

ABSTRACTS



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B-1

Spatial and Transcriptional Profiling Reveals Immune Remodeling and Microenvironmental Heterogeneity in Benign and Malignant Pancreatic Neuroendocrine Tumors

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BACKGROUND

Pancreatic neuroendocrine tumors (PNETs) are rare, clinically heterogeneous malignancies with limited insight into the molecular and immune mechanisms driving progression from benign to malignant states, especially regarding tumor microenvironment (TME) remodeling.

METHODS

We integrated clinical-pathological genomics to dissect transcriptional and immunologic features across PNET subtypes. We performed bulk RNA sequencing and spatial transcriptomics on 23 clinically annotated PNET samples, including functional (insulinomas, gastrinomas) and non-functional (indolent and aggressive) tumors.

RESULTS

Spatial transcriptomics revealed substantial variation in immune infiltration and inflammatory states. Functional insulinomas showed sparse immune presence with low CD4⁺ T-cells (9.5–15.1%) and minimal exhausted T-cells (1.9–4.6%). Indolent and aggressive non-functional tumors displayed increased CD4⁺ infiltration and exhausted T-cells (7.3–15.8%). Macrophage density rose with malignancy, occupying up to 50% of spatial spots in aggressive tumors. The tumor inflammation signature confirmed low inflammation in benign tumors (0.99–2.1%) versus substantial increases in aggressive tumors (up to 27.7%), indicating immune activation.

Bulk RNA-seq gene set enrichment analysis comparing malignant and indolent tumors to benign functional tumors revealed consistent downregulation of pancreatic endocrine pathways (NES -2.23 to -2.64) and biosynthetic programs critical for protein production and proteostasis (NES -2.82 to -1.28) in malignant tumors. Furthermore, Indolent tumors frequently activated extracellular matrix (ECM) pathways (ECM receptor interaction NES 1.59 to 1.82), with some showing moderate MAPK and VEGF signaling (NES 1.36 to 1.90), reflecting stromal and vascular engagement. Immune pathways such as cytokine, JAK-STAT, and complement signaling were moderately enriched (NES 1.55 to 2.17), indicating low-grade immune activation.

Aggressive non-functional tumors showed pronounced heterogeneity. A subset displayed a “hot” phenotype with broad upregulation of inflammatory pathways, including T-cell receptor, antigen processing, JAK-STAT, and cytokine-cytokine receptor signaling (NES 1.55 to 2.61). Others exhibited a “cold” phenotype with downregulation of immune pathways such as leukocyte migration, B-cell

receptor signaling, and T-cell receptor signaling (NES -2.31 to -1.50). Immune deconvolution confirmed immune infiltration correlated with malignancy, with benign tumors showing low immune gene expression (mean 0.19), increasing in indolent tumors (mean 0.34), while aggressive tumors exhibited variable infiltration (0.19 to 0.42), reflecting both “hot” and “cold” immune states.

CONCLUSIONS

We define molecular programs that distinguish benign and malignant PNETs, underscoring a central role of immune remodeling in malignancy. We observed loss of pancreatic identity and diverse tumor microenvironments. The marked heterogeneity within aggressive tumors, comprising “hot” inflammatory and “cold” immunosuppressed phenotypes, highlights the complexity of tumor-immune interactions and offers critical insights for patient stratification and immunotherapy development.

ABSTRACT ID #33416



B-2

Validation of Adversity-Linked Genes in Pancreatic Neuroendocrine Tumors

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BACKGROUND

Health outcome differences exist among patients with pancreatic neuroendocrine tumors (pNET), particularly among those experiencing adverse social determinants of health (SDOH). These groups experience worse overall survival compared to their peers. Our team has previously reported significant intratumoral transcriptomic alterations linked to neighborhood adversity. This study aims to validate the expression of these novel transcriptomic changes in established pNET cell lines versus normal controls for future translational studies.

METHODS

We selected the top 20 differentially expressed genes (DEGs) from our prior transcriptomic analysis based on biological pathways' clinical relevance (malignancy, inflammation, and metabolism). We then evaluated the modulation of expression levels of these DEGs in pNET cell lines (BON-1 and/or QGP-1) compared to normal HPNE cells (hTERT-immortalized normal pancreatic) using western blotting and qPCR for protein and mRNA quantifications, respectively. We reviewed patients who underwent surgical resection for grade 1-2 pNETs at our institution (2006-2022) and created Tissue Microarrays (TMAs) from those patients. Qualitative immunofluorescence analysis was also performed on selected patients' tissue sections to confirm the colocalization of our DEGs with pNET markers: Chromogranin A and Synaptophysin.

