 patients evaluated, 11 patients stopped Octreotide LAR 28 days prior to their first dose of ^{177}Lu-Dotatate and 9 patients continued with SSAs. While only 1 patient on SSAs had clear documentation regarding the timing of injections, 6 of the SSA patients continued to have 28-day washouts between treatments. The 3 other SSA patients received injections within 28 days of treatment (17- 25 days, mean 20.7).

At time of review, 14 of 20 patients (70%) had ongoing PFS which ranged from 386-699 days since last ^{177}Lu-Dotatate administration. For the other 6 patients, time to documented progressive disease (PD) ranged from 209-666 days.

Table: SSA Usage During ^{177}Lu-Dotatate Treatment and Relationship to PFS and PD

	SSA Stopped N= 11	SSAs with 28 Day Washout N= 6	SSAs with Less than 28 Day Washout N= 3
PFS n	7	5	2
Range of Days Since ^{177}Lu-Dotatate	392-650	386-699	390-399
Mean Days	508	525.5	394.5
PD n	4	1	1
Range of Days Since ^{177}Lu-Dotatate	209-456	666	348
Mean Days	337.3	666	348

CONCLUSIONS

This is preliminary data. Further patients and time points are needed to better understand the optimal timing of Octreotide LAR administration during ^{177}Lu-Dotatate treatments. This retrospective review discovered that many patients continued to abide by the 28-day washout, yet 2 patients received injections closer to their treatments and continued to have PFS at the time of review.

ABSTRACT ID #36609

C-24

Time-Dependent Recurrence Risk and Prognostic Factors After Hepatic Resection for Neuroendocrine Liver Metastases

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BACKGROUND

Neuroendocrine liver metastases (NELM) frequently recur after hepatic resection; however, the temporal dynamics of recurrence risk remain poorly understood. We sought to identify time-dependent recurrence risk and prognostic factors to allow us to optimize our postoperative surveillance strategy.

METHODS

In this international multicenter study, 329 patients who underwent initial complete treatment by hepatic resection with or without ablation for NELM during 1995–2024 at three hepatobiliary centers were analyzed. Recurrence-free survival and overall survival were estimated using Kaplan–Meier methods. Time-varying risks of recurrence and death were assessed with kernel-smoothed hazard estimates. Prognostic factors were evaluated using univariable and multivariable Cox regression analyses.

RESULTS

The risk of recurrence was highest immediately after surgery and declined over time yet did not reach zero 10 years after resection. Multivariable analysis identified pancreatic primary tumor (hazard ratio [HR] 1.92), multiple liver metastases (HR 1.80), maximum liver tumor diameter >5 cm (HR 1.64), and neuroendocrine carcinoma (HR 2.57) as independent predictors of recurrence (Table 1). Conditional analysis demonstrated that beyond 2 years of recurrence-free survival, only pancreatic primary tumor remained a significant risk factor (Table 1). Based on time-dependent prognostic factors, we propose a risk-adapted surveillance strategy: Patients with pancreatic primary tumors should undergo imaging every 3–4 months during the first 4 years and then transition to imaging every 6–12 months, with follow-up extending beyond 10 years. Patients with

multiple metastases, maximum tumor diameter >5 cm, or neuroendocrine carcinoma should undergo imaging every 3–4 months during the first 2 years and then transition to imaging every 6–12 months, with follow-up extending beyond 10 years.

CONCLUSIONS

The risk of recurrence and the prognostic factors for recurrence after NELM resection change over time. A tailored surveillance approach may meaningfully reduce unnecessary imaging, radiation exposure, and travel burden for lower-risk patients while improving the likelihood of timely detection and intervention in patients at higher risk.

ABSTRACT ID #36438

C-25

Building an international research agenda for the surgical care of gastro-entero-pancreatic neuroendocrine tumors: results of the CUTNETs modified Delphi consensus phase.

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BACKGROUND

Surgical management remains a cornerstone of the management of gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs), yet surgical indications and procedures are often inconsistent, and rest on fragmented, largely single-center evidence. We aimed to reach consensus on priority research gaps to address in the surgical care of GEP-NETs, with a view to build a research agenda.

METHODS

We conducted a modified Delphi consensus process with an international panel of surgical GEP-NET experts spanning academic and community practice and major surgical and NET societies across the Americas and Europe. An open-ended first round, informed by a scoping review, generated candidate research gaps, organized into 9 clinical and one methodology categories. In two subsequent survey rounds, panelists rated each item's importance on a 1-7 Likert scale. Consensus was determined by modified RAND/UCLA method: items were classified important (accepted) based on the median score, and consensus defined by fewer than one-third of panelists rating outside the three-point region containing the median.

RESULTS

Forty-one experts formed the panel with over 80% replying to each round. Eighty-two items across 10 categories were rated. After 2 rounds, 57 items (70%) reached consensus as important, 2 (2%) as not important, and 23 (28%) reached no consensus. The ten research questions with strongest consensus as important were timing and indications for surgery in well-differentiated Grade 3 NETs (91%), aggressive surgery versus systemic therapy in locally advanced pancreatic NETs (panNETs) (88%), role of neoadjuvant therapy in locally advanced panNETs (88%), when to safely cease observation of small non-functional panNETs (85%), role of liver resection in metastatic panNETs (85%), indications for primary tumor resection with inoperable metastases in small bowel and panNETs (82% each), optimal agent for neoadjuvant therapy in locally advanced panNETs (82%), selection of candidates for liver debulking surgery (79%), and adjuvant therapy after liver debulking (79%). The three research methodologies with strongest consensus were multicenter randomized controlled trials (97%), multicenter prospective cohort studies (94%), and quality-of-life studies (88%). Two questions were rejected: octreotide for postoperative pancreatic fistula prevention and hepatic arterial infusion for liver metastases. Two research questions showed bipolar disagreement: peritoneal cancer index cutoffs for cytoreduction and role of minimally invasive/robotic surgery.

CONCLUSIONS

International experts generated consensus on 57 priority research questions in the surgical care of GEP-NETs, including endorsement of multicenter, collaborative study designs. These priorities will undergo comparative ranking for prioritization to yield a focused actionable collaborative research agenda in the surgical care of GEP-NETs.

ABSTRACT ID #36600

C-26

NETest2.0® Accurately Detects Active Disease and Monitors Recurrence in Neuroendocrine Tumors: Results from the RegisterNET Registry

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BACKGROUND

Reliable biomarkers for disease detection and longitudinal surveillance of neuroendocrine tumors (NETs) remain an unmet clinical need. NETest2.0® is a blood-based, machine-learning–enhanced multigene transcript assay developed to assess NET disease activity. We evaluated its ability to detect disease and monitor recurrence or progression in a large prospective registry cohort.

METHODS

RegisterNET (NCT02270567) is a multicenter observational registry of NET patients. Two analyses were performed. First, NETest2.0® results were compared with contemporaneous imaging findings in 1,290 samples from 886 patients. Second, longitudinal changes in NETest2.0® scores were evaluated in 404 patients with paired samples obtained a median of 7 months apart. Clinical cohorts included post-operative minimal residual disease assessment, recurrence surveillance following curative-intent surgery, watch-and-wait monitoring, and treatment response assessment. Imaging (CT, MRI, or SSTR-PET) served as the clinical comparator.

RESULTS

For disease detection, NETest2.0® demonstrated an AUC of 0.96 with 91.9% sensitivity, 94.9% specificity, 98.4% positive predictive value, and 92.5% overall accuracy. Performance was maintained across tumor grades, primary sites, and imaging modalities.

Among 404 patients undergoing longitudinal surveillance, 286 remained stable or disease-free and 118 experienced recurrence or progression. NETest2.0® scores decreased in stable/responding patients (median −14.6%) but increased in patients with recurrence/progressive disease (median +15.4%; $p<0.0001$). Changes in NETest2.0® scores

yielded an AUC of 0.86 for identifying progression. Using a positive NETest2.0® result with any increase in score, specificity reached 98.3%, positive predictive value 91.1%, and overall accuracy 83.9%.

CONCLUSIONS

NETest2.0® accurately identifies active NET disease and provides clinically meaningful longitudinal surveillance information across diverse management settings. Serial molecular assessment distinguished stable from progressive disease and demonstrated high specificity for recurrence/progression. These findings support incorporation of NETest2.0® into risk-adapted surveillance strategies to complement imaging and potentially reduce unnecessary radiologic monitoring.

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ABSTRACT ID #36584

C-27

Beyond Chromogranin A: Molecular Surveillance with NETest2.0® Improves Detection of Neuroendocrine Tumor Progression

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BACKGROUND

Reliable biomarkers for longitudinal surveillance of neuroendocrine tumors (NETs) remain an unmet clinical need. Chromogranin A (CgA), historically the most widely used circulating biomarker, has limited sensitivity and often correlates poorly with disease progression. We evaluated whether serial molecular assessment using NETest2.0®, a blood-based multigene transcriptomic liquid biopsy, more accurately identifies progression during routine NET surveillance.

METHODS

Patients enrolled in RegisterNET (NCT02270567) with paired blood samples and contemporaneous imaging assessments were analyzed. NETest2.0® scores were generated from a 51-gene RT-PCR transcript signature and compared with serial serum CgA measurements. Disease status at follow-up was determined by CT, MRI, and/or SSTR-PET imaging with RECIST 1.1 criteria applied when appropriate. Longitudinal changes between sequential samples were assessed using predefined NETest2.0® thresholds (>0% and >5%) and compared with the conventional CgA surveillance threshold (>50%).

RESULTS

A total of 191 patients were evaluated, with a median surveillance interval of 6 months. Serial NETest2.0® changes demonstrated significantly superior discrimination of progression compared with serial CgA changes (AUC 0.893 vs. 0.538; $p<0.0001$).

In the primary surveillance analysis, NETest2.0® >0% achieved an AUC of 0.860 and NETest2.0® >5% an AUC of 0.822, both significantly superior to CgA (AUC 0.553; $p<0.0001$ for both comparisons). NETest2.0® >0% demonstrated the highest sensitivity (86.4%), while NETest2.0® >5% provided the optimal balance of performance with 70.5% sensitivity, 93.9% specificity, 77.5% positive predictive value, 91.4% negative predictive value, and 88.5% overall accuracy. In contrast, CgA demonstrated only 18.2% sensitivity and 75.4% overall accuracy. Multivariable and logistic regression analyses identified changes in NETest2.0® as the strongest independent predictor of progression (all

p<0.0001; OR 52.99–61.26), whereas serial CgA changes were not independently associated with progression.

CONCLUSIONS

Serial NETest2.0® assessment significantly outperformed Chromogranin A for identifying progression during NET surveillance. Molecular changes measured by NETest2.0® were strongly associated with clinical outcome and represented the dominant independent predictor of progression. These findings support integration of NETest2.0® into biologically informed follow-up and risk-adapted imaging strategies for NETs.

ABSTRACT ID #36582

C-28

Longer-Term Paltusotine Treatment in Patients With Carcinoid Syndrome: Safety and Exploratory Efficacy Results From a 2-Year Open-Label Extension Study

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BACKGROUND

Paltusotine is a once-daily, nonpeptide, selective somatostatin 2 receptor agonist in development as an oral treatment for patients with carcinoid syndrome (CS).

METHODS

This phase 2, multicenter study examined the safety, tolerabilty, and exploratory efficacy of paltusotine in patients with CS. The study included an 8-week randomized treatment period (RTP) and a 102-week open-label extension (OLE). Patients were adults with a locally advanced or metastatic grade 1 or 2 neuroendocrine tumor (NET) and actively symptomatic CS, either untreated with somatostatin receptor ligand (SRL) therapy (average of ≥4 bowel movements/day or >2 flushing episodes/day on ≥2 days over a 2-week period) or washed out of SRL (symptoms previously controlled on SRL) with

demonstrated symptom worsening after washout. This analysis evaluated the effects of paltusotine treatment through the end of the 2-year OLE.

RESULTS

Thirty-six patients (n=9 untreated; n=27 SRL washout) were enrolled; mean age was 60.8 years (range 35-83), 52.8% were female, and 47.2% had a grade 2 NET. Of 30 RTP completers, 26 continued into the OLE. The mean±SD number of flushing episodes per day was 2.4±1.9 at baseline (n=36), 0.9±1.1 at week 8 (n=30; end of RTP), 0.4±0.6 at week 58 (n=15), and 0.3±0.4 at week 110 (n=12; end of OLE). The mean±SD daily worst flushing severity score (numeric rating scale from 0-10) was 3.4±2.3, 1.5±1.7, 0.5±0.7, and 0.7±1.1, respectively. The mean±SD number of bowel movements per day was 3.6±1.7 at baseline, 2.6±1.3 at week 8 (end of RTP), 2.0±1.0 at week 58, and 2.1±1.2 at week 110 (end of OLE). At the last available assessment (end of RTP, end of OLE, or early discontinuation), the paltusotine dose was 40 mg/day in 11 patients, 80 mg/day in 18 patients, and 120 mg/day in 7 patients. The most common treatment-related adverse events (AEs) were diarrhea (RTP: 25.0%; OLE: 7.7%), abdominal pain (RTP: 16.7%; OLE: 3.8%), and nausea (RTP: 11.1%; OLE: 11.5%). Across the entire study period, no serious AEs were considered treatment-related. Three patients (RTP, n=1; OLE; n=2) had AEs that led to treatment discontinuation; none were considered treatment-related.

CONCLUSIONS

In this phase 2 study, once-daily oral paltusotine reduced the frequency and severity of CS symptoms, and improvements were sustained during longer-term (up to 2 years) treatment. Paltusotine was well tolerated, and the incidence of AEs decreased over the study period. A phase 3, randomized, placebo-controlled trial of paltusotine in the treatment of patients with CS (CAREFNDR; carefndr.com) is currently ongoing.

ABSTRACT ID #36520

C-29

Laser Capture Microdissection-Based Proteomics to Identify Immunotherapy Response Signatures in High-Grade Neuroendocrine Neoplasms

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BACKGROUND

Effective systemic therapy for high-grade neuroendocrine neoplasms (NEN G3) represents a critical unmet need. Immune checkpoint inhibitors (ICI) can produce uncommon, but sometimes very deep and durable responses. However, predictive biomarkers for response are lacking. We performed laser capture microdissection (LCM)-based deep proteomics to discover response-associated signatures.

METHODS

We analyzed archived tissues from 11 patients treated with ICI. H&E/IHC-reviewed 10-µm PEN sections were microdissected (~3,000 tumor cells/slide) and analyzed on a high-sensitivity timsTOF Ultra 2 mass spectrometer. Differential protein expression compared non-responders (NR) with responders (R) using 2-sample t-tests (fold change = NR/R). Overall survival from ICI start was calculated for each group.

RESULTS

Eleven LCM specimens from clinically annotated patients were analyzed (3 R, 8 NR specimens). Deep proteomic profiling was achieved across all specimens. Responders had longer ICI exposure and longer time from ICI start to death/last follow-up (p=0.0078) (Table). We identified 124 differentially expressed proteins (p<0.05; 78 lower and 46 higher in NR). NR tumors showed reduced oxidative stress/ferroptosis-associated proteins (MT1G, GSTP1, GSTO1) and reduced immune-associated proteins (HLA-DRB5,HLA-DPB1, PTPRC, LCP2). MMP15, an ECM-remodeling metalloproteinase, was detected in 7/8 NR and 0/3 R specimens.

CONCLUSIONS

LCM-based deep proteomics identified candidate ICI response signatures in NEN G3. Loss of oxidative stress/ferroptosis and immune-associated proteins in NR, together with NR-restricted MMP15, supports validation of these candidate predictive biomarkers. MT1G was

identified as the most promising novel biomarker. Next steps will test MT1G using a simple IHC assay and to validate the proteomic findings on a larger sample size.

Patient	Primary Tumor	IO Regimen	Best response	OS from ICI start (mo)	Status	MT1G (log2 intensity)
Responders						
1	G3 NET – pancreas	Pembrolizumab	PR	114.3	Alive	0.38
2	NEC – rectum	Ipi/nivo	CR	70.7	Alive	1.67
3	NEC – unknown primary	Ipi/nivo + OV	PR	13.1	Alive	2.65
Non-responders						
1	G3 NET – small bowel	Ipi/nivo	PD	16.4	Deceased	-2.74
2	NEC – rectum	Ipi/nivo + OV	PD	1.8	Deceased	-2.38
3	NEC – espohagus	Ipi/nivo	PD	5.4	Deceased	-1.11
4	NEC – unknown primary	Ipi/nivo	PD	6.3	Deceased	-2.16
5	NEC – tonsil	Ipi/nivo	PD	6.6	Deceased	-1.36
6	NEC – pancreas	Ipi/nivo + OV	PD	4.9	Deceased	-2.67
7	NEC – pancreas	Ipi/nivo	PD	10.0	Deceased	-1.42
8	NEC - rectum	Ipi/nivo	PD	3.7	Deceased	-2.87

ABSTRACT ID #36586

C-30

Real World Analysis of Extrapulmonary Neuroendocrine Carcinoma Patients in South Florida.

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BACKGROUND

Extrapulmonary Neuroendocrine Carcinomas (ep-NECs) are rare and aggressive malignancies with extremely poor prognoses and limited therapeutic options. Real world experience regarding ep-NEC patients representing unique South Florida patient population is currently lacking.

METHODS

We conducted a retrospective review of ep-NEC patients managed between January 2023, and May 2026 at University of Miami. Patients who were primarily treated at our site and had complete clinical and radiographic data were included in the analysis. Median PFS and median OS were calculated using the Kaplan-Meier curve.

RESULTS

Twenty-nine patients met eligibility. 86% were White, 10% Black, and 4% Asian race. 21% patients identified as Hispanic. The median age was 60 years. Our cohort included 41% small cell carcinoma, 35% large cell NEC and 24% poorly differentiated unspecified NEC patients. The most common primary site of origin was of gastrointestinal origin (n=16), followed by pancreas (n=2), unknown primary (n=4), gynecological (n=1) and other organs (n=6; pelvic, prostate, breast and esophagus). Only one patient presented with brain metastasis at diagnosis, while five patients developed brain metastasis later; all six patients with brain metastasis belonged to small cell subtype of NEC. Seven patients had local disease and 22 had metastatic disease. Ki 67 index was available on 19 of 21 patients in the metastatic cohort; 15 of 19 patients were noted to have Ki-67 index >80. The median PFS on frontline platinum doublet chemotherapy (as concurrent chemoradiation

or adjuvant chemotherapy) in patients with local disease (n=7) was 10 months (95% CI:4.86 to 15.13). In contrast, those with metastatic disease at diagnosis (n=22), the median PFS was 4 months (95% CI: 2.89 to 5.10). The median OS for all patients with metastatic disease at the time of data cut-off was 16.09 months. 69% and 48% of the patients received second- and third-line therapy respectively.

CONCLUSIONS

Our analysis of a Hispanic-enriched extrapulmonary neuroendocrine carcinoma (ep-NEC) cohort confirms that most patients present with metastatic disease at diagnosis. Notably, the risk of CNS metastasis in ep-NEC is substantially lower than historically reported for thoracic NEC. Characterized by highly aggressive biology, most ep-NEC patients exhibited a Ki-67 index greater than 80%. Furthermore, attrition is high, with fewer than half of patients progressing to third-line therapy. With a median overall survival (OS) of approximately 16 months, these findings underscore ep-NEC as a critical unmet medical need.

ABSTRACT ID #36627

C-31

Recurrence of Locoregional Small Bowel Neuroendocrine Tumors: Developing a Risk Prediction Nomogram

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BACKGROUND

Locoregional small bowel neuroendocrine tumors (sbNETs) are typically managed with curative-intent resection. Despite their generally indolent biology, recurrence rates of up to 50% have been reported. Evidence guiding individualized follow-up strategies remains limited. We aimed to develop a nomogram to predict recurrence risk after resection.

METHODS

Retrospective review was performed of adults undergoing surgical resection of stage I – III ileal and jejunal NETs from 2000 – 2023 at a quaternary referral center. Patients with unresectable disease or other abdominal malignancies at the time of surgery were excluded. Ki67 was missing for 131 patients with re-review underway. Kaplan Meier estimates and Cox proportional hazards regression were performed. LASSO regression was utilized for nomogram variable selection.

RESULTS

Patients meeting inclusion criteria (n=378) were a median age of 63.1 years [IQR 54.3, 72.3] at the time of surgery. 42.1% were female, 93.1% were white, and 41% had multifocal disease. Ki67 was less than 3% for 51.4% of patients, 3% - 20% for 47.8%, and >20% for 0.8%. Median lymph node retrieval was 13 [6, 23]. 85% had stage 3 disease, 10.2% were stage 2, and 4.8% were stage 1. With a median follow-up of 94 months, 55 patients had recurrence. 34.5% had locoregional-only recurrence, whereas 38.2% developed peritoneal disease and 41.8% had distant hematogenous (liver, lung, bone, pancreas) recurrence. Median time to recurrence was 59.7 months, with 29.1% undergoing subsequent resection. Kaplan-Meier estimate of 5-year recurrence free survival was 91.4% overall, 97.8% for stage I or 2 disease, and 90.8% for stage 3 (p=0.012). On multivariable analysis, risk of recurrence was associated with primary tumor size, multifocal disease, and perineural invasion (Table 1). Although pathologic N2 disease was not significant on multivariable regression, it was identified as an important predictor on LASSO regression and therefore included in the nomogram. The corrected c-index was 0.71.

Table 1: variables included in nomogram based on LASSO regression.

Variable	Level	HR (95% CI)	p-value
Primary Tumor Size	Per 5 mm	1.23 (1.10, 1.38)	0.0004
Multifocal	Yes	2.59 (1.45, 4.61)	0.0012
Perineural Invasion	Yes	3.05 (1.58, 5.90)	0.0009
Pathologic N2	Yes	1.71 (0.94, 3.13)	0.0807

CONCLUSIONS

Our model is well-calibrated to predict recurrence of locoregional small bowel neuroendocrine tumors on the basis of tumor size, multifocality, perineural invasion, and nodal status. A risk-prediction nomogram may help guide patient counseling and inform the frequency and duration of postoperative surveillance. A multi-center validation cohort has been established with data collection underway.

ABSTRACT ID #36613

C-32

Timing of Primary Tumor Resection & Long-Term Survival in Stage IV Small Bowel Neuroendocrine Tumors: A National Analysis

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BACKGROUND

In stage IV small bowel neuroendocrine tumors (SB-NETs), primary tumor resection (PTR) is frequently performed for symptom control or prevention of complications. The impact of operative timing on outcomes remains unclear.