RESULTS

We validated the enhanced expression of our top SDOH-associated pNET DEGs including: WFS1, MAX, cGAS, FAAH, SIRT6, SIGLEC8, and FBOX6, among others. Comparative immunoblotting of our target genes in HPNE versus BON-1 and QGP-1 showed altered expression levels in both types of pNET cell lines with several target genes being highly expressed similarly to known pNET markers, Chromogranin A and SSTR2. In parallel, qPCR assessments using BON-1 cells revealed that our DEGs were overexpressed from ~5 to ~400 fold over HPNE relative expression. As a reference, SSTR2 and Chromogranin A increased ~5 and ~300 fold in BON-1 versus HPNE cells, respectively. Finally, our patients' TMAs demonstrated co-localization of DEGs with pNET markers, Chromogranin A and Synaptophysin confirming intratumoral expression.

CONCLUSIONS

Our novel adversity associated genes have been validated experimentally with protein and mRNA expression levels in established pNET cell lines. Future directions will focus on exploring the role of these genes in driving more aggressive disease.

ABSTRACT ID 33478



B-3

A SST14 based T-cell engager for the treatment of neuroendocrine tumors

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BACKGROUND

Somatostatin receptor 2 (SSTR2) is overexpressed and currently used as a therapeutic target in well-differentiated neuroendocrine tumors (NETs). We designed a novel bispecific T-cell engager targeting SSTR2 via Somatostatin-14 (SST-14), linked with a scFV-based anti-CD3.

METHODS

293T cells expressing SSTR2-GFP or mock-GFP as control, the pancreatic NET cell line BON1, and patient-derived tumoroids from pancreatic NETs were used as target cells, while T cells enriched from PBMCs of healthy donors were used as effector cells. As an alternative, autologous tumor-infiltrating lymphocytes (TILs) and peripheral blood T cells from patients were used. Flow cytometry and ImageStream were used to assess the molecule's interaction with CD3 and SSTR2, and immune synapse formation. T-cell activation and cytotoxicity induced by the engager were measured using ELISA and real-time live-cell imaging. The effect of the molecule alone on tumoroids was quantified by bioluminescence and octreotide was used as control. Cibacron blue-agarose beads coated with 100 µg of albumin were used to detect the interaction between the engager and albumin, and a scrambled SS14 engager was used as a control.

RESULTS

The T-cell engager interacts with the CD3 on T-cells and the SSTR2 on target cells between 100nM and 20nM, inducing the formation of immunological synapses upon interaction. The molecule significantly increases IFN-γ, TNF-α, and Granzyme-B secretion when T cells are co-cultured with SSTR2⁺ 293T cells or BON1cell line. A similar effect is observed when patient-derived tumoroids are cocultured with autologous T cells or TILs. Moreover, at 20 and 100 nM, the engager shows dose-dependent cytotoxicity against SSTR2⁺ 293T cells in the presence of T cells, which is specific for the presence of the SSTR2. The molecule showed an intrinsic antiproliferative effect on patients derived tumoroids, which was comparable to octreotide. It also exhibited specific binding to albumin, in contrast to the control.

CONCLUSIONS

This engager elicits a dose-dependent T cell response against several SSTR2-expressing cells, including NET cell lines and patient derived organoids. In the absence of T cells, the molecule retains its SST14-derived antiproliferative activity, which resembles that of octreotide.

ABSTRACT ID 33480

B-4

Single-nucleus transcriptomic analysis of the tumor microenvironment in small intestinal NETs

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BACKGROUND

Small intestinal neuroendocrine tumors (SI-NETs) are one of the major cancer subtypes of the small bowel and are believed to arise from enterochromaffin (EC) cells, a rare type of enteroendocrine cell, which account for less than 1% of the intestinal epithelium. Previous high-throughput sequencing studies have shown that concurrent primary tumors from the same SI-NET patient display distinct somatic mutational profiles (despite few clear driver mutations). The independent clonal nature of these lesions suggests that other, non-genetic mechanisms are likely involved in their growth and development. The goal of this project has been to characterize the tumor microenvironment in SI-NETs and study its potential role in their pathogenesis.

METHODS

Our sample cohort included nine primary tumors, six lymph node metastases, and patient-matched normal ileal mucosa specimens from five multifocal SI-NET patients. To improve the chances of capturing EC cells from normal ileal tissue, we included 18 additional normal ileal tissue specimens in our study. Single-nucleus RNA (snRNA) sequencing was performed using 10x Chromium Single Cell 5' High-Throughput v2 technology. We used Seurat (v5) and harmony for the data analysis and integration of the samples. The identification of enterochromaffin cells in our data was based on four cell markers: SLC18A1, TPH1, CHGA, and LMX1A. Pseudobulk differential expression analysis was performed with DESeq2.

RESULTS

A total of 251,680 high-quality nuclei were available for our analysis. After the integration of snRNA sequencing data from normal ileal mucosa samples, we detected altogether slightly under 300 enterochromaffin cells (0.2%). Additionally, we identified 32,558 tumor cells (40.3%) among the primary tumors and 20,618 (45.6%) among the metastases. Smooth muscle cells and (myo)fibroblasts represented the most common types of stromal cells within the primary tumors. Differential expression analysis between tumor cells and enterochromaffin cells revealed several statistically significant differentially expressed genes that are involved in cell transport and cell cycle regulation.

CONCLUSIONS

For the first time, we have been able to examine expression changes between tumor cells and their putative cells-of-origin in SI-NETs, elucidating mechanisms that are involved in the growth and development of these tumors. A deeper knowledge of the cellular and molecular mechanisms that underlie SI-NET development is essential for the non-invasive management, early detection and prevention of the tumors.

ABSTRACT ID 33446

B-5

Uncovering Filamin A as an Exosomal Biomarker in PanNET Through Integrative Tissue Proteomics

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BACKGROUND

Pancreatic neuroendocrine tumors (PanNETs) are rare neoplasms, with increasing incidence and poor survival rate. The disease is diagnosed at advanced stages due to the lack of diagnostic sensitivity and specificity of the biomarkers, inaccessible and expensive nature of the imaging techniques available. Proteomics plays a significant role in cancer research and aids in the discovery of biomarkers. This study aimed to identify potential PanNET biomarkers through tissue proteomics and explore their relevance in circulating exosomes.

METHODS

A comparative label-free quantitative proteomic analysis was conducted on 6 PanNET tissue samples (3 Grade I and 3 Grade II) and 6 control pancreatic tissues (3 normal healthy and 3 adjacent non-tumor) after getting ethical approval from the institute's ethical committee (IECPG-452/25.08.2). Multiple group-wise comparisons were performed to identify differentially expressed proteins. Potential biomarker proteins were validated using molecular assays. Functional associations were analyzed via STRING-based pathway and protein interaction analysis. Small extracellular vesicles (sEVs) were isolated from the plasma of PanNET patients and healthy controls to evaluate the exosomal enrichment of candidate proteins.

RESULTS

The proteomic analysis by LC-MS revealed a total of 78.4% identified proteins that were uniquely expressed in PanNETs, with 30 proteins significantly dysregulated between PanNETs and normal healthy controls with $p < 0.05$, fold change > 2 . Among these, 11 proteins were found to be upregulated and 19 were downregulated in abundance value in patients with respect to controls. Functional analysis of the dysregulated proteins with STRING PPI-network revealed four pancreas-specific proteins (DCN, FlnA, COL1A2, and CALR) that showed strong associations with cancer-related pathways like antigen processing and presentation and proteoglycans in cancers. Preliminary validation using western blot and immunohistochemistry highlighted Filamin A (FlnA) as a significantly overexpressed protein in PanNET tissues as compared to healthy controls. Additionally, STRING analysis indicated FlnA's involvement in exosome-related networks. Further analysis of plasma-derived small extracellular vesicles (sEVs)/exosomes demonstrated significant upregulation of FlnA in PanNET patients compared to healthy controls, confirming its presence and enrichment in circulating exosomes.