METHODS

Using the National Cancer Database, we identified patients with stage IV well-differentiated SB-NETs undergoing PTR. Patients were stratified as urgent (≤30 days from diagnosis) or delayed (>30 days) resection. Clinicopathologic and perioperative variables were compared. Overall survival (OS) was evaluated using Kaplan–Meier methods and Cox regression. Timing of surgery was modeled as a time-dependent exposure to minimize immortal time bias, with additional analyses comparing alternative modeling approaches.

RESULTS

Among 5,161 patients, 2,688 (52.1%) underwent urgent resection. On unadjusted analysis, urgent surgery was associated with worse survival. In adjusted analyses, delayed surgery was not associated with improved survival at 5 years (HR 0.91, 95% CI 0.79–1.04; p=0.15), 10 years (HR 0.91, 95% CI 0.79–1.04; p=0.15), or 15 years (HR 0.92, 95% CI 0.82–1.03; p=0.13). Adequate lymph node evaluation (≥8 nodes) was independently associated with improved survival, whereas microscopic and macroscopic residual disease were independently associated with worse survival. Adequate lymph node retrieval & rates of R0 resection were improved in the delayed surgery group.

CONCLUSIONS

After accounting for confounding and immortal time bias, operative timing was not independently associated with long-term survival among patients with stage IV SB-NETs undergoing PTR. In contrast, oncologic quality measures, including adequate lymph

node evaluation and margin-negative resection remained independently associated with improved outcomes & were higher in the delayed surgery group. When surgery is pursued in stage IV disease, resection in a planned and optimized setting may improve oncologic quality.

ABSTRACT ID #36550

C-33

Prognostic Significance of Ki-67 Proliferation Index in Pulmonary Carcinoid Tumors: A Single-Center Retrospective Cohort Study

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BACKGROUND

Pulmonary carcinoid tumors are a rare neuroendocrine neoplasm classified as typical or atypical based on mitotic count and necrosis. Ki-67 is a well-established grading tool in gastroenteropancreatic neuroendocrine tumors, but prognostic value in pulmonary carcinoids remains less defined and is not part of the current WHO diagnostic criteria. We evaluated the association between Ki-67 index and clinical outcomes in a pulmonary carcinoid cohort at a single regional medical center.

METHODS

We conducted a retrospective cohort study of patients diagnosed with histologically confirmed pulmonary carcinoid tumors at Renown Regional Medical Center between January 2020 and December 2025. Patient demographics, tumor characteristics like Ki-67 proliferation markers, and clinical outcomes were collected and analyzed under IRB approval. Ki-67 values were categorized as low (≤5%) or elevated (>5%). Patients were classified as having stable disease if they were alive without documented recurrence or progression at last follow-up. Associations between Ki-67 category, histologic subtype, stable disease status, progression, and recurrence were assessed using Fisher's exact test.

RESULTS

A total of 56 patients were identified, including 45 (80.4%) with typical carcinoids and 11 (19.6%) with atypical carcinoids. Ki-67 was reported in 50 patients (89.3%). Elevated Ki-67 (>5%) was observed in 8 of 11 atypical tumors (72.7%) compared with 1 of 39 typical tumors (2.6%, $p<0.001$). Stable disease, defined as being alive without recurrence or progression at last follow-up, was more common among patients with Ki-67 ≤5% than among those with Ki-67 >5% (78% vs 11%, $p<0.001$). Patients with elevated Ki-67 demonstrated a higher rate of disease progression compared with those with low Ki-67 (33% vs 7%), although this difference did not reach statistical significance ($p=0.06$). Ki-67 was not associated with recurrence ($p=0.62$).

CONCLUSIONS

In a community-based cohort, elevated Ki-67 was strongly associated with atypical histology and adverse clinical outcomes including a lower likelihood of being alive without recurrence or progression at last follow-up with pulmonary carcinoid tumors. These findings support the potential utility of Ki-67 as a prognostic marker, and the concept that pulmonary carcinoids exist along a biologic continuum that may not be completely captured by the existing WHO framework and suggest that routine Ki-67 assessment could improve risk stratification. The incorporation of Ki-67 into pulmonary carcinoid classification in larger multicenter studies evaluating neuroendocrine tumor outcomes may assist in better identifying patients who may benefit from intensified surveillance or individualized management.

ABSTRACT ID #36646

C-34

Improvements in long-term survival for neuroendocrine neoplasm patients (2000-2025) reflecting over 2000 cytoreductive surgeries

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BACKGROUND

This study evaluated the impact of a dedicated surgical program on the outcomes of patients with neuroendocrine tumors (NETs). Because NETs are slow-growing and patients often survive for decades after surgery, long-term survival may be underrepresented in low-volume centers or multi-institutional meta-analyses. In 2017, our group published a single-center experience from 1000 cytoreductions (2000-2016). Since 2017, an additional 1010 cytoreductions have been performed, creating the largest single-institution report to date. We evaluated whether: 1) extended surveillance or increased cohort size impacts the accuracy of computed surgical survival, 2) overall survival has increased over the last quarter century, and 3) survival differs between surgical and non-surgical NET patients.

METHODS

Our institution's Neuroendocrine Cancer Program maintains a database of >9,000 treated patients using electronic medical records and Social Security master death database. Overall survival, length of follow-up, primary and metastatic tumor location, and demographic information were analyzed using Kaplan-Meier curves to calculate median overall survival (mOS) and 10-year survival.

RESULTS

(i) Effect of extended surveillance on original (2000-2016) cohort mOS (n=790): Follow-up increased from 11±8yrs to 15±4yrs, capturing an additional 240 deaths (469 total). Despite these additional data, computed mOS for pancreatic NET (PNET) (122 months, N=89) and Small Bowel NET (SB-NET) (172months, N=569) patients was not significantly different from previously published results. (ii) Impact of expanding the surgical cohort (2000-2025)(N-1611) on mOS: Ninety-day postsurgical mortality was 1.14%. Follow-up was 14±7yrs. PNET (N=387) mOS increased to 139 months (p=0.01) with a larger cohort (387 vs 89). In contrast, increasing the SB-NET cohort (N=964) did not affect mOS (173months). (iii) Improvements in overall survival: Ten-year survival for surgical PNET and SB-NET patients diagnosed between 2015-2025 (67%, 74%) was significantly greater compared to patients

diagnosed between 2007-2025 (58%, 65%) ($p<0.01$). No improvement was observed in non-surgical patients. (iv) Surgical vs non-surgical outcomes: Ten-year survival was significantly greater in surgical patients for PNET (58% vs 33%) and SB-NET (65% vs 56%) than in non-surgical patients ($p<0.01$).

CONCLUSIONS

Surgical cytoreduction in NET patients has low morbidity/mortality rates and results in extended survival. A larger PNET cohort more accurately calculated survival. Survival improved over 25-years, likely reflecting improvements in perioperative management. Surgical cytoreduction should play a major role in NET patient care. Accurate evaluation of survival is difficult without access to large, standardized subspecialty cohorts. Decades of comprehensive surveillance is required for statistical power.

ABSTRACT ID #36617

C-35

Brain Metastases in Patients with Pulmonary Neuroendocrine Tumors: Clinical Characteristics, Risk Factors, and Outcomes

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BACKGROUND

Brain metastases are an uncommon but clinically important complication of pulmonary neuroendocrine tumors (NETs) and are associated with poor prognosis. Risk factors for brain metastases in this population remain poorly defined, and current surveillance practices are not standardized. We aimed to identify clinical and pathologic factors associated with the development of brain metastases in patients with well-differentiated pulmonary NETs.

METHODS

We performed a retrospective study of 206 patients with metastatic, histologically confirmed, well-differentiated pulmonary NETs treated at Moffitt Cancer Center between 2008 and 2024. Patients with other neuroendocrine neoplasms were excluded. Clinical, imaging, pathology, and treatment data were collected. Of these patients, 94 underwent at least one brain MRI, and 29 developed brain metastases. Survival was estimated using Kaplan-Meier methods. Continuous variables were compared using independent t-tests and categorical variables using chi-squared tests. Receiver operating characteristic (ROC) analysis was performed to evaluate Ki-67 as a predictor of brain metastasis risk, identifying a threshold of 19% for risk discrimination.

RESULTS

Among 206 patients, 29 (14%) developed brain metastases. Median age at brain metastasis diagnosis was 58 years, and 23 patients (79.3%) had stage IV disease at initial pulmonary NET diagnosis. Mean[SJR1] Ki-67 index was higher in patients who developed brain metastases than in those who did not (22.0% vs 11.67%, $p<0.001$), and higher histologic grade was also significantly associated with brain metastasis development ($p<0.001$). A Ki-67 threshold of 19% discriminated[SJR2] patients at higher risk for brain metastases. Median time from pulmonary NET diagnosis to brain metastasis was 18 months. At brain metastasis diagnosis, 22 patients (75.9%) had multiple lesions, and 16 (55.2%) ultimately developed more than five brain metastases. Stereotactic radiosurgery was the most common initial brain-directed therapy (48.3%). Median overall

survival was 45 months from pulmonary NET diagnosis and 19 months from brain metastasis diagnosis.

CONCLUSIONS

Brain metastases in pulmonary NETs are relatively common and associated with poor survival. Ki-67 of at least 19% and higher histologic grade at diagnosis were associated with increased brain metastasis risk and may help identify patients who could benefit from closer neurologic surveillance and earlier brain imaging. Prospective studies are needed to define optimal screening and management strategies for this high-risk subgroup.

ABSTRACT ID #36635

C-36

Grade Progression and Morphologic Transformation in Neuroendocrine Tumors: A Single-Institution Retrospective Analysis

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BACKGROUND

Well-differentiated neuroendocrine tumors (NETs) may undergo grade progression over time, often accompanied by increasing Ki-67 and worse outcomes. Rarely, these tumors transform into poorly differentiated, neuroendocrine carcinoma (NEC)-like phenotypes, but the clinicopathologic and molecular features of this process remain poorly defined.

METHODS

We queried our IRB approved institutional pathology database for patients with two tumor specimens obtained ≥12 months apart, at least one demonstrating grade 3 NET, NEC, or high-grade neuroendocrine neoplasm, with at least one specimen reviewed at our center. Patient demographics, clinical features such as tumor primary site, types of treatment, pathologic features such as tumor differentiation, Ki-67, mitoses, p53/RB status, next-generation sequencing (NGS) when available, and survival outcomes were abstracted. Overall survival (OS) was estimated by Kaplan-Meier methodology, measured from the date of grade change to death or last follow-up.

RESULTS

Paired specimens were available for review in 35 of 43 eligible patients. Primary tumor sites included pancreas in 28 patients (65.1%), small intestine in 11 (25.6%), and other sites in 4 (9.3%; lung n=2, rectum n=1, kidney n=1). Over a median interval of 62 months, median Ki-67 increased from 7.5% to 39.3% in the entire cohort. Most patients (37/43, 86.0%) retained well-differentiated morphology at progression, whereas 3 patients (7.0%) demonstrated poorly differentiated or NEC-like morphology and an additional 3 (7.0%) had ambiguous or indeterminate differentiation. Notably, all 6 patients with NEC-like or indeterminate transformation had pancreatic primaries and were characterized by higher Ki-67 indices (median 74.5%) and greater prior treatment exposure compared to those retaining well-differentiated morphology (median 3 prior systemic therapies vs 2). Next-generation sequencing at the time of grade change was available in 26 patients

(60.5%), revealing *TP53* mutations in 11 (42.3%) and *RB1* alterations in 2 (7.7%). MSI-high or high tumor mutational burden was identified in 4 patients (15.4%), all with pancreatic primaries. Therapies received prior to grade change included somatostatin analogs (38/43, 88.4%), radioligand therapy (24/43, 55.8%), and CAPTEM (16/43, 37.2%). The median number of therapies before grade change was three in both pancreatic and small intestinal NETs. Following grade progression or transformation, platinum-based chemotherapy (14/43, 32.6%) and immunotherapy (5/43, 11.6%) were used more frequently. Median overall survival from initiation of first therapy after grade change was 38.5 months.

CONCLUSIONS

Grade progression in NETs is characterized by marked increase in Ki-67, but most often retains well-differentiated morphology, supporting grade escalation and dedifferentiation as distinct biologic processes. True NEC-like transformation was uncommon, restricted to pancreatic primaries, and enriched for *TP53* alterations.

ABSTRACT ID #36633

C-37

Real-World Utilization of Circulating Biomarkers in Well-Differentiated Gastroenteropancreatic Neuroendocrine Neoplasms

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BACKGROUND

The real-world use of circulating biomarkers in well-differentiated gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) is poorly characterized. We evaluated biomarker utilization within 1 year of diagnosis by primary tumor site.

METHODS

The TriNetX US Collaborative Network (2013–2023) was analyzed for adults with well-differentiated neuroendocrine neoplasms of the stomach, pancreas, small intestine, or large intestine/appendix/rectum. Poorly differentiated neuroendocrine carcinomas were excluded. Biomarker utilization was defined as at least one LOINC-coded laboratory order for chromogranin A (CGA), urine or serum 5-hydroxyindoleacetic acid (5-HIAA), serotonin, pancreatic polypeptide, pancreastatin, or neuron-specific enolase (NSE) within 1 year of diagnosis. Utilization was evaluated descriptively by primary tumor site.

RESULTS

Among 27,692 patients, primary sites included stomach (n=2,608), pancreas (n=4,637), small intestine (n=11,939), and large intestine/appendix/rectum (n=8,508). CGA was the most frequently ordered biomarker across all sites, ranging from 16.8% in large intestinal/appendiceal/rectal primaries to 35.6% in pancreatic primaries. Urine 5-HIAA utilization was highest in small intestinal tumors (8.3%) and ranged from 2.9% to 4.5% in other sites. Serum 5-HIAA was infrequently ordered across all sites (0.8%–4.2%). Serotonin utilization was highest in small intestinal tumors (13.7%) and ranged from 5.9% to 8.7% in other sites. Pancreatic polypeptide testing was most common in pancreatic primaries (5.7%) but remained uncommon in other sites (0.6%–1.7%). Pancreastatin utilization ranged from 1.5% to 5.8%, while NSE testing was rare (≤0.3%).

CONCLUSIONS

Circulating biomarker utilization within 1 year of diagnosis was low and varied by primary site among patients with well-differentiated GEP-NENs. CGA remained the most frequently ordered biomarker, while site-relevant testing such as urine 5-HIAA was performed in a minority of patients with small intestinal tumors. These findings demonstrate substantial variation in real-world biomarker use and highlight the need for more standardized, evidence-based testing strategies.

ABSTRACT ID #36638

C-38

Clinical Impact of Endoscopic Ultrasound Tissue Acquisition on Pancreatic Lesions ≤10mm

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BACKGROUND

Subcentimeter pancreatic lesions have variable malignant potential and are increasingly identified due to the widespread use of high-resolution cross-sectional imaging. The impact of EUS-guided tissue acquisition (EUS-TA) on management decisions in this population is not well characterized.

METHODS

We conducted a retrospective cohort study of patients who underwent EUS-TA for pancreatic lesions ≤10 mm over a 5-year period from 2020-2025. The primary outcome was a change in clinical management attributable to EUS-TA findings, defined as any alteration from the planned surveillance strategy, including surgical intervention (major impact) or discontinuation of surveillance (minor impact).

RESULTS

Eighty-seven patients underwent EUS evaluation of a total of 89 pancreatic lesions. TA identified malignant lesions in 53 cases (59.6%), most commonly pancreatic neuroendocrine tumors (PNET, n=41, 77.4% of malignant lesions), while 25 lesions (28.1%) were benign. TA was nondiagnostic in 11 cases (12.3%). EUS-TA findings did not alter management in 71 lesions (79.8%), for which continued surveillance was pursued. However, they changed management in 18 lesions (20.2%), including 12 lesions that underwent surgical resection (13.5%) and 6 in which surveillance was discontinued (6.7%). Among lesions managed with surveillance, mean follow-up was 1.96 ± 1.4 years. During follow-up, 13 lesions (18.3%) progressed in size, whereas 58 (81.7%) remained non-progressive, including lesions that remained stable, regressed, or resolved. EUS-TA was more likely to impact management when symptoms (9.8% vs 27.7%, p=0.047) or pancreatic duct abnormalities (5.6% vs 33.3%, p=0.004) were present. (Table 1). Among 12 surgically managed lesions, final surgical pathology changed the diagnosis in 3 cases (25%) (from PNET to benign, non-diagnostic to Intraductal Papillary Mucinous Neoplasm, and non-diagnostic to PNET). Four surgically resected lesions were confirmed as PNETs, all WHO grade 1, with Ki-67 indices ranging from 1.2% to 4.0%. Repeat EUS-guided sampling was required in 7 lesions (7.9%).

Table 1: Lesion and patient characteristics stratified by management impact after EUS-guided tissue acquisition

Variable	No effect on management N=71	Positive effect on management N=18	P value
Symptomatic presentation	7	5	0.047*
Pancreatic duct abnormality present	4	6	0.004*
Lesion size (>5mm)	66	17	1
Lesion location (head)	31	6	0.427
Lesion malignant on biopsy	44	9	0.424
Genetic syndrome	14	4	0.754
Personal history of pancreatic cancer	7	1	1

CONCLUSIONS

EUS-TA did not alter management in the majority of ≤10 mm in size. Symptomatic patient presentation and pancreatic duct abnormalities may designate lesions more likely to be clinically actionable.

ABSTRACT ID #36625

C-39

Real-World Evidence of Response to 177Lu-DOTATATE PRRT Based on Primary and Metastatic Sites in Patients with Neuroendocrine Tumor

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BACKGROUND

Neuroendocrine tumors (NETs) are rare tumors that commonly originate from the GI tract, pancreas, lung, and other sites. ^{177}Lu-PRRT was approved in 2018 for treatment of GI or pancreatic NETs. Here we report our institutional experience in pts with advanced NETs treated with PRRT and explore whether NETs of different primary and certain metastatic sites respond to PRRT differently.

METHODS

This is a retrospective observational study. Data were collected from the electronic health record. Eligible pts were ≥18 years old, had histologically confirmed metastatic NET, received ≥ 1 cycle of ^{177}Lu-PRRT between 1/1/2015 and 3/31/2025, had baseline and post-treatment imaging available for response assessment. The primary endpoint was overall response rate (ORR) after PRRT. Secondary endpoints included overall survival (OS), progress-free survival (PFS), disease control rate (DCR), and site-specific response by metastatic location. OS is defined as the time from PRRT initiation to death, PFS defined as the time from PRRT initiation to radiographic progression or death.

RESULTS

Two hundred and nine pts were included. Median age was 66 (57-72). Over half (53%) were male. The majority (71%) were Caucasian, 26% were Black. Half of the pts (49%) had grade (gr) 2 disease, 24% had gr 1, 12% had gr 3. For the overall cohort, the median OS was 46.0 (range 39.0-55.0) months (mo), median PFS 11.0 (9.0-12.0) mo. Complete response (CR) was seen in 1.5% of pts, 34.9% had partial response (PR), 52.0% stable disease (SD), with progressive disease (PD) in 11.6%. The overall DCR was 88.4%. The ORR according to primary site was 23.7% in GI (n=97), 52.5% in pancreas (n=40), 23.1% in lung (n=13), 0% in other (n=2), and 52% in unknown primary (n=25). DCR according to primary site was 85.6% in GI, 85.0% in pancreas, 92.3% in lung, 100.0% in other, and 92.0% in unknown primary. The best response of liver, peritoneal, and bone mets are summarized in Table 1.

Table 1.

Metastatic Site	N	CR (%)	PR (%)	SD (%)	PD (%)
Liver	187	2 (1.1)	58 (32.8)	94 (53.1)	23 (13.0)
Peritoneum	78	0 (0)	19 (25.3)	49 (65.3)	7 (9.3)
Bone	117	1 (0.9)	16 (15.0)	79 (73.9)	11 (10.3)

CONCLUSIONS

In this study, pts with pancreatic and unknown primary had a higher ORR to ^{177}Lu-PRRT compared to pts with other primaries. Response to PRRT is commonly seen in liver mets. Peritoneal and bone mets have a lower response rate but stable disease is achieved in the majority of pts.

ABSTRACT ID #36569

C-40

Outcomes with first-line obrixtamig plus standard of care in epNEC by DLL3 expression status: Phase Ib DAREON®-7 study

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BACKGROUND

Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager. This subgroup analysis of the ongoing Phase Ib dose-escalation/expansion DAREON®-7 trial (NCT06132113) examined safety and efficacy of first-line obrixtamig + standard of care (SoC; platinum/etoposide) in patients with extrapulmonary neuroendocrine carcinoma (epNEC) by DLL3 expression status.

METHODS

Patients had advanced epNEC, large cell NEC of the lung (LCNEC-L), or NEC of unknown primary site (CUP-NEC), with confirmed DLL3-expressing tumors (>0% tumor cells [TCs] with moderate-to-strong staining). Patients received 6 cycles of SoC + obrixtamig followed by obrixtamig maintenance (Q3W). Obrixtamig was given as step-up dosing followed by target dose (Part A: 10, 30, or 60 mg; Part B: 60 mg). SoC was given per label. Study endpoints include DLTs, ORR, PFS, DoR (RECIST v1.1, investigator-assessed), and

safety. Subgroup analyses: DLL3^{high} (≥50% of TCs with moderate-to-strong staining) vs DLL3^{low} (<50%) expression status. DLL3 was centrally assessed using an investigational antibody for DLL3 (SP347; Roche Diagnostics).

RESULTS

As of February 3, 2026, 44 patients received ≥1 dose of obrixtamig: epNEC, n=40 (DLL3^{high}/DLL3^{low}: n=21/19); LCNEC-L, n=2 (DLL3^{high}: n=2); CUP-NEC, n=2 (DLL3^{high}/DLL3^{low}: n=1/1). Baseline characteristics were well-balanced across DLL3 subgroups. Efficacy data are in the table. TEAEs (any/Grade ≥3): 100/93%. Obrixtamig-related CRS Grade 1/2: 59/14%; ICANS and potential ICANS-like neurotoxicity: Grade 1/2: 5/0% (all preferred-term ICANS). No Grade ≥3 CRS or Grade ≥2 ICANS were reported.

A notable case was observed in a 63-year-old patient with DLL3^{high} vaginal NEC and liver metastases. Following resection of the primary tumor (August 2024) and initiation of treatment (November 2024), PR was achieved after 6 cycles of SoC + obrixtamig (February 2025). Continued tumor shrinkage in all lesions on obrixtamig maintenance resulted in confirmed CR (April 2026). The patient remains on treatment with ongoing response and resolved early-onset low-grade AEs.