CONCLUSIONS

This integrative approach, spanning tissue proteomics to exosomal profiling, identifies Filamin A as a promising biomarker candidate in PanNET. Its consistent overexpression in both tumor tissues and plasma-derived exosomes underscores its potential as circulating biomarker for non-invasive diagnostic applications.

ABSTRACT ID 33394

B-6

Tumor-Intrinsic Adaptations to Liver Microenvironment Drive Metastasis in Pancreatic and Small Intestinal Neuroendocrine Tumors

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BACKGROUND

Liver metastasis significantly impacts survival in gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including pancreatic (PNETs) and small intestinal neuroendocrine tumors (siNETs). This study aims to uncover molecular mechanisms driving liver metastasis in these tumors.

METHODS

RNA-seq data from primary and liver metastasis patient samples of PNETs and siNETs were analyzed using publicly available datasets. Differential gene expression (DEG) analysis identified genes with significant expression changes in metastases. Pathway enrichment using hallmark gene sets and MSigDB uncovered key pathways and cell-type-specific processes associated with metastasis. To validate that the observed molecular signatures were tumor-derived, rather than artifacts of contamination by non-tumor liver cells, we applied the ESTIMATE algorithm to assess stromal and immune cell content, confirming tumor purity. Logistic regression-based machine learning models prioritized DEGs with high predictive accuracy (AUC values).

RESULTS

DEG analysis of 83 primary PNETs and 30 liver metastases and 44 primary siNETs and 37 metastases revealed distinct tumor-derived signatures in liver metastases, highlighting upregulation of liver metabolic and inflammatory pathways and downregulation of pancreas- and intestine-specific functions, indicating a phenotypic shift enabling tumor survival in the liver microenvironment. Hallmark pathway enrichment and MSigDB analyses reinforced these findings, emphasizing liver-specific metabolic adaptations. Further, ESTIMATE analysis confirmed high tumor purity in metastatic samples. Logistic regression identified several DEGs with strong discriminatory power (AUC > 0.85) between primary and metastatic tumors. Among these DEGs, two genes, ORM1 (PNET: log₂FC = 9.48, AUC = 0.91; siNET: log₂FC = 10.38, AUC = 0.95) and CYP2E1 (PNET: log₂FC = 8.94, AUC = 0.89; siNET: log₂FC = 7.52, AUC = 0.94), were significantly upregulated in both tumor types, suggesting potential roles as biomarkers and therapeutic targets. Ongoing experiments include overexpression and stable knockdown of top DEGs in patient-matched primary tumor- and liver metastasis-derived PNET cell lines, respectively, followed by motility and invasion assays to evaluate their impact on key signaling pathways. Further confirmation and validation of differential expression findings will be performed on in-house constructed tissue microarrays (TMAs) using matched GEP-NET primary and metastatic tumors from our surgical patients.

CONCLUSIONS

This study reveals that liver metastases in GEP-NETs are driven by tumor-intrinsic molecular adaptations, including a shift toward normal liver functions. These findings highlight tumor-specific mechanisms in metastasis and identify key biomarkers with diagnostic and therapeutic potential. This work provides a foundation for precision oncology strategies targeting metastatic GEP-NETs.

ABSTRACT ID 33444

B-7

Changes in the Tumor Microenvironment of Well-Differentiated Metastatic Neuroendocrine Tumors might mediate resistance in patients treated with ¹⁷⁷Lu-DOTATATE

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BACKGROUND

Peptide receptor radionuclide therapy with ¹⁷⁷Lu-DOTATATE (PRRT) improves outcomes in well-differentiated neuroendocrine tumor (NETs). However, heterogeneous responses and relapse suggest that features within the tumor microenvironment (TME) might mediate treatment resistance. We investigated immune- and stromal remodeling pre- and post PRRT across metastatic NET lesions, correlating findings with clinical response and genomic features to identify determinants of PRRT efficacy.

METHODS

We analyzed 34 tumor samples from 12 patients with pancreatic (PNET, n=5) and small bowel NETs (SBNETs, n=7) treated with PRRT that underwent subsequent surgical debulking. Tumor samples included matched pre/post-PRRT tissues from liver metastases categorized as responding, stable, or progressing. Multiplex immunofluorescence profiling enabled TME phenotyping, spatial analysis, and quantification of immune-stromal interactions. Ki-67 proliferation indices and OncoPlus next-generation sequencing were also performed to evaluate somatic mutations and tumor mutational burden (TMB).