CONCLUSIONS

Encouraging efficacy was observed across both DLL3 subgroups, with a trend towards improved outcomes in patients with DLL3^{high} tumors, pending longer follow-up. These results support further development of obrixtamig + SoC in patients with DLL3-expressing epNEC in the ongoing Phase III DAREON®-NEC-1 trial (NCT07544654).

		Efficacy	
	Total (N=44)	**DLL3^{high} (n=24)**	**DLL3^{low} (n=20)**
Confirmed ORR, % (95% CI)	77 (63-87)	88 (69-96)	65 (43-82)
Median PFS, months (95% CI)*	7.7 (6.0-14.5)	9.5 (6.0-NC)	7.6 (4.6-9.0)
9-month PFS rate, % (95% CI)	44 (26-63)	58 (34-83)	34 (10-57)
Median DoR, months (95% CI)*	12.5 (5.5-NC)	NC (5.1-NC)	7.0 (5.5-NC)
*Immature data.			

ABSTRACT ID #36548

C-41

A Phase 1 Trial of the Oncolytic Virus SVV-001 with Nivolumab and Ipilimumab in Patients with High Grade Neuroendocrine Neoplasms.

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BACKGROUND

High-grade neuroendocrine neoplasms (NENs) are aggressive malignancies with limited treatment options. Immune checkpoint inhibitors (ICIs) have demonstrated meaningful but limited efficacy. Seneca Valley Virus (SVV-001) is a novel oncolytic RNA virus that has shown synergistic antitumor activity with ICIs in preclinical models. Additionally, SVV-001 has shown a favorable safety profile and the ability to reverse ICI resistance in vivo, supporting its evaluation in combination with nivolumab + ipilimumab (N+I).

METHODS

NCT06889493 is an investigator-initiated, phase 1 study evaluating intratumoral SVV-001 with N+I in patients with high-grade NENs. A 3+3 dose-escalation design will determine the recommended phase 2 dose (RP2D) with 3 single-injection dose levels (DL1-3) and 2 multiple-injection DLs (4-5), followed by expansion at the RP2D. The primary objective is to evaluate safety with secondary objectives being efficacy. Tumor Endothelial Marker 8 (TEM8), a potential biomarker of SVV-001 sensitivity and its association with efficacy signals will be investigated.

RESULTS

As of 1st July 2026, the trial has reached the end of the single-dose injection milestone with 13 pts (pts) enrolled on DLs 1-3. No DLTs were observed to date. Seven pts (54%) experienced Grade 3 serious adverse events (SAEs) unrelated to SVV-001 [abdominal pain (n=2); pneumonia, intracranial hemorrhage, anorexia, fatigue, biliary obstruction, seizure, fever (n=1)]. Other grade 3 AEs were observed in five (38%) pts; most common were anorexia (n=3), alanine aminotransferase increased and fatigue (n=2). Two

pts (15%) achieved a partial response, 2 (15%) had stable disease, 6 (46%) came off study due to disease progression, and 3 (23%) are currently receiving treatment– the objective response rate was 15% and the disease control rate was 31%. Biomarker analysis is ongoing. The multiple-dose injection DLs will begin enrollment in July 2026.

CONCLUSIONS

Single-dose injection of SVV1 with N+I demonstrates an acceptable safety profile and early signs of efficacy in a disease of a significant unmet need.

ABSTRACT ID #36594

C-42

First-Line Systemic Therapy Patterns and Survival in Advanced Neuroendocrine Carcinoma: An Agent-Level Registry Analysis

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BACKGROUND

National registries cannot resolve individual chemotherapy agents in neuroendocrine carcinoma (NEC) or characterize the clinical basis for non-treatment. We describe agent-level first-line treatment patterns, characterize the untreated population, and benchmark overall survival (OS) in a WHO-annotated institutional NEN registry.

METHODS

We conducted a single-institution retrospective analysis of 469 NEN patients at a CoC-accredited community cancer center from 2018–2025. WHO-aligned differentiation was chart-abstracted for 386 patients. The analytic cohort comprised 121 distant-stage NEC patients. Agent-level first-line treatment was extracted from free-text registry fields unavailable in SEER/NCDB. Kaplan-Meier with log-rank test compared OS by treatment group, and Cox regression estimated age effects on OS within PE-treated patients.

RESULTS

Of 121 distant-stage NEC patients, 62 (51.2%) received first-line platinum-etoposide (PE). Carboplatin-EP was used in 58 patients (93.5%) and has been the exclusive platinum agent since 2022; cisplatin was used in 5 patients (8.1%), with 1 receiving both agents sequentially. Checkpoint inhibitor (IO) was added to PE in 33 patients (53.2% of PE-treated); IO addition did not significantly prolong OS (14.0 vs. 6.0 months, p=0.588), though this comparison was underpowered. Overall PE-treated median OS was 11.0 months. Among 55 patients (45.5%) who received no systemic therapy, median OS was 2.0 months with 63.6% mortality within 3 months. The no-therapy group was significantly older (median age 74 vs. 67 years, p=0.002), supporting clinical ineligibility as the predominant driver of non-treatment.. Within PE-treated patients, age ≥70 independently predicted worse OS (HR 2.07, 95% CI 1.11–3.87, p=0.02).

Table 1. Treatment and Outcomes — Distant-Stage NEC (n=121)

Subgroup	n (%)	Platinum or IO Agent	Median OS
PE-treated — all	62 (51.2%)	Carbo-EP 91.9%; Cis-EP 8.1%	11.0 mo
— PE + IO	33 (53.2% of PE)	Atezo 69.7%, Durva 27.3%	14.0 mo

— PE alone	29 (46.8% of PE)	Carboplatin-EP	6.0 mo
No systemic therapy	55 (45.5%)	—	2.0 mo*

**Median age 74 vs. 67 years (p=0.002); 63.6% died within 3 months. IO vs. PE alone log-rank p=0.588 (underpowered). Four patients received non-PE regimens and are excluded. Carbo/Cis totals non-exclusive: 1 patient received both agents sequentially.*

CONCLUSIONS

Carboplatin-EP has replaced cisplatin-EP as the first-line NEC regimen at this community center. PE-treated median OS of 11.0 months exceeds US real-world benchmarks (~6–7 months in published NEC series) and approaches published multicenter trial outcomes. The no-therapy group's short survival and older age support clinical ineligibility rather than access failure. Prospective performance status documentation is needed to distinguish ineligibility from access barriers in future NEN registry analyses.

ABSTRACT ID #36658

C-43

Survival after resection of entero-pancreatic neuroendocrine tumors: a population-based analysis.

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BACKGROUND

Surgery plays a key role in the management of entero-pancreatic neuroendocrine tumors (EP-NETs). Understanding contemporary outcomes is essential for integration in decision-making and patient counseling. We examined long-term outcomes following resection for EP-NETs.

METHODS

We conducted a population-based retrospective cohort study of patients with EP-NETs (2000-2023) undergoing resection. The outcome of interest was overall survival (OS), as time from surgery to death from any cause, examined using Kaplan-Meier curves. Cox proportional hazard (OS) models examined factors associated with OS.

RESULTS

Of 3,536 patients included, 57.4% presented with metastases, 2,429 had small bowel (SB) NETs (67.6% metastases) and 1,107 had pancreatic NETs (PanNETs) (38.1% metastases). Median follow-up was 6 years (IQR 3-10), and 1,144 patients (32.4%) died during follow-up. 10-year OS was 65.9% (95%CI 64.1-67.8%) after surgery overall, 66.6% (95%CI 64.5-68.7%) for SB-NETs and 59.6% (95%CI 56.8-62.6%) for PanNETs, after adjustment for age, sex, comorbidity burden, and year of surgery. In those with metastases, 10-year adjusted OS was 58.9% (95%CI 56.5-61.5%) for SB-NETs and 50.9% (95%CI 46.9-55.3%) for PanNETs. Advancing age and higher comorbidity burden were independently associated with inferior OS overall and for SB-NET and PanNETs, while female sex was independently associated with superior OS. Of all deaths, 642 were cancer-related. In the sub-group with metastases undergoing resection combined with hepatectomy, 10-year OS was 70% (95%CI 68-72%) for SB-NETs and 10-year OS was 75% (95%CI 73-77%) for PanNETs.

CONCLUSIONS

This study established contemporary long-term outcomes after resection of EP-NETs at the population-level. Patients with EP-NETs selected for surgery experience prolonged OS, driven by age, sex, and comorbidity burden, in addition to tumor factors. This information can be used to inform decision-making, patient counseling, and future trial designs.

ABSTRACT ID #36426

C-44

Phase 1b Study of Zocilurtatug Pelitecan in Patients with Advanced Extra-Pulmonary Neuroendocrine Carcinomas

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BACKGROUND

Extra-pulmonary neuroendocrine carcinomas (epNECs) are aggressive malignancies with poor prognosis and limited treatment options following platinum-based chemotherapy. Delta-like ligand 3 (DLL3) is broadly expressed in neuroendocrine cancers and minimally expressed in normal tissues, making it an attractive therapeutic target. Zocilurtatug Pelitecan (Zoci, formerly known as ZL-1310) is a novel DLL3-targeted antibody-drug conjugate (ADC) utilizing the TMALIN® platform targeting DLL3-expressing tumor cells.

METHODS

This open-label, multicenter Phase 1b study enrolled patients with advanced or metastatic epNEC who progressed on or after platinum-based chemotherapy. Zoci was administered intravenously at 1.6 mg/kg every 3 weeks until disease progression or unacceptable toxicity. Investigator-assessed tumor responses were evaluated by RECIST v1.1 (and PCWG3 for neuroendocrine prostate cancer). DLL3 expression was assessed retrospectively via immunohistochemistry (IHC) using H-score analysis. The data cutoff date was February 18, 2026.

RESULTS

A total of 46 patients in Phase 1b were dosed. Among the modified response evaluable set (n=34), 53% (18/34) had gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC)

and 47% (16/34) had non-GEP NEC. The median number of prior systemic therapy lines was 1. The confirmed objective response rate (ORR) was 38.2% (13/34), and the overall disease control rate was 55.9% (19/34). Tumor reduction was observed across a diverse range of epNEC primary tumor types. Because of limited follow-up, progression-free survival and duration of response remained immature. Across the total safety population (n=46), 97.8% of patients experienced a treatment-emergent adverse event (TEAE), and grade ≥ 3 TEAEs occurred in 30.4% of patients. DLL3 expression, measured by H-score, were obtained in 31 efficacy evaluable patients, with 80.6% (25/31) being positive. The median H-score was 133. The ORR was 50.0% (8/16) in patients with DLL3 H-scores above the median, compared with 26.7% (4/15) in those expressing below the median. However, preliminary analyses did not reveal a definitive association between DLL3 expression and ORR.

CONCLUSIONS

Zoci demonstrates clinically meaningful responses and a manageable safety profile in heavily pretreated patients with epNECs. The frequency and severity of adverse events were consistent with previous clinical experience, establishing a preliminary favorable benefit-risk profile in this population. Responses were observed across a range of expression levels. With the Phase 1b portion complete, the study has expanded into Phase 2 to further evaluate the durability of response and clinical efficacy. Updated data, including durability of response, will be presented.

ABSTRACT ID #36547

P-1

Liver Metastases Independently Predict Worse Overall Survival in Neuroendocrine Carcinoma: A Differentiation-Stratified Analysis

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BACKGROUND

Liver metastases are an established adverse prognostic factor in neuroendocrine neoplasms (NEN). However, prior registry analyses conflate poorly differentiated neuroendocrine carcinoma (NEC) and well-differentiated neuroendocrine tumors (NET) — biologically distinct entities. Whether this survival effect is class-uniform or concentrated in NEC has not been examined in a WHO-annotated cohort.

METHODS

We conducted a single-institution retrospective analysis of 469 NEN patients at a CoC-accredited community cancer center (2018–2025). WHO-aligned differentiation class was chart-abstracted for 386 patients; this analysis includes 197 NEC and 165 NET patients with available survival data. Liver metastasis at diagnosis was coded from SEER collaborative stage fields. Stratified Cox proportional hazards regression was performed within each differentiation subgroup, adjusted for age, and in a combined model including NEC status.

RESULTS

Liver metastasis prevalence was higher in NEC (31.0%, 61/197) than NET (16.4%, 27/165). In NEC, liver metastases independently predicted markedly worse OS: HR 2.01 (95% CI 1.39–2.91, p<0.001); median OS 4.0 vs. 16.0 months (log-rank p=0.0001). In NET, the effect was directionally consistent but underpowered: HR 2.67 (95% CI 1.00–7.11, p=0.050); with only 19 events across 165 patients, median OS estimates are unreliable. In the overall adjusted model (n=362), liver metastasis remained independently significant (HR 2.12, 95% CI 1.50–2.99, p<0.001) after controlling for NEC status (HR 7.87) and age.

Table 1. Liver Metastasis and OS by Differentiation Stratum

Stratum	LM+ (n/total)	Median OS (LM+ vs LM−)	HR (95% CI)
NEC	61/197 (31.0%)	4.0 vs. 16.0 mo	2.01 (1.39–2.91)**
NET	27/165 (16.4%)	Not estimable†	2.67 (1.00–7.11)*
Overall (adj.)	88/362	—	2.12 (1.50–2.99)**

**p=0.050; **p<0.001. †19 events across 165 NET patients (including 27 LM+) preclude reliable median OS estimation. Overall model adjusted for age and NEC status (HR 7.87).*

CONCLUSIONS

In this WHO-annotated cohort, synchronous liver metastases robustly predict worse OS in NEC (median 4.0 vs. 16.0 months) but the NET effect remains underpowered with 19 events. Pooled NEN analyses without differentiation stratification risk generating liver metastasis effect estimates driven by NEC case-mix. These findings support differentiation-stratified analysis as a methodological standard for NEN prognostic research and suggest that the clinical significance of hepatic involvement — and by extension, the urgency and expected benefit of liver-directed intervention — may differ substantially between NEC and NET.

ABSTRACT ID #36659

P-2

Directional Misclassification of WHO Neuroendocrine Differentiation in a CoC Registry: Implications for SEER and NCDB Outcomes Research

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BACKGROUND

Accurate histologic grade coding is foundational to neuroendocrine neoplasm (NEN) registry-based research, as grade drives treatment selection, survival stratification, and external validity. Cancer registries use NAACCR-defined grade fields populated from pathology reports, which may not consistently capture WHO-recommended Ki-67-based grading for NEN. Systematic discordance would introduce non-random misclassification bias into SEER- and NCDB-based analyses relying on registry grade as the primary tumor characteristic.

METHODS

We conducted a single-institution analysis linking our CoC-accredited NEN registry (n=469) to WHO-aligned differentiation class chart-abstracted for 386 patients. Concordance was defined as agreement at the poorly versus well-differentiated level; within-class grade differences (e.g., G1 vs. G2 NET) were not counted as discordant. Of 386 chart-abstracted patients, 152 were analyzable (excluded: undetermined registry grade n=214, mixed differentiation class n=23). Directional asymmetry was tested with the binomial test.

RESULTS

Among 152 analyzable patients, concordance between registry-assigned grade and chart-abstracted WHO class was 95.4% (145/152). Discordance was identified in 7 patients (4.6%) and was entirely asymmetric: all 7 were under-coded (registry grade below WHO differentiation class; 7:0 ratio, binomial p=0.008). All discordant cases were NEC tumors assigned registry G1 (n=4) or G2 (n=3) rather than G3 — reflecting systematic failure to capture NEC in low registry-grade fields. Concordance was highest for NET G1 (97%, 121/125) and perfect for registry-assigned G3 (100%, 17/17 chart-confirmed NEC).

Table 1. Registry vs. WHO Grade Concordance (n=152)

Concordance Category	n	%	Note

Concordant	145	95.4	Agreement at poorly vs. well-differentiated level
Discordant — Total	7	4.6	7:0 ratio favoring under-coding (p=0.008)
— Under-coded	7	4.6	Registry G1 (n=4) or G2 (n=3); all chart-confirmed NEC
— Over-coded	0	0.0	None identified

152/469 included; excluded: undetermined registry grade (n=214 of 386 chart-abstracted), mixed differentiation (n=23), not chart-abstracted (n=83; some overlap). Binomial p=0.008. NEC=neuroendocrine carcinoma.

CONCLUSIONS

Registry grade under-coding in NEN is systematic: all 7 discordant cases were NEC tumors assigned registry G1 or G2, yielding a 7:0 directional ratio (p=0.008). Because NEC OS is measured in months vs. years for G3 NET, misclassification of NEC into low registry-grade fields attenuates grade-based survival differences in SEER and NCDB — producing upward bias in apparent low-grade survival. These findings underscore the need for WHO-aligned differentiation fields in prospective CoC registry updates and caution against use of registry grade as a WHO class surrogate in NEN outcomes research.

ABSTRACT ID #36662

P-3

Two decades of advances in neuroendocrine neoplasms care: has survival changed over time?

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BACKGROUND

The incidence of gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs) has risen worldwide over the past two decades, paralleling significant evolution in care through new systemic therapies, consensus guidelines, and the emergence of specialized multidisciplinary centres. Whether these advances have translated into improved overall survival (OS) for patients with GEP-NENs remains unknown. We examined temporal trends in OS after GEP-NEN diagnosis.

METHODS

We conducted a population-based retrospective cohort study using linked administrative datasets. Adults diagnosed with GEP-NENs between 2000 and 2019 were identified and followed until death, last contact, or five years after diagnosis. All had an opportunity for 5 years of follow-up. The primary outcome was death from any cause. OS was computed from date of diagnosis under a time-to-event framework. Restricted cubic spline (RCS) models assessed non-linear associations between year of diagnosis and the log-transformed hazards of death. Multivariable Cox regression examined the association of time period of diagnosis with OS, adjusting for age, sex, primary site, and metastatic status. Analyses were stratified by primary site and metastatic status at diagnosis.

RESULTS

Of 9,420 patients included, median age was 60 years and 51.4% were male. Metastases at diagnosis were present in 40.6%. The actual 5-year OS was 75.8% (95%CI 74.9-76.7%) overall, 88.8% (95%CI 87.9-89.6%) for non-metastatic disease, and 57.0% (95%CI 55.4-58.6%) for metastatic disease. A non-linear relationship was identified between year of diagnosis and hazards of death, with hazards dropping below 1 after 2013, consistent with improving OS in more recent years. Diagnosis between 2013-2019 was independently associated with lower hazards of death (adjusted HR 0.91, 95%CI 0.83-0.99). On stratified analysis, the reduction in hazards of death was confined to non-metastatic disease, with

no improvement observed for metastatic disease. By primary site, OS improved for pancreas, stomach, and rectum NENs, but not for small bowel and appendix NENs. When pancreas and small bowel NENs were further stratified by metastatic status, improvement was observed only for non-metastatic diagnoses.

CONCLUSIONS

Over two decades, OS for GEP-NENs has modestly improved. Gains were driven by non-metastatic diagnoses, particularly for primary NEN sites where incidental and early-stage detection has risen most sharply. This suggests that observed improvements reflect stage migration.

ABSTRACT ID #36340

P-4

Time to Treatment Initiation (TTI) and Survival Outcomes in Metastatic Extrapulmonary Neuroendocrine Carcinoma (EP-NEC)

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BACKGROUND

Advanced EP-NEC is typically treated with platinum plus etoposide, yet outcomes remain poor. Early systemic therapy is commonly pursued given the aggressiveness; however, data from small-cell lung cancer suggest that shorter TTI does not necessarily improve overall survival. The impact of TTI in advanced EP-NEC remains poorly defined.

METHODS

We conducted a multicenter retrospective study of adults with biopsy-confirmed stage IV EP-NEC treated across three Mayo Clinic sites from 2005–2025. TTI was defined as days from pathologic diagnosis to first-line systemic therapy and analyzed using a receiver operating characteristic–derived cutoff of ≤14 versus >14 days and as a continuous variable. Overall survival (OS) and progression-free survival (PFS) were evaluated using Kaplan–Meier and multivariable Cox models.

RESULTS

Among 248 patients, median age was 61 years and median TTI was 19 days. Median OS was 13.9 months (95% CI, 11.7–16.7), and median PFS was 5.7 months (95% CI, 5.3–6.3). Patients with TTI >14 days had longer median OS than those treated within ≤14 days (16.4 vs 10.1 months), with improved OS on unadjusted analysis (HR, 0.69; 95% CI, 0.50–0.96; p=0.028), although this was not significant after multivariable adjustment (HR, 0.74; 95% CI, 0.53–1.05; p=0.097). TTI >14 days was also associated with longer median PFS (6.5 vs 4.8 months), with improved PFS on unadjusted analysis (HR, 0.67; 95% CI, 0.51–0.88; p=0.0038) and after multivariable adjustment (HR, 0.75; 95% CI, 0.56–1.00; p=0.047). When analyzed as a continues variable, TTI was not independently associated with OS (HR, 0.99; 95% CI, 0.98–1.00; p=0.173) or PFS (HR, 0.99; 95% CI, 0.98–1.00; p=0.089).

CONCLUSIONS

In this large multicenter cohort of stage IV EP-NEC, earlier systemic therapy initiation (≤14 days) was not associated with improved OS. Although TTI >14 days was associated with

improved PFS, continuous TTI showed no significant association with OS or PFS, suggesting that this finding may reflect patient selection or clinical context rather than a direct effect of delayed treatment. These findings may provide reassurance when short delays are needed for biomarker testing or clinical trial enrollment.

ABSTRACT ID #36623

P-5

Functional Neuroendocrine Neoplasms (NENs) With Parathyroid Hormone–Related Peptide (PTHrP)-Mediated Hypercalcemia: A Retrospective Study

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BACKGROUND

PTHrP-mediated hypercalcemia in NENs is extremely rare, with only a few reported cases. This study aimed to characterize its clinical features, management, and outcomes.

METHODS

This retrospective multicenter study included adults with confirmed NENs and documented PTHrP-mediated hypercalcemia across three Mayo Clinic sites. Clinical, laboratory, and treatment data were extracted from the electronic medical record. Outcomes included calcium normalization, recurrence patterns, and treatment response. Data were analyzed descriptively.

RESULTS

A total of 15 patients with NENs and PTHrP-mediated hypercalcemia were identified. Median age at hypercalcemia onset was 62 years (interquartile range [IQR], 57.5–67.5), and 11 (73%) were male. All tumors were pancreatic in origin and well differentiated, with a median Ki-67 index of 8% (IQR, 5–12.6). Hypercalcemia was present at NEN diagnosis in 11 (73%) and developed later during disease progression in 4 (27%). At hypercalcemia onset, 13 (87%) had metastatic disease, all with liver involvement, while 2 (13%) had locally advanced disease. Supportive management included hydration plus bisphosphonates in 12 (80%) and denosumab in 1 (7%). Among 13 patients receiving supportive therapy, normocalcemia was achieved with supportive therapy alone in 2 (15%), and only after the addition of subsequent cancer-directed therapy in 9 (69%) patients. Among 2 nonresponders (15%), 1 normalized after switching to denosumab and 1 remained hypercalcemic despite multiple supportive and cancer-directed therapies in the setting of continued disease progression. Cancer-directed treatment to achieve normocalcemia was used in 13 (87%) patients, which included systemic treatment (CAPTEM, SSAs, PRRT, everolimus, temozolomide) in 10 (77%) patients and locoregional therapy in 3 (23%), all of whom underwent surgery. Overall, hypercalcemia recurred in 6 of 14 patients who achieved normocalcemia (43%), with a median time to recurrence of 8.1 months.

Recurrence coincided with radiographic progression in 4 (67%), while 2 (33%) recurred without radiographic progression. Among patients with recurrence, 1 responded again to bisphosphonate therapy, while the remaining 5 patients were refractory to further supportive and cancer-directed therapies. Notably, among the 3 patients who underwent debulking surgery, calcium normalized immediately after surgery and did not recur.

CONCLUSIONS

Supportive therapy alone achieved normocalcemia in a minority of patients with PTHrP-secreting pNETs. Most patients required cancer-directed therapy, and recurrent hypercalcemia was frequently refractory to additional treatment. Surgical cytoreduction was associated with rapid and durable calcium control in selected patients.

ABSTRACT ID #36624

P-6

Meeting exercise guidelines is associated with improved quality of life in patients with advanced neuroendocrine neoplasms: Results from NET Voices

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BACKGROUND

Patients with neuroendocrine neoplasms (NENs) can have disease-related symptoms and treatment side effects that may affect their quality of life (QOL). Using data from NET Voices, a prospective web-based cohort of 273 patients with advanced NENs of any primary site that we previously introduced at NANETS Medical Symposium (Mulvey abstract ID 21430), we evaluated four measures of QOL and their associations with moderate to vigorous physical activity (MVPA).

METHODS

Participants completed repeated assessments of anxiety, depression, sleep quality, physical functioning, and physical activity over three e-visits spanning 18 months. MVPA was measured using a self-reported questionnaire and categorized as meeting the guideline of ≥150 minutes/week. Linear mixed-effects models were used to evaluate the associations of MVPA and clinical and demographic factors with repeated measures of QOL.

RESULTS

Among 273 participants enrolled in NET Voices to date, 120 who reported all study variables were analyzed: 76 women (63%), median age 68 years (range 38-86). A total of 7 had body mass index underweight (6%), 59 healthy weight (49%), and 54 overweight-obese (45%). There were 63 participants with histologic grade 1 (52%), 46 grade 2 (38%), and 11 grade 3 (9%). A total of 10 participants had no comorbidities (8%), 57 one to two (48%), and 53 three or more (44%). Few participants (12%) reported difficulty paying for basics. Most participants (71%) met MVPA guidelines. All four QOL scores were on average good; anxiety median was 55 [range 40-72], depression 52 [41-70], sleep 5 [0-19], and physical functioning 87 [13-100]. Higher score was worse in the former three, better in the

latter. Participants who met MVPA guidelines reported statistically significantly less depression (mean change -2.3 with 95% confidence interval [-4.4 to -0.2], p=0.035), better sleep (-1.5 [-2.8 to -0.1], p=0.035), and better physical functioning (8.2 [1.1 to 15.3], p=0.024). Models showed no evidence that anxiety was associated with MVPA (-0.7 [-2.9 to 1.6], p=0.568), but anxiety was worse among women (3.2 [0.8 to 5.5], p=0.008), participants who were younger (4.0 [1.5 to 6.6], p=0.002), underweight 6.3 [2.2 to 10.3], p=0.003), with higher grade tumor (5.8 [1.9 to 9.6], p=0.003), and who reported difficulty paying for basics 5.0 [1.8 to 8.1], p=0.002).

CONCLUSIONS

Patients living with advanced NENs who met exercise guidelines reported better QOL compared to patients who exercised less. This result is promising and paves the way for possible future exercise intervention studies and behavioral changes NENs patients might undertake to improve QOL.

ABSTRACT ID #36605

P-7

Characterization of Gastroenteropancreatic Neuroendocrine Neoplasms in Older Adults

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BACKGROUND

Approximately 20% of patients with gastroenteropancreatic neuroendocrine neoplasms (GEPNENs) are older adults (OAs), defined as age ≥70 at diagnosis. In practice, treatment decisions are individualized based on comorbidities, performance status, and goals of care. An evidence-based approach to medical decision-making is needed. We aimed to characterize the clinicopathologic features of OA-GEPNENs, treatment patterns, and survival outcomes.

METHODS

We conducted a retrospective review of OA-GEPNEN (any grade, differentiation, or stage) identified between 2011-2023 using an IRB-approved database at the University of California, San Francisco. We compared demographic and clinicopathologic characteristics across treatment groups using Chi-squared and Mann-Whitney tests. Overall survival (OS) by age group was analyzed using the Kaplan-Meier method with log-rank test.

RESULTS

Of 1,023 patients, 165 (16.1%) had OA-GEPNEN; n=90 (55%) with GI) and n=75 (45%) with pancreatic NEN. The median age at diagnosis was 75 years; 52% female, and 68% White. Among 146 patients with tumor grade information, 42% grade 1, 36% grade 2, and 22% grade 3. At presentation, 46% had distant disease and 13% of tumors were poorly-differentiated. Overall, 125 paients (76%) were treated; 45% underwent surgical resection, 36% received somatostatin analogs, 19% chemotherapy, 13% focal radiation, 10% peptide receptor radionuclide therapy, and 16% liver-directed therapy. Chemotherapy use correlated with tumor grade (G1: 2% vs. G3: 59%, p<0.001), and males were more likely to receive chemotherapy (29% vs. 9%, p=0.001). Among patients with pancreatic NENs, median OS from diagnosis was 78 months, 39% of deaths were attributed to cancer. Patients diagnosed at age ≥80 were more likely to be female (68% vs. 40%, p=0.045) and less likely to undergo resection (18% vs. 53%, p=0.041) than those age 70-79. Among patients with stage I–III pancreatic NEN, those with age ≥80 had significantly worse OS

(median 80 vs. 175 months, p=0.012), however, there was no significant difference in patients with stage IV disease (median 18 vs. 41 months, p=0.17).

CONCLUSIONS

In this single-center retrospective cohort, age and sex-related differences in patient characteristics, treatment patterns, and outcomes suggest additional work is needed to refine treatment strategies for OA-GEPNENs and reduce barriers to care. Ongoing work is focused on understanding the impact of treatment on OS. Future analyses will incorporate the OA-GI-NEN cohort, additional comorbidity measures, age at treatment initiation, cause of death between stages, treatment tolerability, and cancer-specific survival. Ultimately, our findings will be compared with population-level datasets and a UCSF cohort of patients with early-onset NENs.

ABSTRACT ID #36546

P-8

WHO Mitotic/Ki-67 Grading Completeness and Distribution in Neuroendocrine Neoplasms (NENs), in the Surveillance, Epidemiology, and End Results (SEER) Program

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BACKGROUND

NENs are a heterogeneous group of malignancies whose classification has evolved over time. The implementation of the WHO mitotic count/Ki-67 grading and histological classification developed for gastroenteropancreatic (GEP) NENs in the Surveillance, Epidemiology, and End Results (SEER) program in 2018 provided the first opportunity to characterize population-level grade & histological distributions.

METHODS

We analyzed SEER data from 2018–2022 for NENs (WHO mitotic/Ki-67 grading was not captured in SEER prior to 2018) arising at GEP, lung and other primary sites. Grading was assessed using the WHO mitotic count/Ki-67 classification (G1–G3), with cases also characterized by histological differentiation coding (well-, moderately-, poorly- and un-differentiated) where available. Demographic characteristics were evaluated by sex, race/ethnicity, and age group.

RESULTS

Among 40,849 NEN cases diagnosed from 2018–2022, grade, G remained unassigned in 23,970 (58.7%). Of the 13,446 (32.9%) cases with a definitive WHO grade, 10,280 (76.5%) were G1, 1,755 (13.1%) were G2, and 1,411 (10.5%) were G3. Within the GEP NEN sites, appendiceal (94%) and colorectal (87%) NENs were overwhelmingly G1 while esophageal (90%) and anal (78.3%) were predominantly G3. Other sites with high G3 NENs included cervix and uterus (89-91%). Females comprised 54.7% of G1 and 53.7% of G2 cases, while G3 tumors were more common among males (57.3%). Higher-grade tumors occurred more frequently in older adults, with 59.1% of G3 cases diagnosed among individuals aged 65 years or older compared with 40.7% of G1 cases. Of note, lung NENs were also classified according to the 2018 WHO GEP NEN criteria in the SEER program and exhibited a relatively greater proportion of G3 tumors (19.7%). Of the 3,433 patients across all sites (8.4%) with histological differentiation, 89% were well-, 4% were moderately- and 7% were

poorly differentiated. However, these patients were coded only with histological differentiation and excluded from grade coding.

CONCLUSIONS

The incorporation of WHO classification into the SEER program provides the first opportunity for a population-based analysis of grade distribution for NENS. However, several opportunities for improvement still exist: a) grade was unrecorded in nearly 60% of cases that underscores a fundamental limitation of current cancer registry infrastructure b) grade & histological classifications were mutually exclusive limiting ability to classify G3 NENs and c) GEP NEN classification was used for lung NENs as well in contrast to current guidelines. Additional details regarding grade and histological distribution across sites and demographic information will be presented at the conference.

ABSTRACT ID #36573

P-10

Characterizing the Epidemiology and Treatment Patterns of Carcinoid Syndrome Among Neuroendocrine Neoplasms in a Large Population-Based Database

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BACKGROUND

Neuroendocrine neoplasms (NENs) may secrete serotonin and other vasoactive substances causing carcinoid syndrome (CS), which can impair quality of life and reduce survival. Expanding upon prior epidemiological findings, this study characterizes CS at extra-pancreatic NEN diagnosis and its treatment within 1 year after diagnosis.

METHODS

Patients aged ≥65 years with NENs diagnosed between April 2017 and December 2021 and with continuous Medicare coverage were included; pancreatic NENs, small-cell/large-cell neuroendocrine carcinoma, and non-neuroendocrine lung cancer cases were excluded. CS was defined by ≥1 claim for CS or carcinoid heart disease (CHD) or ≥2 claims for diarrhea or flushing 3 months before or 6 months after extra-pancreatic NEN diagnosis. Patient characteristics and treatments were compared between patients with and without CS using chi-square, Fisher exact, and multivariable logistic regression tests. Sensitivity analyses assessed possible coding bias.

RESULTS

Of 8966 patients with extra-pancreatic NENs, 17.4% had CS at NEN diagnosis. The rate of CS among patients with extra-pancreatic NENs was consistent across the study period. Patients with CS were more likely than patients without CS to be female (P=0.001) and to have midgut tumors, regional/distant/unknown stage disease, and grade 2 tumors

(*P*<0.001 for each). Somatostatin receptor ligands (SRLs) were the most common treatment overall, and SRL use was significantly higher among patients with versus without CS (36.1% vs 11.4%; *P*<0.001). Patients with CS also had higher rates of liver-directed surgery (6.0% vs 1.8%; *P*<0.001), liver-directed therapy (4.6% vs 1.8%; *P*<0.001), other therapy (1.7% vs 0.9%; *P*=0.005), radiopharmaceuticals (1.8% vs 0.3%; *P*<0.001), and CHD surgery (1.0% vs <0.1%; *P*<0.001) than patients without CS. Across all tumor grades, patients with CS received more treatments than those without CS.

CONCLUSIONS

Among extra-pancreatic NENs, CS incidence remained steady over time (2017-2021). These findings emphasize the need to characterize the full disease course of NENs and CS at a population level. SRL use was lower than anticipated, suggesting potential barriers to use or misclassification of CS diagnoses due to incorrect coding.

ABSTRACT ID #36529

P-11

NANETS NETPact Survey on Barriers to Providing Care for Neuroendocrine Cancer: A Dual-Perspective Analysis of Patient and Provider Experiences

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BACKGROUND

Neuroendocrine Neoplams (NENs) are a heterogeneous group of neoplasms with rising incidence and prevalence in the United States, yet substantial barriers to optimal care persist despite advances in diagnosis and treatment. To better charcterize these barriers, the North American Neuroendocrine Tumor Society (NANETS) NETPact initiative conducted parallel surveys of patients/caregivers and healthcare providers (HCPs) to capture dual perspectives on access and quality of care.

METHODS

Two cross-sectional, web-based surveys were administered as part of the NANETS NETPact patient advocacy initiative. The patient survey collected 181 responses from patients and caregivers affected by NENs, and the provider survey captured 64 responses from multidisciplinary HCPs involved in neuroendocrine neoplasm care. Survey domains included access to specialist care, diagnostic challenges, treatment patterns, financial and insurance barriers, care coordination, clinical trial awareness, and priorities for improvement.

RESULTS

Among patients, 72% reported diagnostic challenges, with 32.8% waiting more than 2 years from symptom onset to diagnosis. Nearly 29% traveled more than 100 miles for specialist care, and 10.8% lacked specialist access entirely. Financial barriers were prevalent, with 47.6% reporting out-of-pocket cost barriers and 72.1% citing travel costs as burdensome. Only 28% reported being informed about clinical trials. Among providers, insurance and reimbursement barriers were rated as the most impactful obstacle (52.9% rating them very or extremely significant), followed by healthcare system fragmentation (67.3% rating moderately to extremely significant) and challenges with clinical trial enrollment (74% encountering these sometimes to always). Both groups identified expanding the workforce of NEN-knowledgeable professionals as the top priority for improvement (75.0% of patients; 66.7% of providers).

CONCLUSIONS

The NANETS NETPact Survey reveals persistent, multilevel barriers to NEN care in the United States, with notable concordance between patient and provider perspectives. These findings support an urgent need for expanded NEN-specific education, improved insurance coverage for diagnostics and therapies, enhanced multidisciplinary care coordination, and increased clinical trial awareness, highlighting actionable opportunities for targeted education and advocacy through NANETS and its NETPact initiative.

ABSTRACT ID #36572

P-12

Clinical Profile of Brain Metastases in Lung and High-Grade Neuroendocrine Neoplasms

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BACKGROUND

Brain metastases are an uncommon but significant complication of neuroendocrine neoplasms (NENs). While routine brain imaging is recommended for selected aggressive pulmonary neuroendocrine carcinomas, it is not routinely performed in patients with well-differentiated neuroendocrine tumors (NETs). Real-world data describing the distribution of diagnosis-time brain metastases across the spectrum of NETs and NENs remain limited. We evaluated the prevalence, clinicopathologic characteristics, treatment patterns, and survival associated with brain metastases at diagnosis in a large community-based cohort.

METHODS

We performed a retrospective study of 386 patients with NETs/NENs treated at a large community cancer center. Brain metastases were defined using the diagnosis-time brain metastasis variable; subsequent CNS progression was analyzed separately. Prespecified cohorts included lung-primary, high-grade, and combined lung/high-grade disease. Overall survival (OS) was measured from diagnosis until death or last follow-up. Radiation records were reviewed to identify any radiation therapy and possible brain-directed radiation. Survival was estimated using Kaplan-Meier methods and compared with the log-rank test; adjusted Cox modeling was exploratory.

RESULTS

Among 386 patients, brain metastases at diagnosis were identified in 43 (11.1%). Notably, all diagnosis-time brain metastases occurred within the predefined lung/high-grade cohort (43/257, 16.7%), whereas no patients outside this group had brain metastases at presentation. Brain metastases occurred in 42/217 (19.4%) lung-primary patients and 42/211 (19.9%) high-grade patients. Among affected patients, 42/43 (97.7%) had pulmonary primary tumors, 38/43 (88.4%) had small cell carcinoma, and 42/43 (97.7%) had poorly differentiated/high-grade neuroendocrine carcinoma. Median age was 69 years, and 22 patients (51.2%) were male. Extracranial metastatic disease was present in 28/43 (65.1%), most commonly involving distant lymph nodes (23.3%), liver (20.9%), bone (20.9%), and other metastatic sites (27.9%). Among 36 evaluable patients, 33 (91.7%) received radiation therapy and 29 (80.6%) had documentation consistent with brain-directed radiation.

Within the lung/high-grade cohort (n=255; 131 deaths), diagnosis-time brain metastases were associated with significantly shorter median OS compared with patients without brain metastases (4.9 vs. 32.4 months; log-rank p=0.005). Exploratory evaluation of subsequent CNS progression likewise identified brain metastases only among patients with lung/high-grade disease.

CONCLUSIONS

In this large community cohort, diagnosis-time brain metastases demonstrated striking disease specificity, occurring exclusively in pulmonary and/or high-grade neuroendocrine neoplasms and not among patients with well-differentiated or extrapulmonary NETs. These findings support current selective CNS staging practices and reinforce that routine brain imaging appears unnecessary for asymptomatic patients with well-differentiated NETs, while emphasizing the importance of brain evaluation in aggressive pulmonary/high-grade neuroendocrine neoplasms. Prospective studies are warranted to validate these findings and further refine risk-based CNS imaging strategies.

ABSTRACT ID #36647

P-13

Prognostic Associations of Metastatic Site at Diagnosis in Neuroendocrine Neoplasms

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BACKGROUND

Metastatic site at diagnosis may capture clinically important heterogeneity in neuroendocrine neoplasms (NENs), but real-world patterns and site-specific survival associations remain incompletely characterized.

METHODS

We analyzed patient-level records from a single-institution retrospective NEN dataset. Tumor class was grouped as NEC/poorly differentiated NEC, NET/well-differentiated NET, mixed/MiNEN, or unknown/other. Metastatic sites at diagnosis were abstracted as liver, brain, bone, lung, distant lymph node, or other; review further categorized other-site entries. Overall survival (OS) was evaluated using Kaplan-Meier/log-rank methods and exploratory Cox models adjusted for tumor class, age, sex, and primary site group.

RESULTS

Among 386 patients, 165 (42.7%) had metastatic disease at diagnosis; one patient had missing metastatic-status data. Tumor class included NEC/poorly differentiated NEC (n=198), NET/well-differentiated NET (n=166), mixed/MiNEN (n=12), and unknown/other (n=10). The most common metastatic sites were liver (n=90; 23.3% of all patients; 54.5% of metastatic patients), other (n=56; 14.5%; 33.9%), bone (n=44; 11.4%; 26.7%), brain (n=43; 11.1%; 26.1%), distant lymph node (n=38; 9.8%; 23.0%), and lung (n=14; 3.6%; 8.5%). NEC/poorly differentiated NEC had a higher metastatic-at-diagnosis frequency than NET/well-differentiated NET (119/198, 60.1% vs 38/166, 22.9%; p<0.001) and higher liver, brain, bone, distant lymph node, and other-site involvement. Other-site review found 36 definite/probable and 20 unclear entries; leading categories were peritoneal/abdominal serosal, pleural/effusion, adrenal, and soft tissue/skin.

OS analyses included 386 patients and 150 deaths. Median OS was 64.0 months overall. In unadjusted analysis, median OS was 12.4 months with metastatic disease versus not reached without metastatic disease (p<0.001). Increasing metastatic burden was associated with shorter OS (0 sites: not reached; 1 site: 47.9 months; ≥2 sites: 5.36 months; p<0.001). In exploratory adjusted Cox models, any metastasis (HR 2.10, 95% CI 1.48–2.98), liver metastasis (HR 2.23, 95% CI 1.55–3.22), and bone metastasis (HR 2.84, 95% CI 1.91–4.22) remained associated with worse OS; the bone model had proportional-hazards concern.

CONCLUSIONS

Metastatic patterns differed substantially by tumor class in this real-world NEN cohort. Metastatic disease, multisite burden, liver metastasis, and bone metastasis were associated with worse OS, supporting cautious incorporation of metastatic pattern into future risk-stratification models. Findings remain vulnerable to residual confounding by grade, treatment, and disease biology.

ABSTRACT ID #36644

P-14

Composite Metastatic Organ Burden Refines Prognostic Stratification Beyond AJCC M1 Substaging in Neuroendocrine Neoplasms

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BACKGROUND

AJCC 8th edition introduced M1 substaging (M1a: hepatic only, M1b: extrahepatic only, M1c: hepatic + extrahepatic) for neuroendocrine neoplasms (NEN). Prior validation studies derive largely from gastrointestinal NET registries and SEER data with limited differentiation granularity. Whether composite metastatic organ burden—operationalized as number of concurrently involved sites—adds discriminative power beyond categorical M1 substaging in a mixed-site cohort enriched for lung primary and poorly differentiated histology remains uncertain.

METHODS

Single-institution CoC-accredited NEN registry, 2018–2025. 469 patients; WHO-aligned differentiation class manually abstracted (NEC 51%, NET G1/G2 28%, Well-differentiated 14%, Mixed 6%). Metastatic site involvement at diagnosis coded from SEER collaborative stage fields (bone, brain, liver, lung, distant lymph nodes, other). M1 subcategory assigned per AJCC 8th edition. Composite metastatic burden operationalized as continuous count of involved organ sites. Cox proportional hazards regression performed with age adjustment. Kaplan-Meier analysis used for subgroup comparisons; log-rank test for pairwise significance

RESULTS

Of 386 patients with linked differentiation and survival data, 164 (42.5%) had distant metastasis. M1 substaging distribution: M1a (liver only) n=35 (21%), M1b (extrahepatic only) n=75 (46%), M1c (hepatic + extrahepatic) n=54 (33%). Median OS by M1 subcategory: M1a 19 months, M1b 12 months, M1c 4 months. All pairwise comparisons were significant (M1a vs M1b p=0.04; M1a vs M1c p=0.002; M1b vs M1c p=0.04). This cohort is notable for lung-predominant primary site with M1b constituting the largest M1 subgroup, reflecting extrahepatic pulmonary spread. Continuous composite burden (sites per patient) independently predicted mortality after age adjustment: HR 1.66 per additional site (95% CI 1.47–1.87, p<0.001). Within M1 patients, those with ≥2 concurrently involved organ sites had significantly worse OS than single-site involvement: median OS 5 vs 17 months; HR 1.88 (95% CI 1.25–2.83, p=0.003).

Table 1. M1 Substaging and Composite Burden: Survival Outcomes

M1 Category	n	Median OS (mo)	HR vs Reference
M1a - Hepatic Only	35	19	reference
M1b - Extrahepatic only	75	12	1.6 (p=0.04)
M1c - Hepatic + extrahepatic	54	4	4.2 (p=0.002)
≥2 organ sites (within M1)	82	5	hr 1.88 (P=0.003)
Single organ site	82	17	Reference

All M1 pairwise OS comparisons significant by log-rank test. Composite burden HR adjusted for age at diagnosis.