RESULTS

Median time between PRRT and surgical debulking was 10.5 months. Four patients had progression in some, 5 patients in all and 3 patients in none of the liver tumors after PRRT and prior to debulking. Across all samples, PRRT increased CD8⁺ T cell infiltration (20%, $p = 3.9 \times 10^{-31}$), CD31⁺ vascular remodeling (18%, $p < 1 \times 10^{-10}$), and PD-L1 upregulation (5%, $p = 1.3 \times 10^{-4}$). Spatial analysis confirmed post-PRRT CD8⁺ proximity to PD-L1⁺, FoxP3⁺, and CD31⁺ cells, indicating immune exclusion.

Progressing PNET liver metastases showed an immune-silent baseline with CD4⁺ dominance (90%, $p < 1 \times 10^{-10}$) and minimal CD8⁺ (5%), CD31⁺ (2%), and FoxP3⁺ (0%) cells. In contrast, responding PNET liver metastases exhibited elevated CD8⁺ (20%), CD31⁺ (18%), and PD-L1⁺ (5%) infiltration, while exhausted CD8⁺PD-L1⁺ subsets remained unchanged (3%, $p = 0.50$). Stable SBNET liver metastases had elevated

FoxP3⁺ (16%) and CD68⁺PD-L1⁺ (1%) macrophages while progressing SBNETs showed higher CD8⁺ (56%), PD-L1⁺ (9%), and CD8⁺PD-L1⁺ (2.2%) infiltration. Genomically, PNETs harbored higher Ki-67 indices (~11.33% vs. ~8.9%), a greater number of somatic mutations (average 2.8 vs. 1.5 mutations), and higher TMB (4.54 vs. 3.44 mutations/Mb).

CONCLUSIONS

PRRT induces CD8⁺ infiltration and angiogenic remodeling but is limited by immunosuppressive features. SBNETs exhibiting cytotoxic infiltration and PD-L1 expression after PRRT may benefit from immune checkpoint blockade. In contrast, PNETs characterized by CD4⁺ and CD68⁺ dominance with minimal checkpoint expression may require priming with multikinase inhibitors to remodel the TME prior to checkpoint inhibition to enhance PRRT efficacy.

ABSTRACT ID 33448

B-8

Deciphering the Functionality of MAX Phosphorylation Dynamics in Pancreatic Neuroendocrine Tumors

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BACKGROUND

Pancreatic neuroendocrine tumors (PNETs) are the second most common pancreatic malignancy, with patients exposed to adverse social determinants of health (aSDOH) exhibiting worse outcomes (larger tumors and higher rates of lymph node metastasis). We identified Myc associated factor X (MAX) expression to be altered in adversity. MAX regulates the activity of the Myc oncogene, and its dysregulation enhances aggressive growth of some cancers, but its effect remains unstudied in PNETs. The transcriptional activities of MAX can be altered by phosphorylation at residue Serine 11, but the function of Serine 2 phosphorylation remains elusive. This study aims to design tools to evaluate the biological role of the phosphorylation dynamics of MAX in PNETs.

METHODS

MAX and phospho-MAX Ser11 were evaluated using western blotting in HPNE, a normal immortalized human pancreatic cell line, versus human PNET cell lines: BON-1 and QGP-1. Additionally, recombinant vectors expressing eGFP-tagged phospho-mutants of MAX individually and in combination (S2A, S2D, S11A, S11D, S2A+S11A, S2A+S11D, S2D+S11A, S2D+S11D) were constructed using site-directed mutagenesis. These mutants were expressed in BON-1 cells and evaluated for correct size and cellular localization using western blotting and fluorescence microscopy, respectively. Finally, BON-1 cells transfected with our eGFP-MAX variants were selected using geneticin for ~3 weeks, then imaged using fluorescence microscopy to confirm colony formation.

RESULTS

On western blotting we confirmed that MAX Ser11 is phosphorylated in HPNE cells, but not in BON-1 and QGP-1. Compared to wild type MAX, all N- and C- terminally tagged phospho-mutants showed identical reactivity to anti-GFP and anti-MAX antibodies and similar nuclear cellular localization according to fluorescence microscopy. Furthermore, after geneticin selection, we confirmed that BON-1 cells proliferated similarly while overexpressing our GFP-tagged MAX phospho-mutants, ruling out cytotoxicity.