CONCLUSIONS

Composite metastatic organ burden provides discrimination beyond AJCC M1 subcategory alone in a community NEN cohort enriched for lung primary and high-grade histology. The M1a-M1b-M1c gradient was preserved, and ≥2 concurrently involved sites identified a subgroup with markedly worse prognosis even after site-based substaging. These findings support prospective collection of site-specific metastatic burden as a standard registry variable, particularly in mixed-site cohorts where extrahepatic (M1b) disease predominates.

ABSTRACT ID #36648

P-15

Germline pathogenic/likely pathogenic (P/LP) variants in epithelial neuroendocrine neoplasms: The case for universal germline genetic testing

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BACKGROUND

Current National Comprehensive Cancer Network (NCCN) guidelines for germline testing in neuroendocrine neoplasms (NENs) rely on organ-specific, syndrome-driven algorithms that may not adequately capture hereditary risk. We sought to analyze prevalence of P/LP germline variants in epithelial NENs and investigate relevant associations.

METHODS

Germline genetic testing results were analyzed from 3,611 probands. Cohort 1 included 3,409 patients identified by ICD-10 code C7A (2015–2025). Cohort 2 included 201 consecutively curated patients with pathology information (2019–2021). Except 59 single-gene tests, multigene panels included a mean of 67 and 62 genes in Cohorts 1 and 2, respectively. Data was classified as P/LP, variant of uncertain significance (VUS), or negative. Comparisons of variant classification frequencies between cohorts were performed using chi-square or Fisher's exact tests. Multivariable logistic regression evaluated clinical and demographic predictors of P/ LP variant detection, with results reported as likelihood ratios (LR) and two-sided p-values (<0.05 considered significant).

RESULTS

Among all 3,611 probands, mean age was 56 years in Cohort 1 and 53 years in Cohort 2, with females comprising 63% and 71%, respectively. VUS and negative results differed between cohorts (VUS 21.9% vs 32.9%, p = 0.002; negative 67.4% vs 55.0%, p <0.001), while P/LP rates were similar (10.6% vs 12.1%, p = 1.0), permitting pooled analysis. Overall, 387 patients (10.7%) harbored P/LP variants, with 399 P/LP variants identified across 49 genes.

Sixty percent of P/LP variants were accounted for by CHEK2, MEN1, BRCA2, ATM, FH, HOXB13, PALB2, and BRCA1. Clinically actionable variants per NCCN guidelines were identified in 348 patients (9.6%). Among 479 probands with curated family history, meeting NCCN criteria for multigene testing or having a family history was not predictive of P/LP detection. Logistic regression demonstrated that male sex was a significant predictor of P/LP variants (LR = 4.538, p = 0.03), while age at diagnosis and primary site were not predictive, nor were interaction terms significant.

CONCLUSIONS

In this 10-year, multicohort study of patients at a commercial laboratory, over one in ten patients with epithelial NENs harbored a germline P/LP variant, frequently outside classic hereditary NEN syndromes and inadequately predicted by NCCN criteria, family history, age, or tumor site. These findings suggest that current germline testing frameworks may miss clinically relevant hereditary cancer risk. Broader approaches to germline testing may be needed to improve identification of hereditary cancer risk and enable personalized prevention and surveillance strategies.

ABSTRACT ID #36500

P-16

Patient-Reported Outcomes and Demographic Representation in Contemporary Phase III/IV Neuroendocrine Tumor Clinical Trials: A Systematic Trial-Level Review

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BACKGROUND

Neuroendocrine tumors (NETs) are rare, heterogeneous malignancies in which treatment decisions must balance disease control, symptom burden, and long-term health-related quality of life (HRQoL). As the therapeutic landscape has expanded substantially since 2006 - spanning somatostatin analogues, targeted therapies, and peptide receptor radionuclide therapy (PRRT) - it remains unknown how consistently patient-reported outcomes (PROs) have been incorporated, and whether enrolled populations reflect the racial, ethnic, and age diversity of patients seen in clinical practice.

METHODS

We identified phase III/IV trials and major extension studies enrolling adults with well-differentiated gastroenteropancreatic, bronchopulmonary, and thymic NETs, including carcinoid syndrome trials from June 2006- June 2026. ClinicalTrials.gov registry records and primary publications were systematically abstracted for: study phase, baseline demographic availability, Black/African American and Hispanic/Latino enrollment reporting, and age-stratified reporting (≥65 and ≥75 years), PRO inclusion, PRO instrument type,and sponser type.

RESULTS

Thirty-six studies met inclusion criteria: 23 industry-sponsored (63.9%), 8 academic (22.2%), and 5 cooperative-group (13.9%). PROs were included in 29 of 36 trials (80.6%), with longitudinal collection in all 29; disease- or symptom-specific NET instruments - predominantly EORTC QLQ-GI.NET21 - were used in 13 trials (36.1%), and PROs served as a primary endpoint in 6 trials. Among 24 mature trials with extractable baseline demographic data, African American enrollment was separately reported in 18 (75.0%) and Hispanic ethnicity in only 9 (37.5%). Across 17 trials with extractable AA enrollment counts, approximately 143 of 3,561 enrolled patients were AA (4.0%). Explicit age ≥65 enrollment was available in 5 of 24 mature trials (20.8%), and age ≥75 was not separately enumerated in any trial (0/24). This is particularly notable given that the median age at NET diagnosis in the United States exceeds 60 years, and that functional status,

polypharmacy, and symptom burden trajectories differ meaningfully in patients aged 75 and older.

CONCLUSIONS

PRO integration in modern NET clinical trials was broader than the prior literature suggests, with 80.6% of trials including longitudinal PRO collection and disease-specific NET instruments used in over one-third. However, critical gaps persist: Hispanic/Latino ethnicity was absent from nearly two-thirds of mature trial records, older-adult enrollment was rarely stratified by age ≥65 or ≥75 years despite a clinically older patient population, and no trial reported age ≥75 enrollment data. Future NET trials should standardize race/ethnicity reporting alongside PRO collection, enumerate older-adult enrollment at pre-specified age thresholds, and align with the NIH CEAL and FDA diversity action plan frameworks to improve the interpretability, equity assessment, and real-world applicability of NET clinical evidence.

ABSTRACT ID #36535

P-17

Overall Survival and Prognostic Factors in Patients with Gastroenteropancreatic Neuroendocrine Carcinoma: A Large Population-Based Analysis

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BACKGROUND

Gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs) are rare, poorly differentiated, high-grade neuroendocrine malignancies characterized by aggressive clinical behavior, for which systemic chemotherapy has long remained the standard of care. Contemporary population-level outcomes data with systemic chemotherapy for patients with GEP-NECs remain sparse.

METHODS

We queried the Surveillance, Epidemiology, and End Results (SEER) database to identify patients with GEP-NECs. Key inclusion criteria included gastroenteropancreatic site of origin, histology consistent with neuroendocrine carcinoma, poorly differentiated morphology, receipt of systemic chemotherapy, and diagnosis after 2015. Demographic, clinicopathologic, and treatment variables were extracted. OS was estimated using the Kaplan-Meier method. Univariate analysis was performed using the log-rank test to identify covariates for consideration in the multivariable model based on a threshold for statistical significance of $p<0.05$. Multivariable Cox proportional hazards regression was performed using forward stepwise selection based on the Akaike Information Criterion (AIC) to identify covariates independently associated with OS.

RESULTS

A total of 862 patients were included. Median age at diagnosis was 63 years (IQR 53–70), 59% were male, and 66% were non-Hispanic White. Median OS for the entire cohort was 12 months (95% CI 10–13). Younger age was not associated with improved survival (HR 1.00, p=0.979); age >75 years was associated with inferior OS (HR 1.37, p=0.010). On univariable

analysis, esophageal primary (HR 1.29, p=0.029), liver metastases (HR 2.29, p<0.001), and lung metastases (HR 1.70, p<0.001) were associated with worse OS. In contrast, anal primary (HR 0.45, p=0.003), gastric primary (HR 0.71, p=0.020), and isolated lung metastases without liver involvement (HR 0.62, p=0.041) were associated with improved OS. No significant differences in survival were observed by sex, race, income status, marital status, or rurality. On multivariable analysis, liver metastases (HR 2.06, p=0.006), lung metastases (HR 1.44, p=0.008), age >75 years (HR 1.51, p=0.009), and gastric primary site (HR 0.67, p=0.033) remained independently associated with OS.

CONCLUSIONS

In this contemporary population-based analysis of chemotherapy-treated GEP-NECs, metastatic burden and advanced age emerged as key prognostic factors, with liver metastases conferring a twofold higher risk of death. Unlike well-differentiated neuroendocrine tumors, younger age at diagnosis did not confer a survival advantage, suggesting uniformly aggressive disease biology of GEP-NECs across age sub-groups. Notably, sociodemographic factors were not independently associated with survival, suggesting tumor biology may outweigh traditional disparities-related determinants in this aggressive disease. The persistently short survival observed despite treatment with systemic chemotherapy highlights an urgent need for more effective novel therapeutic strategies.

ABSTRACT ID #36619

P-18

Treatment Comparisons in the Management of MEN1-Related and Sporadic Pancreatic Neuroendocrine Neoplasms: A Retrospective Study

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BACKGROUND

Pancreatic neuroendocrine neoplasms (pNENs) are a major source of morbidity and mortality for individuals with multiple endocrine neoplasia type 1 (MEN1). MEN1 pNEN management studies are limited; thus, current treatment guidelines are heavily derived from sporadic pNEN clinical data although differences exist between etiologies. While there is an interest in etiology specific guidelines, data directly comparing treatment patterns and response between etiologies are limited. We conducted a multicenter observational cohort study to compare treatment utilization and outcomes between MEN1 and sporadic pNENs.

METHODS

We identified patients with MEN1-related pNENs (n=189) and sporadic pNENs (n=378) who were treated at Mayo Clinic. Sporadic cases were matched across disease stage. Electronic medical records were reviewed to confirm diagnoses. Data involving patient demographics, tumor characteristics, treatment interventions, progression, recurrence, therapy-related endocrine insufficiency status, and therapy-related exocrine insufficiency status were collected.

RESULTS

Patients were seen at the Mayo Clinic from 1977-2025. Individuals with MEN1 were diagnosed earlier and included more women than the sporadic group. 36% of patients lacked a family history indicative of MEN1 syndrome. 74% of MEN1 patients had localized disease and 80.4% of pNENs were nonfunctional.

For localized disease, MEN1 pNENs were less likely to receive surgical or minimally invasive interventions compared to sporadic pNENs (55% vs. 66%). Decreased treatment implementation was observed for MEN1 pNENs under 2cm and functional pNENs. There were no cumulative differences found in the utilization of parenchyma-sparing surgical approaches compared to traditional approaches across etiology groups; however, those with MEN1-related pNENs were more likely to undergo a total pancreatectomy ($p < 0.001$)

although rare for localized disease. High rates of post-resection disease stability were found in both etiology groups (73% *MEN1 vs.* 87% *sporadic*).

For metastatic disease, MEN1 pNENs were less likely to receive systemic therapy compared to sporadic pNENs (64% vs. 91%). Treatment patterns and response were highly heterogeneous. No differences in treatment duration or odds of progression were identified between groups. More individuals with MEN1 pNENs developed therapy-related endocrine insufficiency (16% vs 8%) and exocrine insufficiency (31% vs 25%) compared to their sporadic counterparts.

CONCLUSIONS

MEN1-related pNENs are less likely to receive interventional treatment for both localized and metastatic disease than sporadic pNENs. Minimal differences in treatment approach for localized disease were identified, reflecting largely aligned guidelines. Treatment for metastatic disease was highly heterogeneous. Larger retrospective or prospective studies are needed to further evaluate differnces in systemic therapy response between etiology groups.

ABSTRACT ID #36610

P-19

The Impact of Physical Activity on Fatigue and Quality of Life in Patients with Neuroendocrine Tumors: A Cross-Sectional Study

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BACKGROUND

Physical activity is beneficial across the cancer continuum, from prevention through treatment and survivorship. It has been associated with a 10–20% reduction in the incidence of several solid tumors and a 40–50% decrease in cancer-specific mortality in breast, prostate, and colorectal cancers, along with improvements in fatigue and quality of life. The role of exercise in patients with neuroendocrine tumors (NETs) remains poorly characterized. We aimed to describe baseline physical activity among patients with NETs and examine its association with fatigue and disease-related symptoms.

METHODS

We conducted a retrospective analysis of cross-sectional data from consecutive patients with a confirmed diagnosis of NET seen at the Huntsman Cancer Institute Neuroendocrine Tumor Clinic between January and March 2026. Patients with more than 50% missing responses on any questionnaire were excluded. Physical activity, fatigue, and disease-related symptoms were assessed using the Rapid Assessment of Physical Activity (RAPA), EORTC QLQ-FA12, and EORTC QLQ-GINET21. Demographic and clinical data were extracted from electronic medical records. Associations between physical activity and patient-reported outcomes were evaluated using linear regression. The study was approved by the Institutional Review Board, and informed consent was waived since the questionnaires were administered as part of standard clinical care.

RESULTS

Preliminary analyses included 95 patients (62.1% male; 37.9% female; mean age 62.1 ± 11.1 years; mean BMI 29.5 ± 7 kg/m^2). Most tumors originated in the small bowel (45.3%), were well differentiated (89.5%), and had distant metastases (81.1%). Based on RAPA, 54.7% of patients were classified as underactive, and 41.3% reported no regular strength or flexibility training. Lower physical activity levels were significantly associated with greater fatigue ($p < 0.001$), with a RAPA score <5.29 identifying patients with meaningful increases in fatigue. Disease- or treatment-related symptoms were not significantly associated with

physical activity. More physically active patients also reported better social and sexual functioning ($p < 0.05$).

CONCLUSIONS

These preliminary findings represent one of the first comprehensive assessments of physical activity in patients with NETs and demonstrate that higher activity levels are associated with reduced fatigue and better quality-of-life outcomes, consistent with evidence from other solid tumors. Given that over half of the patients were underactive and many reported no strength or flexibility training, this study highlights an opportunity to implement structured exercise interventions to optimize patient outcomes. Prospective studies are needed to establish evidence-based exercise recommendations for this population, and a prospective trial is in development at our institution.

ABSTRACT ID #36621

O-1

Long-Term Oncologic Outcomes After Liver Transplantation for Neuroendocrine Liver Metastases: A Multisite Mayo Clinic Study

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BACKGROUND

The liver is the most common site of metastasis in patients with neuroendocrine tumors (NETs). Liver transplantation (LT) is a potentially curative option for highly selected patients with neuroendocrine liver metastases (NELM). In this study we aimed to evaluate oncological outcomes of patients with NELM who underwent LT.

METHODS

We performed a multi-site retrospective analysis of patients with unresectable NELM treated with LT at Mayo Clinic (Arizona, Florida, and Rochester) from 1990 to 2026. Baseline characteristics, including tumor biology (Ki-67, grade), timing of diagnosis and transplant, and patterns of recurrence were evaluated. Overall survival (OS) and disease-free survival (DFS) were determined using Kaplan-Meier methods and independent multivariable predictors of mortality and disease recurrence were identified via Cox proportional hazards regression models.

RESULTS

Forty-seven patients (median age 48 years; 68.1% male) were identified. Primary tumor origins were predominantly pancreatic (48.9%) and small bowel (46.9%). Most patients had grade I (32%) or II (60%) tumors. Median OS was 108.3 months (95% CI 73.3-216) and median DFS was 47.9 months (95% CI 28.2-77.7). Ten-year OS and DFS were 44.3% (95% CI 30.9-63.5%) and 20.1% (95% CI 10.6-38.0%), respectively. Post-transplant recurrence occurred in 31 patients (66%) at a median of 28.2 months. Common sites included lymph nodes (n=18), bone (n=16), and the liver allograft (n=15). Ten patients developed recurrences at least 5 years after LT, including one more than 10 years after LT. Exploratory analysis of patients requiring pre-transplant PRRT (n=7) revealed an inferior median DFS (7.8 months), reflecting aggressive baseline biology. Salvage therapies included

somatostatin analogs (n=19), radiation (n=12) and PRRT (n=11). Post-transplant PRRT yielded a median post-reoccurrence survival of 54.5 months vs 30 months without PRRT, though this survival benefit is likely confounded by selection and immortal time biases.

CONCLUSIONS

LT for NELM provides durable survival in strictly selected patients achieving a 10 year OS 44.3%. Careful patient selection is essential to optimizing long-term outcomes after LT. The persistent risk of late recurrence (5+ years) and subsequent systemic treatment highlights of the need for long-term oncologic surveillance. Upon recurrence, multimodality salvage therapies, including PRRT, may contribute to prolonged disease control in selected patients.

ABSTRACT ID #36606

O-2

Real-World Patient Journey in Extrapulmonary Neuroendocrine Carcinoma (epNEC): Perspectives of Patients from the VOICE Study

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BACKGROUND

Evidence on epNEC patient journey is scarce. This study represents one of the largest efforts to date, comprehensively characterizing the patient journey and unmet needs from the patient perspective.

METHODS

A cross-sectional survey was conducted (Nov 2025 to Feb 2026) of US adults with epNEC recruited via prominent national patient advocacy groups and online panels. Data on diagnosis (dx), treatment (tx), biomarker testing, and unmet needs were analyzed. Health-related quality of life (QoL) was assessed using the Patient-Reported Outcomes Measurement Information System – Global Health (PROMIS-GH-10) and the Work Productivity and Activity Impairment Specific Health Problem (WPAI:SHP).

RESULTS

Among 226 pts (median age 51 years, 67% male, 59% White, 56% employed, 79% gastroenteropancreatic [GEP] NEC, 26% Stage IV). Fatigue (62%) and pain (60%) were the most common symptoms prior to dx. Among symptomatic patients with diagnostic delays (n=28), main reasons for delay were inconclusive test results (46%) and referrals to multiple specialists (39%).

Across first-line (1L) and second-line (2L), primary tx goals for patients were prolonging life, improving QoL and minimizing side effects. 1L tx discussions emphasized efficacy (68%), side effects (61%) and prognosis (53%), while 2L shifted to prognosis (62%), efficacy (61%), and daily life impact (56%). Chemotherapy dominated 1L (73%) while tx was heterogenous in 2L. Although only 66% underwent prior biomarker testing, 94% were willing to undergo testing to inform tx selection.

The top three impacts of receiving dx include relief from identifying symptom cause, emotional distress and positive lifestyle changes. Disease burden was substantial with mean PROMIS-GH-10 Global Physical and Mental Health T-scores of 40.8 and 46.7, both below the general population norm (mean 50; lower T-scores indicate poorer health). Among employed pts, overall work impairment was 63% (absenteeism, 23%; presenteeism, 55%).

CONCLUSIONS

epNEC is characterized by non-specific symptoms, diagnostic delays, evolving tx decisions including biomarker-guided care, and significant impact to QoL and ability to work. Addressing these areas may improve patient-centered care and outcomes.

ABSTRACT ID #36560

O-3

Multidisciplinary Clinic for Gastrointestinal Neuroendocrine Tumors: Impact on Diagnosis and Management

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BACKGROUND

Gastrointestinal neuroendocrine tumors (GI-NETs) are heterogeneous neoplasms requiring coordinated multidisciplinary expertise. While multidisciplinary clinics (MDCs) improve outcomes across cancer types, data specific to GI-NET MDCs remain limited. We evaluated the impact of a dedicated GI-NET MDC on diagnosis and management.

METHODS

Retrospective analysis of new patients evaluated at our GI-NET MDC (February 2020–May 2026). The MDC integrated medical oncology, surgery, interventional radiology, pathology, endocrinology, and nuclear medicine. Outcomes included changes in diagnosis, staging, and management; additional testing; same-day multidisciplinary access; and plan adherence within 6 months.

RESULTS

237 patients were evaluated (54.4% female; 71.7% White, 13.5% Black, 4.2% Asian, 3.4% Hispanic/Latino). Referral sources were external (54.9%) and internal (45.1%). Visit types: newly diagnosed first opinion 103 (43.5%), newly diagnosed second opinion 76 (32.1%), and second opinion 58 (24.5%). Patients were seen by ≥2 specialties same day in 147 (62.0%).

Variable	N (%)
Pancreas (including small PNET)	116 (48.9%)

Small bowel	59 (24.9%)
Appendix	19 (8.0%)
Gastric/Duodenum	20 (8.4%)
Other/Unknown/Ruled out	23 (9.7%)
Stage I / II / III / IV	68 (29.1%) / 28 (12.0%) / 52 (22.2%) / 86 (36.8%)
Grade 1 / 2 / 3 / Unknown	91 (38.9%) / 72 (30.8%) / 33 (14.1%) / 38 (16.2%)
Functional tumor	36 (15.2%)
MEN1 syndrome	12 (5.1%)
Mortality	26 (11.0%)

Diagnostic changes occurred in 10 patients (4.2%), including reclassification to paraganglioma (n=2), NET ruled out (n=2), primary site changed (n=2), and histology reclassified (n=4). Staging was revised in 11 (4.6%), with upstaging in 7 and downstaging in 2. Additional testing was ordered prior to MDC in 101 (42.6%) and recommended after MDC in 47 (19.8%). Management was changed in 55 (23.2%), including recommendations to start systemic therapy (n=16), surgery (n=15), different systemic therapy (n=9), IR procedures (n=8), different surgery (n=4), and changed sequencing (n=2). The MDC was the first to establish a treatment plan in 124 (52.3%). Deviation from MDC recommendations occurred in 17 (7.2%).

CONCLUSIONS

A dedicated GI-NET MDC led to diagnostic changes in 4.2%, staging revisions in 4.6%, and management changes in 23.2% of patients. The MDC established the initial treatment plan for over half the cohort, with 92.8% plan adherence. These findings support the clinical value of multidisciplinary evaluation for GI-NETs.

ABSTRACT ID #36632

O-4

Analysis of DLL3 expression levels and characteristics of patients with advanced extrapulmonary neuroendocrine carcinomas from an ongoing phase I trial

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BACKGROUND

Specific delta-like ligand 3 (DLL3) surface expression in extrapulmonary neuroendocrine carcinomas (epNECs) makes it a promising therapeutic target, but prospective data on DLL3 expression patterns in epNEC are lacking. Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager. The first-in-human Phase I trial (NCT04429087) showed obrixtamig activity in DLL3-positive epNEC, especially in DLL3^{high} tumors. We report updated DLL3 expression data and patient/tumor characteristics in epNEC from NCT04429087.

METHODS

DLL3 immunohistochemistry was performed with an investigational DLL3 antibody (SP347) at the Roche CDx CAP/CLIA Laboratory. DLL3 expression was categorized as: negative (absent or weak tumor cell [TC] membrane/cytoplasm staining), positive

(moderate-to-strong staining in any TCs), high (≥50% moderate-to-strong TC staining), or low (<50% moderate-to-strong TC staining).

RESULTS

As of September 4, 2025, 282/365 screened patients with epNEC were DLL3-evaluable, of whom 235 (83.3%) had DLL3-positive tumors (DLL3^{high}: n=120 [42.6%], DLL3^{low}: n=115 [40.8%]); 47 (16.7%) were DLL3-negative. Of 93 DLL3-positive treated patients, 51 (54.8%) had DLL3^{high} and 42 (45.2%) had DLL3^{low} tumors. The prevalence of DLL3^{high} tumors was 47.5%/68.8% in males/females, and 57.1%/70.0% in patients with liver/brain metastases. DLL3^{high} prevalence by primary tumor site, gastrointestinal (GI)/genitourinary (GU)/cancer of unknown primary site (CUP), was 44.9%/67.7%/60.0%. Patient characteristics in obrixtamig-treated DLL3^{high} and DLL3^{low} epNEC subgroups are in Table 1.

Table 1. Baseline characteristics in obrixtamig-treated DLL3^{high}/DLL3^{low} subgroups.

	DLL3^{high} (n=51)	**DLL3^{low} (n=42)**
Male/female, n(%)	29 (56.9)/22 (43.1)	32 (76.2)/10 (23.8)
Primary tumor site: GI/GU/CUP, n(%)	22 (43.1)/21 (41.2)/ 6 (11.8)	27 (64.3)/10 (23.8)/ 4 (9.5)
Lactate dehydrogenase ≤ULN/>ULN, n(%)	22 (43.1)/29 (56.9)	16 (38.1)/26 (61.9)
Prior lines of therapy: 1/2/3/>3, n(%)	12 (23.5)/17 (33.3)/ 9 (17.6)/13 (25.5)	11 (26.2)/12 (28.6)/ 10 (23.8)/9 (21.4)
Median duration of prior anticancer treatment, weeks(range)	22 (5-349)	22 (8-148)
Prior radiotherapy/surgery/anti PD-(L)1, n(%)	22 (43.1)/28 (54.9)/ 14 (27.5)	11 (26.2)/24 (57.1)/ 9 (21.4)
Liver/brain metastases, n(%)	40 (78.4)/7 (13.7)	30 (71.4)/3 (7.1)
Median sum of diameters of target lesions, mm(IQR)	87.5 (64.0-123.0)	117.3 (66.2-176.0)

CONCLUSIONS

In the largest prospectively screened epNEC cohort, high (83.3%) prevalence of DLL3 expression was seen, underscoring DLL3 as a promising target for clinical development of DLL3-targeted therapies, including obrixtamig. Obrixtamig safety/efficacy in patients with DLL3-positive epNEC are being assessed in several ongoing trials, including DAREON®-5 (NCT05882058), DAREON®-7 (NCT06132113), and DAREON®-NEC-1 (NCT07544654), with data expected to inform/support further development.

ABSTRACT ID #36587

O-5

Genetic Predisposition Testing Program for Pancreatic Neuroendocrine Neoplasms (PanNENs): Interim Analysis of a Multicenter University of California Cohort

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BACKGROUND

Previous reports suggest pathogenic/likely pathogenic germline variants (P/LPVs) occur in ~20% of patients with PanNENs, but the downstream consequences remain incompletely defined; data from diverse populations are limited. Previously presented as a Trial-in-Progress at NANETS 2024 (Abstract ID 28698), we report the first interim analysis of an ongoing study.

METHODS

This multicenter observational study (IRB#22-37899) includes University of California sites in San Francisco (UCSF), Los Angeles (UCLA), and San Diego (UCSD). Accrual is complete at UCSF and UCSD, with enrollment ongoing at UCLA. New and existing patients with PanNENs were eligible (any stage). Prior dedicated germline testing and on-study testing were included; patients without prior large-panel testing (>80 genes) were offered UCSF's Expanded Hereditary Cancer Panel (88-97 genes). The primary objective was the frequency of P/LPV germline variants.

RESULTS

Among 215 enrolled patients at UCSF and UCSD, 131/215 (61%) had prior germline testing (any panel size). Overall, 117/215 (54%) were male, the median was age 56 (32% , and 125/215 (58%) with locoregional disease. Most patients identified as White 143/215 (67%), 37/215 (17%) Hispanic or 28/215 (13%) as Asian.

Results are available for 203/215 (94%) participants. Among these, at least one P/LPV identified in 44/203 (22%). Most (41/44, 93%) had well-differentiated tumors; differentiation was unknown in 3/44 (7%). Tumors were grade 1/2 in 40/44 (91%), G3 in 1/44

(2%), and unknown in 3/44 (7%). Overall, 14/44 (32%) , 41% female; 7/44 (16%) identified as non-White, 3/44 (7%) as Hispanic. P/LPVs included MEN1 (8), MUTYH (7), CHEK2 (5), and pancreatitis-associated genes CFTR (9) and SPINK1 (2). Additional P/LPVs were noted in BRCA1, BRCA2, NBN, ERCC4, LZTR1, PALB2, RINT1, TP53, and TSC1. Variants of uncertain significance (VUS) identified in 118/203 (58%). Of decision survey respondents, 93/95 (98%) agreed or strongly agreed that pursuing genetic testing was the right decision.

CONCLUSIONS

P/LPVs were identified in genes associated with hereditary endocrine neoplasia, DNA repair, or pancreatitis. P/LPVs spanned high-, moderate-, and low-penetrance alterations (including carrier status) in addition to VUS, underscoring the complexity of germline testing in this population. Our cohort is relatively diverse, providing new insight into Hispanic and Asian subgroups. Participants reported high satisfaction with their decision to undergo genetic testing. Accrual is still ongoing at UCLA (total target N=300). Information regarding the consequences of P/LPVs will be reported in future analyses (e.g. impact on tumor pathogenesis, cascade testing, screening recommendations, and second cancers).

ABSTRACT ID #36536

O-6

Building the Future Neuroendocrine Oncology Workforce: Education, Multidisciplinary Collaboration, and Fellowship Development- Proceedings from the 2026 Healing NET Foundation Summit

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BACKGROUND

Neuroendocrine neoplasms (NENs) require highly specialized multidisciplinary care, yet formal
training pathways remain limited. To address growing workforce shortages and increasing
complexity of care, the Healing NET Foundation convened its 2026 Summit to evaluate educational initiatives, provider wellness, workforce development, and fellowship planning.

METHODS

Approximately 120 participants, including 40 faculty members, attended the 2026 Healing NET
Foundation Summit in Tampa, Florida. Attendees included physicians, surgeons, endocrinologists, gastroenterologists, pathologists, radiologists, nuclear medicine physicians,
advanced practice providers (APPs), nurses, advocacy leaders, caregivers, researchers, and industry representatives. Structured presentations, breakout workgroups, multidisciplinary tumor
board demonstrations, and advocacy sessions were conducted over three days.

RESULTS

Participants identified major workforce vulnerabilities, including clinician burnout, limited formal neuroendocrine training opportunities, and impending retirement of experienced specialists. Strong consensus emerged supporting development of a flexible apprenticeship-based

fellowship model incorporating multidisciplinary rotations, mentorship, tumor board participation, and substantial clinical exposure. Participants further endorsed a two-week mini-
fellowship followed by a six-month apprenticeship model. The Healing NET Foundation Virtual
Tumor Board was recognized as a highly successful educational initiative, while APP and nursing education were identified as critical workforce priorities. Burnout prevention and provider wellness were emphasized as essential components of workforce preservation.

CONCLUSIONS

The summit demonstrated broad agreement that the future of neuroendocrine care depends upon
deliberate investment in mentorship, multidisciplinary collaboration, workforce development,
and innovative training pathways. Participants supported launching a pilot mini-fellowship in
2027 followed by a structured apprenticeship model to cultivate the next generation of neuroendocrine specialists.

ABSTRACT ID #36651

O-7

Circulating tumor DNA (ctDNA) monitoring for minimal residual disease (MRD) in gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

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BACKGROUND

GEP-NETs present unique challenges in post-surgical surveillance due to variable disease behavior and limited predictive biomarkers. ctDNA has emerged as a promising tool MRD detection in other gastrointestinal malignancies. However, ctDNA shedding in NETs is generally lower and more variable compared to adenocarcinoma. This study investigated the feasibility of post-operative ctDNA testing in GEP-NET.

METHODS

We conducted a retrospective analysis of 40 patients who underwent curative intent surgery for GEP-NET with at least one post-operative ctDNA sample. Demographic and baseline characteristics were summarized using descriptive statistics. Event time distributions were estimated using Kaplan-Meier methods with confidence intervals calculated using Brookmeyer and Crowley methodology. Median follow-up was reported using the reverse Kaplan-Meier method. The association between longitudinal ctDNA positivity and disease-free survival was assessed using a Cox regression model with a time-dependent covariate for first occurrence of a positive ctDNA test.

RESULTS

ctDNA testing was successful in 39 of 40 patients (97.5%). Primary sites of disease included pancreas (48%), small bowel (35%), ampullary (5%), appendiceal (5%), colon (5%), and gallbladder (2%) NETs. Median follow-up was 39.7 months (95% CI: 23.7, 48.4). The median number of post-operative ctDNA samples was 6 (range: 1-15). Eight of 39 patients had positive ctDNA, and all eight experienced recurrence resulting in a positive predictive value of 100% (95% CI 63, 100). Three additional recurrences were observed without detectable ctDNA, yielding a sensitivity of 73% (95% CI 39, 94). ctDNA was negative in 31 patients, with a negative predictive value of 90% (95% CI: 74, 98). Median time from first

positive ctDNA to radiographic recurrence detection was 152 days (range: -17, 1022). ctDNA positivity was associated with higher grade tumors, higher Ki-67, and perineural invasion. Time-dependent covariate analysis demonstrated that becoming ctDNA positive following surgery significantly increased the risk of progression or death (HR=33.7; 95% CI: 6.9, 164.8; p<0.0001).

CONCLUSIONS

Post-operative ctDNA testing is feasible in GEP-NET patients following curative intent surgery. All ctDNA-positive patients experienced disease recurrence, and ctDNA positivity preceded radiographic detection in most patients. These retrospective findings support ctDNA monitoring as an emerging valuable surveillance tool in GEP-NET and warrants continued investigation.

ABSTRACT ID #36630

O-8

Evaluation of Large Language Model-Based Extraction of Neuroendocrine Neoplasm Variables from Pathology Reports

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BACKGROUND

Manual extraction of clinical information at scale remains challenging, especially for heterogeneous conditions like neuroendocrine neoplasms (NENs). This process often requires searching through unstructured clinical records, which is labor-intensive. Recent studies suggest that large language models (LLMs) can effectively automate data extraction for clinical research. This study aims to evaluate LLM performance for outcomes research in NENs by comparing LLM-extracted data with a reference dataset curated by human abstractors.

METHODS

We developed a data extraction pipeline using OpenAI's GPT-4o LLM through a secure, IRB-approved platform authorized for use with protected institutional and clinical data. A total of 364 pathology reports were downloaded from the electronic medical record (EMR). For each report, the LLM was instructed to extract five diagnostic variables relevant to NENs: biopsy site (primary or metastatic), differentiation (well, moderately, or poorly-differentiated), Ki-67 index, histological grade (G1-G3), and stage (localized, regional, or distant). LLM prompt instructions were designed to mirror the extraction guidelines used during the manual extraction process. To account for output variability, the LLM processed each report three times, and the most frequently recorded output was retained as the final output for each variable for comparison.

RESULTS

We compared the accuracy of LLM-generated outputs with manually extracted outputs. Missing values were coded as "Unknown", and concordance included the cases in which both results were "Unknown". The LLM achieved the highest accuracy for differentiation (89%, 95% CI 85-91%), followed by Ki-67 index (85%, 95% CI 81-89%), biopsy site (85%, 95% CI 81-88%), and grade (83%, 95% CI 79-86%), but performance was considerably lower for stage (51%, 95% CI 46-56%).

CONCLUSIONS

The LLM demonstrated promising performance for extracting key diagnostic variables from pathology reports, though further optimization is needed, particularly for more complex variables, such as stage. Discordance across differentiation, Ki-67 index, biopsy site, and grade were primarily explained by the different pathology reports used for each patient during the manual extraction process. Lower accuracy observed for stage reflects the complexity of stage assignment, which requires information beyond pathology reports. Future work will focus on refining prompt design and incorporating additional clinical data sources to improve extraction accuracy and broaden the scope of automated data abstraction. Overall, our findings suggest a potential use of LLMs in extracting variables from EMRs to facilitate research on NENs.

ABSTRACT ID #36534

O-9

Real-World Management of Extrapulmonary Neuroendocrine Carcinoma (epNEC) from the Perspective of Healthcare Providers in the VOICE Study

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BACKGROUND

epNEC is a rare and aggressive cancer with limited evidence on real-world patient management. This study aimed to assess real-world patient journey, experiences and unmet needs across the care pathway from the perspective of healthcare providers (HCPs).

METHODS

A cross-sectional, web-based comprehensive survey of US oncologists treating ≥1 patient with epNEC in the past 12 months was administered between Jan-Feb 2026. Data on referral and diagnosis (dx), treatment (tx) selection, biomarker testing and unmet needs were analyzed.

RESULTS

Among 100 HCPs (median age 45 years; 77% male; 82% medical oncologists or hematologists/oncologists; 61% community setting), 31% reported ≥1 month from initial patient contact to referral to oncologist. Referral delays were reported by 75% of HCPs, primarily due to initial misclassification (68%). A total of 28% reported frequent diagnostic challenges differentiating epNEC from neuroendocrine tumors (NET), largely due to overlapping features (68%); 73% cited improved access to specialized pathology review as a key unmet need.

Most HCPs (80%) agreed that epNEC requires more urgent tx than NET. Platinum-etoposide (PE)-based regimens were the most common tx in 1L (59%), followed by immunotherapy (I/O)-based regimen (25%); 2L choices were heterogeneous. Tx goals shifted from prolonging survival in 1L to improving symptoms and quality of life in 2L.

However, 61% and 64% reported neutral or dissatisfaction with available 1L and 2L tx, with the greatest unmet need in efficacy.

Biomarker testing was widely valued, with 95% and 92% of HCPs considering it important for dx and tx decisions, respectively. Awareness and testing of DLL3 was high (83% and 68%, respectively). Among HCPs who had not tested for DLL3 (32%), 78% were willing to order DLL3 testing to inform tx selection. Overall, 91% would consider DLL3-targeted therapy for eligible patients.

CONCLUSIONS

HCPs reported challenges across the epNEC care pathway, characterized by diagnostic delays, limited access to pathology review, and limited satisfaction with current tx. High willingness to adopt biomarker-driven approaches, particularly DLL3-targeted strategies, highlights an opportunity to improve tx selection.

ABSTRACT ID #36561

O-10

Care Partner Experiences and Burden in Extrapulmonary Neuroendocrine Carcinoma: Findings from the VOICE Survey

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BACKGROUND

Care Partners (CPs) play a critical role in supporting patients with Extrapulmonary Neuroendocrine Carcinoma (epNEC), yet evidence describing their experiences and unmet needs remains limited. This study characterized the caregiving journey and burden among CPs of individuals with epNEC.

METHODS

A cross-sectional survey was conducted among US adults who had cared for an individual with epNEC within the previous 12 months. Participants were recruited through patient advocacy groups (PAGs) in February 2026. Survey domains included diagnosis and referral, caregiving responsibilities, quality of life (QoL), work productivity, and unmet needs. Care partner burden was assessed using the CareGiver Oncology Quality of Life tool (CarGOQoL; range 0-100; higher scores indicate better QoL) and the Caregiver Work Productivity and Activity Impairment (WPAI:CG; higher percentages indicate more impairment).

RESULTS

A total of 102 CPs completed the survey (mean age, 37 years; 56% White; 12% Rural; 65% college educated or above; 72% employed), with most being the care recipient's child (52%). Care recipients had a mean age of 60 years, were 52% male, 58% White, and 82% had gastroenteropancreatic-NEC. Approximately 60% of care recipients took >1 month to seek medical care after noticing symptoms, with common delays attributed to personal (48%; e.g., lack of awareness of symptoms) and financial (41%) factors. Most CPs (90%) began providing care before treatment initiation; common responsibilities included participating in discussions with clinicians (75%) and accompanying care recipient to

appointments (69%), while assistance with daily hygiene (26%) was reported as the most burdensome task.

Emotional distress, depression, and anxiety were reported as the most significant impacts of diagnosis on CPs' day-to-day lives. CarGOQoL scores demonstrated notable burden in psychological well-being (mean: 51), private life (mean: 59), and physical well-being (mean: 61). Mean activity impairment attributable to epNEC was 51%. Among employed CPs, overall work impairment was 58%, including absenteeism of 22% and presenteeism of 51%.

Oncologists were the primary source of information regarding epNEC management (70%), followed by PAGs (52%) and other healthcare professionals (51%). Interestingly, 41% of CPs reported utilizing artificial intelligence as a source of information. CPs identified care partner support groups, specialists offering novel therapies, and greater involvement in treatment decision-making as their highest unmet needs.

CONCLUSIONS

CPs play a central role throughout the epNEC diagnostic and treatment journey and experience substantial emotional, physical, and work productivity-related burden. Improved access to specialist care and caregiver support resources may help address unmet needs and enhance support for this underserved population.

ABSTRACT ID #36533

O-11

Empirically informed conceptual framework for shared decision-making for neuroendocrine tumors care: a multicentre international qualitative study.

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BACKGROUND

Shared decision-making (SDM) has been associated with better outcomes, improved satisfaction, and reduced decisional regret in cancer care, but can be challenging to implement. In neuroendocrine tumors (NETs) care, decision-making (DM) is particularly complex due to lack of clear algorithms and multiple decision points over time. We examined decisional ownership, which is the felt sense of involvement in decision-making, among patients with NETs across three health systems.

METHODS

We conducted semi-structured interviews with patients treated for locoregional and advanced NETs in the USA, Canada, and Australia. Participants were purposively sampled until thematic saturation. Narrative inquiry was used to explore DM and decisional ownership experiences. Data were analyzed inductively using thematic analysis with iterative coding and team member triangulation.

RESULTS

: Twenty-four patients were interviewed (U.S. n=10; Australia n=7; Canada n=7). Distinct patterns of decisional ownership were identified. In the USA, high DO with patient-driven DM was described, especially when supported by personal research and time with physicians. In Australia, a mix of high and low decisional ownership with both patient and doctor-driven DM was reported, emphasizing self-efficacy, collaborative discussion, and team expertise. In Canada, low decisional ownership and doctor-driven DM was described, perceived as the expected pathway and constrained by system barriers. For both high and low decisional ownership, the major underpinning of the DM experience

was trust. Across all settings, trust, rather than decisional control or the presence of choice, emerged as the primary mechanism shaping patients' DM experiences. Trust was built through SDM-enabling practices, including access to specialized NET expertise, clear and honest communication, continuity and coordination of care, and alignment with patients' preferred decisional roles. We developed a conceptual framework positioning decisional ownership as the outcome of SDM experience, mediated by trust which is influenced by actionable care practices.

CONCLUSIONS

Decisional ownership in NETs care differed across health systems but are consistently determined by trust rather than by the degree of decisional control patients hold. Both patient- and clinician-led decision-making can be experienced positively when supported by trusted relationships and coherent care processes. Eliciting patients' preferred role in DM and strengthening access to specialized NETs teams, care navigation supports, and communication tools are actionable strategies to support positive SDM experiences in NETs care.

ABSTRACT ID #36339

O-12

Assessment of AI-assisted Clinical Trial Matching for Neuroendocrine Neoplasms

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BACKGROUND

For many patients with neuroendocrine neoplasms and their physicians, finding an appropriate clinical trial can be difficult.

METHODS

We characterized the performance of clinical trial matching using common techniques: search engine query (Google), free generalist LLM chatbots (ChatGPT, Gemini 3.5 Flash, Claude Sonnet 5 Max), clinical trial specific AI (ancora.ai), and ClinicalTrials.gov. For search engine query and generalist chatbots, we wrote: “neuroendocrine cancer clinical trials near me.” For clinical trial specific AI and ClinicalTrials.gov, we selected neuroendocrine neoplasms from a dropdown menu. We characterized trial results into possibly relevant “true” matches or irrelevant “false” matches. Trials that were non-therapeutic, clearly labeled non-recruiting, or greater than 100 miles away were excluded. We characterized the overlap and uniqueness of results from each source. We then characterized the specificity of the clinical trial specific AI by searching as a patient in three hypothetical cases, with a moderate level of clinical knowledge (organ of origin, metastatic status, and last therapy). We then broadened our search to the entire United States, comparing generalist against clinical-trial specific AI for our hypothetical pancreatic NET case.

RESULTS

We found from search engine query of local clinical trials returned 8 true matches and 7 false matches. Fewer results from generalist LLM chatbots (1-4 true and 0 false matches), most comprehensive results from clinical trial specific AI (15 true and 0 false matches), and poor signal-to-noise ratio from ClinicalTrials.gov (12 true and 29 false matches). Four trials were reported by all three modalities (search engine, trial specific AI, & ClinicalTrials.gov), one by search engine query alone, seven by clinical trial AI alone, and none by ClnicalTrials.gov alone. When search criteria were narrowed to three specific cases with knowledge of organ of origin, metastatic status, and last treatment, the clinical trial specific AI returned only 0-1 possibly relevant and 1-2 irrelevant trials. On our broadened nationwide AI-driven search, generalist LLMs produced a range of results (no

specific trial listing, 0 true with 2 false matches, 6 true with 0 false matches), and clinical trial specific AI returned 5 true with 4 false matches.

CONCLUSIONS

Search engine query provided admirably robust results though required labor-intensive parsing of false matches. ClinicalTrials.gov provided noisy search results with many irrelevant trials. AI-assisted clinical trial search provided variable results depending on the specifics of the query.

ABSTRACT ID #36660

O-13

Clinicopathologic Characteristics and Outcomes of MEN1-Associated Bronchopulmonary Neuroendocrine Neoplasms Carcinoid Tumors: The Mayo Clinic Experience

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BACKGROUND

Bronchopulmonary neuroendocrine tumors (bNETs) are uncommon manifestations of multiple endocrine neoplasia type 1 (MEN1), that contribute to morbidity and mortality. Contemporary data describing the presentation, management, and outcomes of MEN1-associated bNETs remain limited.