CONCLUSIONS

We successfully generated the necessary tools to explore our novel adversity associated gene: MAX. Future ex vivo experiments will evaluate growth curve rates of MAX phospho-mutants and the effects of MAX phosphorylation on its transcriptional network (Myc and Mad). Our study of MAX and its phosphorylation dynamics could validate a new biomarker for prognosis and a novel therapeutic target for treatment of patients with PNETs, reducing health disparities.

ABSTRACT ID 33449

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B-9

Spatial Transcriptomics Reveals Local Subtype-Specific Identity and Signaling within Multifocal Small Intestinal Neuroendocrine Tumors

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BACKGROUND

Small intestinal neuroendocrine tumors (SI-NETs) frequently present as multifocal lesions, but the spatial and molecular mechanisms underlying their development and heterogeneity remain unclear. This study aimed to characterize the phenotypic subtypes of tumor cells across anatomical sites in multifocal SI-NETs and identify local microenvironmental factors influencing tumor development.

METHODS

Spatial transcriptomics was performed on 72 tissue microarray cores derived from four patients with multifocal SI-NETs, that included tumoral and non-tumoral tissues from various anatomical layers of the small intestine and regional metastatic sites. Unsupervised clustering, over-representation analysis (ORA), and ligand-receptor (L-R) pair analysis were used to define tumor subtypes and associated signaling networks. External datasets (GSE98894 and GTEx) were used for validation. Protein expression of selected genes was evaluated by immunohistochemistry.

RESULTS

Unsupervised clustering revealed four major tumor subtypes: mucosal, mesenteric, lymphatic, and deep, based on anatomical location and transcriptomic profiles. Each subtype exhibited distinct gene expression patterns and L-R interactions. The mesenteric and lymphatic subtypes exhibited distinct L-R pairs, such as *NRG1 - ERBB3 (HER3)* and *CXCL12 - CXCR4*, respectively. *5HT - HTR1D* was found in all subtypes except mucosal. Across the four subtypes, *SST - SSTR1/2*, *PTN - NCL*, *MDK - NCL* and *GJD2 - GJD2* were consistently detected, suggesting fundamental roles in SI-NET biology.

CONCLUSIONS

While further validation is needed, our findings indicate that multifocal SI-NETs consist of spatially distinct tumor subtypes affected by local cellular interactions, providing insight into SI-NET intra-tumoral heterogeneity, possible microenvironmental-triggered tumorigenesis, and potential subtype-targeted therapeutic strategies.

ABSTRACT ID 33417

NANETS 2025 Symposium Abstracts

B-10

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

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BACKGROUND

Imipridone ONC206, a derivative of dordaviprone (ONC201), is a caseinolytic protease P (ClpP) agonist and dopamine receptor D2/3 (DRD2/3) antagonist with nanomolar potency. Dordaviprone demonstrated responses in patients with neuroendocrine pheochromocytoma-paraganglioma (PC-PG) including tumors with SDHB/FH mutations. We characterized the mechanism of action, in vitro efficacy relative to standard of care (SOC) and dordaviprone, response determinants and acquired resistance for ONC206 in PC models.

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/ONC206. Resistant hPheo1 cells were generated by passaging with increasing ONC206 concentrations.

RESULTS

Co-crystallization with ClpP revealed an allosteric ligand interaction with distinctions in the ONC206-ClpP resolved crystal structure relative to the dordaviprone-bound or apo complexes. ONC206 was a more potent agonist than dordaviprone in cell-free human ClpP casein/peptide assays. Adrenal gland tumors emerged as most sensitive when ONC206 cytotoxicity was assessed in a panel of 432 human cancer cell lines. Accordingly, PC lines exhibited increased nanomolar sensitivity to ONC206 (~6 fold) relative to dordaviprone in cell viability assays. ONC206 induced dose- and time-dependent apoptosis in PC but not fibroblast cells. ONC206 demonstrated superior 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 ONC206 sensitivity while ClpP knockout impaired ONC206 sensitivity. Proteomics indicated inhibition of mitochondrial metabolism by ONC206, 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 ONC206 altered chromatin accessibility while RNAseq demonstrated upregulated stress response, apoptosis and downregulated metabolism-related pathways. Western blot confirmed ONC206 downregulated mitochondrial proteins, neuroendocrine markers and upregulated stress response. Whole exome

sequencing of acquired resistant cells revealed diverse ClpP missense and/or termination mutations, further confirmed using PCR and/or western blot. Seahorse analysis showed ONC206 inhibited mitochondrially-derived ATP in parental but not acquired resistant lines. Overexpression of wild-type ClpP restored ONC206 sensitivity in acquired resistant lines.