METHODS

Patients with MEN1 evaluated across three Mayo Clinic sites between 1/1/2005 and 12/1/2025 (n=945) were screened for thoracic, thymic, or mediastinal carcinoid diagnoses. Manual electronic medical record review confirmed concurrent MEN1 and bNET. Demographic, clinicopathologic, imaging, treatment, recurrence/progression, and survival data were abstracted.

RESULTS

Seventeen patients with MEN1-associated bNETs were identified. Median age at diagnosis was 41.1 years; 6 (35.3%) were male. Histology included bronchial carcinoids in 15 patients (88.2%), large cell neuroendocrine carcinoma in 1 (5.9%), and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia in 1 (5.9%). Histologic subtype was available in 9 patients; 5 typical carcinoids (29.4%), 3 atypical carcinoids (17.6%), and 1 mixed tumor (5.9%); 8 tumors (47.1%) were not further subclassified. All tumors with documented hormonal status (n=11) were nonfunctional. Somatostatin receptor PET imaging was performed in 11 patients, demonstrating uniformly avid disease in 6 (55%), heterogenous avidity in 1 (9%), and mild avidity in 4 (36%).

Concurrent MEN1-associated manifestations included primary hyperparathyroidism in 15 patients (88.2%), pituitary tumors in 12 (70.6%), pancreatic NETs in 16 (94.1%), adrenal lesions in 5 (29.4%), and breast tumors in 3 (17.6%). Surgical resection was performed in 9 (52.9%) patients. Among 7 evaluable surgical patients, recurrence occurred in 3 (42.9%), after a median of 23.5 months (range 19.8-27.8).

Management was heterogenous and included somatostatin analog therapy in 7 patients (41.2%), cytotoxic chemotherapy in 3 (17.6%), targeted therapy (everolimus or sunitinib) in 2 (11.8%), radiation therapy in 4 (23.5%), and ablative therapy in 2 (11.8%). Disease progression occurred in 1 non-surgical patient after 6 years of follow-up, and 2 patients (11.8%) died during follow up.

CONCLUSIONS

MEN1-associated bNETs are rare and frequently coexist with other MEN1 manifestations, supporting comprehensive multisystem surveillance. Tumors were predominantly nonfunctional bronchial carcinoids, while treatment approaches were heterogenous, reflecting the lack of standardized management strategies and guidelines. Despite substantial post-surgical recurrence, overall outcomes were favorable, with low rates of disease progression and mortality. Larger, prospective, multi-institutional studies are needed to define optimal screening, surveillance, and management strategies for MEN1-associated bNETs.

ABSTRACT ID #36590

O-14

Clinical Characteristics and Outcomes of MEN1-Associated Thymic Neuroendocrine Tumors Across Mayo Clinic Sites

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BACKGROUND

Thymic neuroendocrine tumors (tNETs) are an uncommon but historically lethal manifestation of multiple endocrine neoplasia type 1 (MEN1), accounting for a disproportionately large share of MEN1-related mortality. Evidence guiding surveillance and management strategies remains limited to small retrospective series. We evaluated the clinical characteristics, management, and outcomes of MEN1-associated tNETs across Mayo Clinic sites.

METHODS

We retrospectively reviewed 945 patients with MEN1 evaluated at three Mayo Clinic sites between 1/1/2005 and 12/1/2025. Patients were further filtered for a thoracic, thymic, or mediastinal carcinoid diagnosis, followed by manual electronic medical record review confirming concurrent MEN1 and tNET diagnosis. Demographic, clinicopathologic, imaging, treatment, recurrence/progression, and survival data were abstracted.

RESULTS

Four patients with MEN1-associated tNETs were identified. Median age at diagnosis was 36.4 years, and 3 patients (75%) were male. Histology demonstrated well-differentiated atypical carcinoid tumors in 2 patients (50%) and well-differentiated NET subtype not specified in 1 patient (25%). One diagnosis was based on characteristic imaging findings. One tumor (25%) was functional, manifesting as ectopic Cushing syndrome. Somatostatin receptor PET imaging revealed avid lesions in all 4 patients.

Concurrent MEN1-associated manifestations were common, including primary hyperparathyroidism in 3 patients (75%), pituitary tumors in 3 patients (75%), pancreatic NETs in 3 (75%), adrenal lesions in 3 (75%). None had breast tumors. Surgical resection was performed in all 4 patients. Among the 3 patients with available follow up data,

recurrence occurred in 2 (66%), with a median time to recurrence of 63.3 months (range 40.8-85.8 months).

Management was heterogenous and multimodal, including somatostatin analog therapy in 2 patients (50%), cytotoxic chemotherapy in 3 patients (75%), targeted therapy (everolimus or sunitinib) in 2 patients (50%), and radiation therapy in 3 patients (75%). One patient (25%) died during follow up due to complications of his tNET.

CONCLUSIONS

MEN1-associated tNETs are rare and present alongside a high burden of concurrent MEN1 manifestations, reinforcing the need for systematic multisystem surveillance. Despite surgical resection being performed in all patients in this cohort, recurrence rates were high (66%) and multimodal therapy was frequently required. These findings reinforce the high morbidity associated with MEN1-related tNETs and highlight the need for prospective, multi-institutional studies to optimize surveillance, surgical timing, and adjuvant treatment strategies in this high-risk patient population.

ABSTRACT ID #36592

O-15

Neuroendocrine Tumors and Risk of Subsequent Primary Cancers in Early-Onset Disease: A Population-Based Retrospective Cohort Study in the United States

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BACKGROUND

Neuroendocrine tumors (NETs) are increasingly diagnosed and often follow a prolonged clinical course, making survivorship risks clinically important. Although patients with NETs are known to be at risk for subsequent primary cancers (SPCs), the influence of age at NET diagnosis on SPC risk remains unclear. In this study, we aimed to evaluate whether early-onset NETs are associated with distinct patterns of SPC risk in a large nationwide cohort.

METHODS

We conducted a retrospective cohort study using the Surveillance, Epidemiology, and End Results database from 2000 to 2021. Patients with NETs were classified as having early-onset disease if diagnosed before age 50 years and average-onset disease if diagnosed at age 50 years or older. The primary outcome was development of a first SPC after the index NET diagnosis, defined according to SEER multiple-primary rules. Death before SPC was treated as a competing event. Fine-Gray competing-risk regression models were used to estimate adjusted subdistribution hazard ratios (sHRs) and 95% confidence intervals (CIs). Sensitivity analyses were performed by restricting follow-up to 5 years and by separately evaluating patients with very early-onset NETs, defined as diagnosis before age 30 years.

RESULTS

Among 100,717 patients with NETs, 21,146 (20.9%) had early-onset disease. Median follow-up was 47 months. 7,870 patients (7.8%) developed an SPC. SPCs occurred in 5.1% of

patients with early-onset NETs compared with 8.5% of those with average-onset NETs. In adjusted competing-risk analysis, early-onset NET was associated with significantly lower SPC risk compared with average-onset NET (sHR, 0.56; 95% CI, 0.53-0.60; P<.001). Findings remained consistent in sensitivity analyses restricted to 5 years of follow-up (sHR, 0.58; 95% CI, 0.54-0.61) and were more pronounced among patients diagnosed before age 30 years (sHR, 0.23; 95% CI, 0.17-0.31). Higher SPC risk was seen among patients diagnosed at ages 30 to 49 years and among those with gastric, pancreatic, and small intestinal NETs. The most frequent SPC sites overall included lung and bronchus, breast, prostate, colorectal cancer, and melanoma, with a distinct distribution of SPC sites among early-onset patients.

CONCLUSIONS

Early-onset NETs were associated with lower overall SPC risk compared with average-onset NETs. However, clinically meaningful heterogeneity was observed, with selected early-onset subgroups demonstrating elevated risk. These findings suggest that survivorship strategies for patients with NETs may benefit from incorporating age at diagnosis, sex, and primary tumor site to better individualize long-term SPC surveillance.

ABSTRACT ID #36593

O-16

Establishing content validity of patient-reported outcome (PRO) measures in extrapulmonary neuroendocrine carcinomas (epNEC): A cognitive debriefing (CD) interview study

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BACKGROUND

Background: Extrapulmonary neuroendocrine carcinoma (epNEC) is a rare, aggressive, high-grade neuroendocrine cancer arising outside the lungs, with heterogeneous symptoms based on the location of the tumors. Utilizing patient reported outcome (PRO) measures in clinical trials is key for capturing the patient perspective, ensuring that their symptoms and daily life experiences are well reflected in evaluating treatments. This study assessed the content validity of PROs including relevance, comprehension, and recall periods of selected PROs for use in patients with epNEC.

METHODS

Methods: Following the *ISPOR PRO Good Research Practices* guidance and given the rarity of epNEC, a 3-step systematic approach was used. First, three oncologists with epNEC expertise assessed relevance of the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) selected items. Next, a focus group of four patient representatives and two additional oncologists assessed the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core Questionnaire (QLQ-C30), EORTC Item Library 46 single item (IL46) and the EORTC Gastrointestinal Neuroendocrine Tumor module (QLQ-GI.NET21). Finally, 1:1 cognitive debriefing interviews with six patients with epNEC across the US, Germany and Italy assessed the content validity of PROs.

RESULTS

Clinicians reported several physical functioning (PF) impairments in patients with epNEC, driven by disease burden and treatment related toxicities (n=3/3) and confirmed the relevance of the selected PRO-CTCAE items (n=2/2). Focus groups expanded findings by highlighting major impacts on daily functioning and independence, and confirmed the relevance of all other PROs, except the QLQ-GI.NET21, which was then excluded due to

low relevance in epNEC (n=6/6). Patient interviews (n=5/6) confirmed the comprehension and relevance of the QLQ-C30 PF items, however, recall periods were interpreted inconsistently with typically around half of the participants (n=3/6) thinking of the current time. IL46 performed well for comprehension (n=4/5) and relevance (n=5/5) with a “past week” recall period (n=4/4). Other QLQ-C30 domains were considered relevant (n= 6/6 for most items). PRO-CTCAE items were easy to comprehend for the two participants who debriefed them.

CONCLUSIONS

Collectively, the clinician interviews, focus group and patient interviews confirm the high symptom and impact burden of epNEC and support the content validity (comprehension, relevance, and recall period) of the QLQ-C30 and IL46 and the comprehension of the PRO-CTCAE in epNEC.

ABSTRACT ID #36427

O-17

The Role of NET Specialists in Diagnostics and Treatment – Comparison Global vs USA in 2019 – 2025

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BACKGROUND

This analysis assesses changes in NET (neuroendocrine tumor) specialist involvement in the patient care pathway over the six-year period 2019–2025, in the USA and globally.

METHODS

SCAN (Survey of Challenges in Access to Diagnostics and Treatment for Neuroendocrine Tumour Patients) evaluates NET healthcare delivery trends, with baseline data collected in 2019 and follow-up in 2025. Available in 14 languages in 2019 and 15 in 2025, the survey was disseminated by International Neuroendocrine Cancer Alliance (INCA) and its partner organizations. A total of 2,359 and 2,764 NET patients completed the online self-reported survey in 2019 and 2025 respectively, including 511 and 360 patients from the USA.

RESULTS

Over two-thirds of patients were aware of NET specialists in both cohorts and survey years – globally (73.1%/2,359; 75.1%/2,764;) and in the USA (71.4%/511; 69.4%/360) with no significant change over the six-year period.

Approximately half of NET patients reported consulting a NET specialist in the past 12 months – this percentage increased both globally (53.2%/n=2,359 vs. 57.2%/n=2,764, $p<0.05$) and in the USA (47.2%/n=511 vs. 51.4%/n=360)

The misdiagnosis burden improved significantly, with multiple prior misdiagnoses before NET diagnosis declining from 36.2% (n=511) in 2019 to 26.1% (n=360) in the USA and from 30.5% (n=2,359) to 25.3% (n=2,764) globally ($p<0.05$). The percentage of patients diagnosed

at a hospital without a NET specialist declined in the USA (42.3%/n=511; 36.1%/n=360;), following the global trend (41%/n=2,359; 34.6%/n=2,764).

NET specialist involvement in diagnostics increased significantly globally (21.6%/2,359 vs. 26.6%/2,764, p<0.05), but it remained stable in the USA (11.5%/511 vs. 13.9%/360, p<0.05 vs. global). NET specialist involvement in treatment increased significantly globally for about half of all NET patients (46.2%/2,359 vs. 50.9%/2,764, p<0.05), while it remained stable and significantly lower in the USA than the global rate (42.3%/511 vs. 44.1%/360, p<0.05 vs. global). NET specialist involvement in ongoing monitoring remained unchanged in both cohorts yet significantly lower in the USA: globally for about half of all NET patients (49.5%/2,359 vs. 53.1%/2,764) compared to the USA (43.4%/511 vs. 45.3%/360, p<0.05 vs. global). NET specialist participation in multidisciplinary team (MDT) increased significantly globally (41.5%/2,359 vs. 46.2%/2,764, p<0.05), with increase reported in the USA, while still significantly below the global rate (33.5%/511 vs. 39.2%/360, p<0.05 vs. global).

CONCLUSIONS

Between 2019 and 2025, NET specialist involvement in diagnostics, treatment, monitoring, and MDT management in the USA remained significantly below global rates. These findings underscore the need to strengthen specialist-led care pathways in the USA.

ABSTRACT ID #36518

O-18

Prognostic significance of B7H3, DLL3, and survivin expression in neuroendocrine neoplasms

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BACKGROUND

B7-H3, DLL3, and survivin are emerging therapeutic targets in neuroendocrine neoplasms (NENs), but their prognostic significance remains unclear. We evaluated their expression in NENs and their association with survival and tumor grade.

METHODS

We analyzed 42 patients with NENs who underwent IHC staining for B7-H3, DLL3, and survivin. Tumors were classified according to the WHO 2019/2022 grading system (G1-G3). B7-H3 and DLL3 were evaluated using exploratory thresholds due to lack of validated cut-offs (1-50% for B7-H3; 1% and 50% for DLL3), while survivin positivity was defined as ≥1%. Because isolated B7-H3 expression was common whereas DLL3 and survivin were less frequent and associated with worse disease, patients were stratified into three groups based on 1% positivity: Group 1 (all biomarkers negative), Group 2 (B7-H3-positive only), and Group 3 (other biomarker combinations). OS and PFS were analyzed using Kaplan-Meier methods and Cox proportional hazards models. Multivariable analyses adjusted for primary tumor site, stage, prior chemotherapy and radiation. Associations with tumor grade were evaluated using proportional odds models.

RESULTS

Gastrointestinal tumors comprised 62% of cases, 36% had stage III-IV disease, and 48.8% had grade 3 disease. Median follow-up was 106 months. B7-H3 positivity was in 64% of tumors at the 1% cutoff and 33% at 50%, while DLL3 and survivin positivity were 27% and 26%, respectively. Survivin positivity was associated with worse OS (HR 2.82, p=0.041), while DLL3 (HR 2.39, p=0.057) and B7-H3 > 50% (HR 2.70, p=0.073) showed trends toward worse OS. Compared with Group 1, Group 2 had worse OS (HR 6.54, 95% CI 1.17-36.5, p=0.032) and PFS (HR 12.8, 95% CI 1.60-103, p=0.016). Group 3 (17 patients, 40.5%) had the worst outcomes (OS HR 19.3, 95% CI 4.17-88.9, p<0.001; PFS HR 26.8, 95% CI 4.13-174, p<0.001). Grade 3 disease occurred in 76.5% of Group 3. Within Group 3, patients positive for all 3 biomarkers were more likely to have grade 3 disease. Higher B7-H3 and survivin expression correlated with higher tumor grade (p=0.008 and p=0.047, respectively).

CONCLUSIONS

Combined B7-H3, DLL3, and survivin expression identified patients with worse survival after adjusting for clinicopathologic factors, while higher B7-H3 and survivin expression correlated with higher tumor grade. These findings support their potential as prognostic biomarkers and as candidates for targeted therapies. Prospective validation in larger cohorts is warranted to establish NEN-specific cutoffs, characterize expression heterogeneity, and determine prognostic value across disease stages.

ABSTRACT ID #36656

O-19

Real World Trends in Telotristat Utilization for Carcinoid Syndrome in the United States: A National Epic Cosmos Analysis

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BACKGROUND

Carcinoid syndrome (CS) is a rare functional syndrome affecting patients with metastatic neuroendocrine tumors (NET).Telotristat etiprate (Xermelo), a first-in-class oral tryptophan hydroxylase inhibitor, was FDA-approved in February 2017 for CS diarrhea inadequately controlled by somatostatin analog (SSA) therapy. Despite regulatory approval, real-world prescribing patterns, disparities, and geographic trends remain largely undescribed. We examined national telotristat utilization trends using a large electronic health record database.

METHODS

Using Epic Cosmos, we identified adults (age >=18) with a diagnosis of CS (ICD-10: E34.00, E34.09) and a prescription for telotristat etiprate from FDA approval (February 28, 2017) through (May 1, 2026). Prescribing trends were stratified by year, U.S. census region, race, gender, and payer status. Counts below 10 were suppressed per Cosmos privacy standards.

RESULTS

A total of 3,572 patients with CS received a telotristat prescription across the study period, with 3,131 prescribed between 2017-2025. Annual prescribing increased from 108 patients in 2017 to a peak of 543 in 2025, representing a 403% increase from 2017. Among 14,197 patients with CS identified in 2025, telotristat recipients (n=543) represented 3.8% of the diagnosed CS population, up from 1.4% (108 of 7,862) in 2017. Regional distribution in 2025 favored the South (n=256; 47%), followed by the Midwest (n=110; 20%), Northeast (n=89; 16%), and West (n=82; 15%). White patients comprised 85% of recipients in 2025 (n=459), while Black patients represented only 9% (n=49). Commercial insurance was the predominant payer (71% in 2025). Female patients received more prescriptions than males across all years (n=852 vs. n=623).

CONCLUSIONS

Telotristat prescribing for refractory CS diarrhea has increased steadily since FDA approval, yet total utilization remains low overall, reflecting the rarity of NETs and the narrow eligible refractory population requiring management beyond SSA therapy. Prescribing is concentrated in the South and showed marked difference by race and payer status with white and commercially insured comprising the majority of recipients. These findings suggest meaningful gaps in equitable access and warrants further investigation into access barriers to this first in class therapy for SSA refractory CS diarrhea.

ABSTRACT ID #36574

O-20

Histotripsy for Neuroendocrine Tumors Liver Metastases: Safety and Clinical Outcomes in a Single-Institution Series

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BACKGROUND

Histotripsy is a novel, non-invasive, non-thermal ablative modality that employs focused ultrasound pulses to induce mechanical cavitation and precise tumor cell destruction. Preclinical and early clinical data suggest potential immune-stimulatory effects. While histotripsy has shown promise in hepatocellular carcinoma and colorectal liver metastases, data in neuroendocrine tumor (NET) liver metastases is limited. We report a single center review of using histotripsy for NET liver metastases.

METHODS

We performed a retrospective analysis of patients with pathologically confirmed NET and liver metastases evaluated for histotripsy at Cleveland Clinic from 2022–2025. Clinical data including demographics, primary site, grade, Ki-67, functional status, SSTR2 expression, prior therapies, histotripsy procedural details, adverse events (CTCAE v5.0), and outcomes were collected. Radiographic response was assessed using RECIST 1.1 criteria at 30, 90, and 180 days where available. Descriptive statistics were used.

RESULTS

Of the 66 patients evaluated, 13 patients were treated. Median age at time of histotripsy was 61 years [range 26–69] and 85% of patients were female and 85% white. Primary tumor sites were small bowel/midgut (n=7), pancreas (n=2), lung (n=2), and other (n=2). Tumors were well-differentiated, with median Ki-67 index of 8% (range 2–28%). Eleven patients (85%) had functional tumors, and all were SSTR2-positive. All patients had received prior systemic therapy (somatostatin analogs ± PRRT in 62%), 5 had prior resection and 2 had other locoregional liver therapy.

Histotripsy was delivered in a single session for 12 patients; one patient received two sessions. 53.8% of patients had 1 lesion treated (Range 1-5).

On radiographic assessment of the treated lesions at 30–180 days, 1 patient (8%) had complete response, 5 (38%) had a partial response, 4 (31%) had stable disease, and 3

patients had progression, yielding 77% local control. Necrosis within treated lesions was confirmed on follow-up imaging in 3/13 (23%) of patients. Six patients (55%) had clinical benefit with symptom improvement of carcinoid symptoms.

Most patients experienced minimal to no adverse events. Adverse events included grade 1 abdominal pain (n=3), grade 1 hematoma (n=1), grade 1 hemoptysis (n=1), grade 2 nausea (n=1), and grade 2 abdominal pain (n=1). There were no grade ≥3 adverse events, including prolonged hospitalizations, or treatment-related mortality.

CONCLUSIONS

In this single-institution series, histotripsy for NET liver metastases was safe and feasible, associated with local control rates, and improvement in carcinoid symptoms. Additional clinical data is needed to better define its optimal role in management.

ABSTRACT ID #36642

O-21

Clinical Utility and Impact of the Healing NET Foundation Virtual Multidisciplinary Tumor Board in the Care of Patients with Neuroendocrine Neoplasms

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BACKGROUND

Neuroendocrine neoplasms (NENs) are relatively rare malignancies characterized by substantial clinical and biological heterogeneity, and access to specialized expertise remains limited in many practice settings. Virtual tumor boards (VTBs) have emerged as a strategy to facilitate multidisciplinary expert consultation; however, data evaluating their impact remain limited.

METHODS

An electronic survey was distributed to faculty members and attendees of the Healing NET Foundation VTB. The VTB includes specialists in medical oncology, surgical oncology, endocrinology, gastroenterology, pathology, radiology, cardiology and nuclear medicine who review complex NEN cases and provide consensus recommendations. Survey items assessed respondent characteristics, case complexity, perceived barriers to specialty NEN care, educational value, and clinical impact of VTB recommendations. Descriptive statistics summarized survey responses. Exploratory subgroup analyses were performed using chi-square or Fisher's exact tests.

RESULTS

The survey was sent to 61 individuals and 45 responded (74%). Most practiced in academic settings (34/45, 76%), specialized in NEN care (44/45, 98%), and had >20 years of clinical experience (27/45, 60%). Cases presented to the VTB were predominantly highly complex (27/45, 60%), commonly involving advanced or heavily pretreated disease (36/45, 80%) and rare tumor subtypes or unusual presentations (34/45, 76%). Overall, 39/45 (87%) respondents agreed or strongly agreed that the VTB reduced barriers to specialty care. The most commonly mitigated barriers were lack of subspecialty expertise (34/45, 76%) and geographic distance (31/45, 69%). Frequently discussed topics included systemic therapy selection and sequencing (41/45, 91%), surgical or interventional management (37/45, 82%), PRRT suitability (20/45, 44%), and imaging interpretation (19/45, 42%).

Participants reported that VTB recommendations led to therapy modification (38/45, 84%), pursuit of surgery or intervention (29/45, 64%), additional diagnostic evaluation (19/45, 42%), consideration of PRRT (19/45, 42%), and clinical trial referral (8/45, 18%). Among evaluable presenters, 26/37 (70%) reported a direct impact on patient management. All (8/8, 100%) respondents from non-academic settings versus 18/29 (62%) of respondents from academic centers reported management impact (p=0.08). Confidence in treatment plans improved following VTB discussion in 11/19 (58%) presenters. All respondents reported learning clinically useful information, with 33/45 (73%) rating the experience as very helpful. Nearly all participants (43/45, 96%) expressed willingness to continue participating.

CONCLUSIONS

A multidisciplinary NEN-focused VTB was perceived to improve access to subspecialty expertise, support management of highly complex cases, and frequently influence clinical decision-making. These findings support virtual multidisciplinary collaboration as an effective strategy to enhance NEN care and education across diverse practice settings.

ABSTRACT ID #36604

O-22

Drivers and Barriers to Workforce Development in Neuroendocrine Neoplasms: Insights from the NANETS "Why NENs" Early-Career Survey

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BACKGROUND

The neuroendocrine neoplasm (NEN) workforce remains relatively small despite rising disease incidence and increasing therapeutic complexity. Understanding the factors that drive entry into and retention within the NEN field is critical to developing a sustainable multidisciplinary workforce.

METHODS

A cross-sectional, anonymous electronic survey was distributed to NANETS members (September-December 2025). The survey evaluated respondent specialty, training stage, NEN practice characteristics, mentorship experiences, institutional support, research involvement, and long-term career goals. Respondents completing at least one survey item were included in this preliminary analysis. Descriptive statistics summarized categorical variables as frequencies and percentages.

RESULTS

Responses from 50 respondents were included in the final analysis. Respondents represented surgery (n=20, 40%), medical oncology (n=18, 36%), endocrinology (n=5, 10%), pathology (n=3, 6%), and translational science (n=3, 6%). Most respondents were within 0–2 years of completing formal training (20, 40%), 17 (34%) within 3-5 years of training completion, and 13 (26%) still in training. NENs were a primary clinical and/or research focus for 35 respondents (70%), and 35 (70%) reported high-volume NEN practices.The most common factors driving initial interest in NENs were exposure during training (n=35, 73%) and strong mentorship (n=30, 63%), while scientific curiosity (n=14, 29%) and institutional opportunity (n=13, 27%) were less frequently reported. For career retention,

ongoing mentorship was the most cited factor (n=32, 67%), followed by access to opportunities (n=26, 54%) and supportive colleagues (n=26, 54%). Overall, 30 (67%) rated mentorship as “critical” to their career development, and 38 (84%) reported currently receiving formal (n=6, 13%) or informal (n=32, 71%) mentorship. Only 15 respondents (34%) reported active leadership or collaboration in NEN trials/research, while 26 (59%) expressed interest but had not yet become involved. Among those not engaged, the most common barriers were uncertainty regarding how to start (n=21, 68%), lack of mentors (n=12, 39%), and inadequate infrastructure (n=10, 32%). Key unmet needs included protected time (n=21, 48%), multidisciplinary collaboration (n=20, 45%), and trial access (n=19, 43%). Future aspirations included becoming dedicated NEN clinicians (n=25, 60%), educators/mentors (n=22, 52%), and program leaders (n=19, 45%).

CONCLUSIONS

Among early-career professionals, mentorship and exposure during training are key drivers of entry into and retention within the NEN field. However, substantial barriers remain in translating early interest into meaningful academic and research engagement. These findings highlight actionable opportunities for professional societies and institutions to strengthen mentorship pathways, expand infrastructure, and foster the professional development of the next generation of NEN specialists.

ABSTRACT ID #36608

O-23

Structured Chart Abstraction Improves Progression Ascertainment in a Neuroendocrine Neoplasm Registry: A Quality Improvement Initiative

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BACKGROUND

Accurate progression documentation is essential for cancer registry quality reporting and outcomes research. We identified a documentation gap in which standard NAACCR recurrence fields failed to capture progression events in patients with neuroendocrine neoplasms (NENs). We implemented a quality improvement (QI) initiative to standardize progression ascertainment and inform registry redesign.

METHODS

We conducted a QI project using our institutional NEN registry at a CoC-accredited community cancer center. Registry records for 481 patients diagnosed from 2018–2025 were audited to establish baseline progression documentation. WHO-aligned differentiation class was chart-abstracted for 386 patients. A standardized abstraction workflow was developed, incorporating reviewer training, predefined abstraction criteria, and structured review of oncology notes, imaging reports, and tumor board records.

RESULTS

Baseline audit revealed 325 of 481 patients (67.6%) coded 'never disease-free,' reflecting metastatic presentation, and 146 patients (30.4%) coded disease-free with zero disease-free survival — the field was effectively uncoded. Standard registry captured 7 progression events (1.5%); chart abstraction identified 76 (19.7%) — 13-fold improvement. Despite this gain, 103 deceased NEC patients had no documented progression date, identifying a persistent workflow gap. The improved dataset enabled stratified PFS analysis: NEC median time to progression 4.0 months versus 6.8 months for NET/WD (log-rank p=0.023).

Table 1. Standard Registry vs. Chart-Abstracted PFS Completeness

Finding	Standard Registry	Chart Abstraction	Result
PFS events captured	7/481 (1.5%)	76/386 (19.7%)	13× improvement
Coded 'never disease-free'	325 (67.6%)	N/A	Structural mismatch
Disease-free; 0-mo DFS	146 (30.4%)	N/A	Field effectively uncoded
Deceased NEC, no progression	—	103 patients	Residual workflow gap

NEC median TTP	Not estimable	4.0 months	—
NET/WD median TTP	Not estimable	6.8 months†	p=0.023

NEC=neuroendocrine carcinoma; NET/WD=well-differentiated NET; TTP=time to progression. Log-rank p=0.023, NEC n=197 vs. NET/WD n=166. †Heavy censoring in the NET subgroup limits precision of the 6.8-month estimate.

CONCLUSIONS

This QI initiative identified a critical registry workflow failure in NEN progression documentation. Standardized chart abstraction increased event capture 13-fold and enabled PFS analyses not previously possible from standard registry fields. However, absent progression data in 103 deceased NEC patients demonstrate that retrospective abstraction cannot serve as a long-term solution. These findings directly informed redesign of our institutional registry workflow, with implementation of prospective, point-of-care progression documentation to support quality reporting and clinical research.

ABSTRACT ID #36663

T-1

Alliance A092204: Phase II Study of Cabozantinib in Combination with Cemiplimab versus Cabozantinib in Adolescents and Adults with Adrenocortical Cancer

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BACKGROUND

Systemic chemotherapy with etoposide, doxorubicin, and cisplatin, in combination with the adrenolytic agent, mitotane is the current standard of care for advanced adrenocortical carcinoma (ACC). Toxicities are frequent, and outcomes are poor, underscoring the need for more effective treatment combinations. It is known that cabozantinib (cabo) monotherapy and anti-PD-1 monotherapy have meaningful activity in ACC; thus, combination of cabo with the anti-PD-1 therapy cemiplimab (REGN2810; cemi) may provide synergy. This randomized phase II trial evaluates whether cabo+cemi improves progression-free survival (PFS) versus cabo alone.

METHODS

Patients aged ≥12 years with locally advanced unresectable or recurrent/metastatic ACC, with measurable disease (RECIST v1.1), performance status ECOG 0–2 (≥18 years), Lansky ≥50 (12-<16 years), or Karnofsky ≥50 (16–<18 years), and body surface area ≥1.2 m^2 are eligible. Up to 3 prior lines of systemic therapy are allowed and treatment-naïve patients are eligible. Patients who received mitotane ≤6 months prior to registration must have discontinued mitotane and have a level <2 mg/L to be eligible due to interactions with cabo. A total of 48 patients (to achieve 46 evaluable) will be randomized 1:1 to cabo (Arm A) or cabo+cemi (Arm B) using Pocock–Simon dynamic allocation, stratified by prior systemic therapy (naïve vs ≥1 line) and corticosteroid-producing status (yes vs no);

crossover from Arm A to Arm B is permitted at disease progression. The primary endpoint is PFS (time from registration to progression or death) compared between arms in an intention-to-treat population. The design hypothesizes that cabo+cemi will result in meaningfully superior PFS of at least 10 months versus 5 mo with cabo alone (HR 0.5, α=0.10, 80% power). Secondary endpoints include safety and tolerability, objective response, duration of objective response, time to progression, and overall survival with cabo-cemi.

RESULTS

Enrolment is ongoing.

CONCLUSIONS

Clinical trial identification: NCT06900595

Support: U10CA180821, U10CA180882, UG1CA233331, UG1CA189822, UG1CA233180, UG1CA233339
https://acknowledgments.alliancefound.org

ABSTRACT ID #36396

T-2

Hepatic artery infusion therapy for gastro-entero-pancreatic neuroendocrine tumor liver metastases: a patient-derived preclinical study.

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BACKGROUND

Liver metastases (LM) are common in neuroendocrine tumors (NETs) and remain difficult to control. Current systemic therapies achieve modest tumor responses. Trans-arterial embolization, while effective, carries procedural morbidity and requires repeated interventions. Hepatic artery infusion pump (HAIP) therapy enables highly selective, high-concentration intrahepatic drug delivery with minimal systemic toxicity, with well-established efficacy in colorectal LM. Its potential in NETs has not been systematically studied. The optimal agents for hepatic arterial delivery in this histology are unknown. A critical first step is to characterize NET drug sensitivity to candidate HAIP-deliverable agents, alone and in combination with approved systemic therapies.

METHODS

Using an integrated platform combining a large NET biobank with patient-derived organoid (PDO) and avian xenograft (PDXovo) models, we will test HAI-deliverable agents: floxuridine (FUDR), paclitaxel, dacarbazine, gemcitabine, and streptozocin. First, PDOs from liver will be treated with each agent across multiple concentrations and combinations, with sunitinib as positive control and normal liver and cholangiocyte lines as toxicity controls. Drug efficacy will be assessed by apoptosis (Annexin V), metabolic activity (ChromaLive Yellow), and endoplasmic reticulum stress (ChromaLive Red) using confocal imaging. Second, Avian patient-derived zenografts (PDXovos) will quantify intratumoral drug penetration using fluorescent drug probes and immunostaining. They will be used to validate top-performing agents, with tumor volume and blood flow quantified by high-frequency ultrasound and histologic markers including chromogranin A, Ki-67, and cleaved caspase-3. The two most effective agents will be tested in cross-titration with approved systemic therapies (sunitinib, cabozantinib, everolimus, Lutathera).

RESULTS

We plan to study liver metastasis-derived PDOs from 12 patients (6 male, 6 female) and PDXovos from 6 patients (3 male, 3 female) with gastro-entero-pancreatic (GEP)-NETs. This will build on a platform that has generated over 10,000 PDOs and 100 PDXovos from prior GEP-NET specimens with >95% model generation success. Treatment of the first PDO cohorts is now underway, with initial drug-response rounds currently in progress. Initial results are expected in October 2026.

CONCLUSIONS

This will be the first systematic, mechanistically grounded evaluation of HAI therapy in GEP-NETs, to define which agents, alone or combined with contemporary systemic therapy, warrant clinical testing in unresectable NET liver metastases. Pairing an established HAIP program with a successful patient-derived NET models platform provides a direct path to early-phase trials.

ABSTRACT ID #36567

T-4

Trial-in-Progress: A Phase 2 Study of ONC206 (JZP3507) in Patients With Advanced Pheochromocytoma and Paraganglioma

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BACKGROUND

Effective treatment options for patients with metastatic pheochromocytoma and paraganglioma (PCPG) remain limited, highlighting a significant unmet therapeutic need. JZP3507 (formerly ONC206), an oral, brain-penetrant second generation imipridone with nanomolar potency, acts as a selective ClpP agonist and DRD2/3 antagonist. Encouraging clinical responses have been demonstrated with dordaviprone in patients with advanced paraganglioma. Similarly, in vitro models have shown efficacy with JZP3507 across multiple tumor types, including PCPG. JZP3507 has been shown to disrupt mitochondrial function and induce apoptosis of tumor cells. Phase 1 clinical trials demonstrated the safety and tolerability of multiple doses and schedules of JZP3507 in patients with advanced CNS tumors, with most treatment-related adverse events being mild to moderate, including fatigue, lymphocyte count decrease, and vomiting. This study will assess the safety and efficacy of JZP3507 in patients with locally advanced or metastatic PCPG.

METHODS

This is an open-label, dose-optimization, multicenter, two-stage phase 2 clinical study (NCT07282587). Eligible patients include those aged ≥18 years with histologically confirmed unresectable PCPG, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, an Eastern Cooperative Oncology Group (ECOG) Performance

Status of 0 to 2, and adequately controlled blood pressure (≤150/90 mm Hg) and who have exhausted or declined further standard systemic treatments. Patients with active cardiac disease, active infection requiring treatment, or previous exposure to JZP3507 or dordaviprone are not eligible. In stage 1, 150 mg JZP3507 will be administered twice daily on 3 consecutive days per week in 28-day cycles. If stage 1 meets the pre-specified response threshold (confirmed response in >6 patients), the study will proceed to stage 2, and participants will be randomized 1:1 to one of two JZP3507 dose levels (to be determined post stage 1). Treatment will continue until disease progression, unacceptable toxicity, or patient/physician request to discontinue treatment. The primary endpoint is overall response rate (patients with confirmed complete or partial response) by RECIST v1.1. Imaging will be collected pre-baseline, at baseline, and every 12 weeks (±7 days) thereafter until disease progression per RECIST v1.1. Key secondary endpoints include evaluation of PCPG growth and symptoms (including progression-free survival, overall survival, antihypertensive medication dosing, and biochemical disease markers [plasma metanephrines]) and safety, pharmacokinetics, and quality of life. Exploratory endpoints include incidence and time to new metastases by location and subsequent anticancer therapy. Total anticipated enrollment is 90 patients (as of June 1, 2026, 8 patients have been enrolled).

RESULTS

Non-applicable

CONCLUSIONS

Non-applicable

ABSTRACT ID #36549

T-5

Cohort-level safety and efficacy results for [212Pb]VMT-a-NET in advanced somatostatin receptor subtype 2-expressing neuroendocrine tumors: Cohorts 1–3

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BACKGROUND

[^{212}Pb]VMT-a-NET is an alpha-particle radiation-delivering agent targeted to somatostatin receptor type 2 (SSTR2)-expressing tumors. Here, we present safety and efficacy results from the dose-finding phase 1/2a clinical trial (NCT05636618).

METHODS

This phase 1/2a dose-escalation study uses a Bayesian Optimal Interval to identify an optimal dose of [^{212}Pb]VMT-a-NET for participants with advanced, well-differentiated neuroendocrine tumors (NETs) expressing SSTR2. Eligible participants must have unresectable or metastatic disease, documented radiologic progression following at least one prior systemic treatment, and evidence of SSTR2 expression (Krenning Score ³2) in ≥1 lesion confirmed on an FDA-approved SSTR2 PET scan. Patients previously treated with systemic peptide receptor radionuclide therapy are excluded from enrollment. During the dose-finding phase, participants may receive up to four administrations of [^{212}Pb]VMT-a-NET at their assigned dose level, and they are monitored for dose-limiting toxicities (DLTs) for 42 days and safety throughout the study. Efficacy is evaluated by investigators according to RECIST criteria v1.1. Dosimetry is included as a supportive analysis.

RESULTS

As of 17-April-2026, 68 participants had been enrolled across Cohorts 1, 2, and 3 and received at least one dose of [^{212}Pb]VMT-α-NET: 2 participants in Cohort 1 (92.5 MBq; 2.5 mCi), 46 in Cohort 2 (185 MBq; 5 mCi), and 20 in Cohort 3 (222 MBq; 6 mCi). No DLTs, grade 4 or 5 TEAEs, treatment-related discontinuations, serious renal events, dysphagia, or clinically meaningful treatment-related myelosuppression were observed. The median follow-up for all treated participants was 10.6 months (range 1-25). Efficacy has been summarized for 25 participants (2 in Cohort 1 and 23 in the first half of Cohort 2 whose median follow-up was 15.3 months [range 1-25]). Investigator-assessed RECIST v1.1 objective responses were observed in 10 of 23 participants (43.5%) of the first half of Cohort 2, including 9 with confirmed PR. Both participants in Cohort 1 continued to exhibit stable disease after 2 years of follow-up. Subsequently cohort 4 opened to test a front-loading regimen (222/185/185/148 MBq; 6/5/5/4 mCi). Updated safety for all participants and updated efficacy for participants with sufficient follow-up beyond the 25 participants summarized here will be presented at the congress.

CONCLUSIONS

Treatment with [^{212}Pb]VMT-α-NET continues to demonstrate a favorable safety profile across all treated participants (n = 68) and shows signs of sustained efficacy at the 92.5 MBq and 185 MBq dose levels. The therapy has been well-tolerated with no observed DLTs or serious treatment-related adverse outcomes.

ABSTRACT ID #36595

T-6

DAREON®-NEC-1: Phase III trial of first-line obrixtamig plus carboplatin and etoposide (SoC) vs SoC in patients with DLL3-positive epNEC

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BACKGROUND

Extrapulmonary neuroendocrine carcinomas (epNECs) are heterogeneous, highly aggressive neoplasms. The current first-line standard of care (SoC) is platinum-based chemotherapy, but prognosis remains poor despite early treatment, indicating an urgent unmet medical need for better treatment options. Delta-like ligand 3 (DLL3) is widely expressed in epNECs. Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager that binds simultaneously to DLL3 on tumor cells and CD3 on T-cells, leading to tumor cell lysis. In the Phase Ib DAREON®-7 trial (NCT06132113), first-line obrixtamig + SoC showed encouraging clinical outcomes and manageable safety in patients with DLL3-positive epNEC. DAREON®-NEC-1 (NCT07544654) is an ongoing Phase III, multicenter, open-label, randomized trial evaluating first-line obrixtamig + carboplatin/etoposide (SoC) vs SoC in patients with DLL3-positive epNEC.

METHODS

Patients with poorly differentiated, unresectable, locally advanced or metastatic epNEC, including neuroendocrine carcinoma (NEC) of unknown primary site, are eligible. Patients must be treatment-naïve except for one mandatory cycle of platinum/etoposide before

randomization and have adequate archival FFPE tumor tissue with DLL3-positive expression status. Patients with asymptomatic CNS metastases are eligible if neurologically stable and radiotherapy is completed more than 14 days prior to randomization. Mixed histologies are permitted if the NEC component is >70% of the tumor tissue. Patients with leptomeningeal disease, carcinomatous meningitis, Merkel cell carcinoma, medullary thyroid carcinoma, or neuroendocrine prostate cancer are not eligible. Patients are randomized 1:1 to SoC with or without obrixtamig; stratification includes by DLL3 expression status ($DLL3^{high}$: ≥50% of tumor cells with moderate-to-strong staining; $DLL3^{low}$: <50%), assessed centrally using an investigational antibody for DLL3 (SP347; Roche Diagnostics). After one cycle of SoC, patients in the obrixtamig + SoC arm receive obrixtamig in a step-up dosing regimen, followed by target dose with SoC treatment for up to 5 cycles, followed by obrixtamig maintenance treatment every three weeks until disease progression, unacceptable toxicity, or other protocol-defined discontinuation criteria, for up to 36 months. SoC is administered per label. Cross-over is not permitted. The primary endpoint is overall survival. Secondary endpoints include progression-free survival (RECIST v1.1; investigator assessed), patient-reported outcomes (EORTC QLQ-C30), and safety. Planned enrolment is approximately 390 patients across 150 sites in North America, South America, Europe, Asia and Oceania.

RESULTS

N/A

CONCLUSIONS

N/A

ABSTRACT ID #36580

Previously presented at European Society for Medical Oncology (ESMO), FPN: #2432TiP, Timon Vandamme et al. - Reused with permission

T-7

Zanzalintinib Maintenance in Patients with High Grade Neuroendocrine Neoplasms (HG-NENs)

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BACKGROUND

Metastatic high-grade neuroendocrine neoplasms (HG-NENs) are aggressive and often fatal, necessitating urgent upfrontchemotherapy, such as platinum and etoposide. However, regimens are harsh and patients will receive a limited number oftreatments before considering a break or observation, as there are no approved maintenance regimens. Unfortunately, theoverwhelming majority will progress within a few weeks to months of treatment break, again with very aggressive disease.There is an unmet need for a maintenance regimen that delays further chemotherapy administration, and that allows for abetter quality of life.

Our prior study NCT04412629 showed efficacy of the multi kinase inhibitor cabozantinib in patients with recurrent orprogressive HG-NENs. Zanzalintinib, a novel, oral, multi-targeted inhibitor of VEGFR, MET, and the TAM (TYRO3, AXL, andMER) kinases, has a similar kinase inhibition profile to cabozantinib but has a shorter half-life and has shown preferentialin vivo tumor distribution. The purpose of this study is to test zanzalintinib as a maintenance therapy in the HG-NEN population.

METHODS

This is a single arm Phase II study.

A total of 32 eligible patients will be offered zanzalintinib starting at 60 mg orally daily in 28-day cycles. Treatment willcontinue until disease progression or unacceptable toxicity. Eligible patients have HG-NENs of any origin except for smallcell lung and Merkel cell cancer, have received their first instance of chemotherapy and have achieved at least stabledisease as of the most recent imaging modality. Other key eligibility criteria include age >=18 years, ECOG 0-1. Keyexclusion criteria are concurrent malignancies, known untreated brain metastases and uncontrolled significantcardiovascular disorders, significant bleeding risk or unhealed wounds.

Primary endpoint is Progression Free Survival (PFS). Secondary endpoints include overall response rate (ORR), overallsurvival (OS) and safety. There are mandatory pre and on-

treatment (pre C2) biopsies. Recruitment is ongoing. Resultsfrom this trial will inform on the use of zanzalintinib as a maintenance therapy in patients with HG-NENs who are eligiblefor a chemotherapy break.

RESULTS

Supported by Exelixis.

Clinical trial identification NCT06926634.

CONCLUSIONS

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ABSTRACT ID #36626