CONCLUSIONS

ONC206 is a potent novel agent that is superior to SOC and dordaviprone in PC. ClpP mediates response and acquired resistance to ONC206 in PC.

ABSTRACT ID 33451

B-11

Mechanisms and Models for Cdk5 dependent Neuroendocrine Tumors

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BACKGROUND

Neuroendocrine tumors (NETs) occur in various forms: sporadically and as a consequence of causally-linked mutations. They are generally characterized by their indolent course, debilitating symptoms, and untreatable lethality. Advances that have improved outcomes for these cancers have been limited. Following the discovery that mechanisms that cause neurodegeneration in the central nervous system can also cause NET tumorigenesis, we have been studying various types of NETs to understand the mechanistic causes, create novel clinically accurate models, and identify diagnostic biomarkers. Our hypothesis is that diverse genomic variations converge upon common pro-neoplastic signaling mechanisms such as the aberrant activation of the protein kinase, Cdk5, to drive progression of most Neuroendocrine tumors.

METHODS

Experimental models including human tumors, cell lines, and organ-specific inducible bitransgenic animal models were utilized for the characterization of NETs. Whole exome sequencing, bulk transcriptomics, phosphoproteomics, and immunohistochemistry tissue microarray profiling were performed. Biomarker directed anti-Cdk5 targeted therapies will be tested in vivo using inducible autologous bi-transgenic tetracycline response element mouse models of PNETs, PCs, and GINETs. Cdk5 inhibitors with broad therapeutic windows will be used as the biomarker-directed therapy.

RESULTS

We will summarize some of the most notable advances made in our NET research program based on the understanding that aberrant Cdk5 activation plays a pivotal role in oncogenesis. The models demonstrate that pancreatic NETs (PNETs) and pheochromocytomas (PCs) exhibit markedly elevated expression of p25, the cleaved activator of Cdk5, resulting in persistent and mis-localized kinase activity that drives tumor progression. Immunohistochemical analyses of human NET tissues and genetically engineered mouse models confirmed high p25 levels and aberrant Cdk5 activity across all NET tumor types including GI, pulmonary, and pituitary forms. Notably, this oncogenic signaling axis appears independent of initiating genomic lesions, suggesting that Cdk5/p25 activation represents a convergent downstream mechanism in NET pathogenesis. The transgenic mouse models with neuroendocrine cell type-specific inducible p25 expression recapitulate key features of human NETs, including chromogranin A positivity and elevated proliferation indices. We will present selected findings on the potential of experimental and preclinical treatment approaches for Cdk5 dependent NETs.

CONCLUSIONS

The inducible mouse models provide a useful preclinical tool for testing new therapies. The downstream effectors of Cdk5 can serve as predictive molecular signatures for the early detection of tumors in NET patients. The next step involves developing a clinically relevant multiplex assay system that could allow quantitation of biomarker levels from the core biopsies of patient tumors.

ABSTRACT ID 33398

B-12

Influence of patient cohort size on PFS prediction accuracy using baseline SSTR image models

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BACKGROUND

The prediction of progression-free survival (PFS) after peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumor (NET) patients based on baseline somatostatin receptor (SSTR) imaging holds significant promise for personalized treatment strategies. However, small sample sizes remain common, raising concerns about overfitting and model reliability. This study evaluates the influence of patient cohort size on PFS prediction accuracy using baseline SSTR image models.

METHODS

Eighty-one NET patients underwent baseline PET/CT [⁶⁸Ga]Ga-DOTA-TATE imaging (median: 65 days, IQR:83) prior to initiating PRRT. Patients received between 1 and 4 cycles of [¹⁷⁷Lu]Lu-DOTA-TATE PRRT, and PFS was subsequently monitored. Patients were classified into poor and good responders (PFS=26 months threshold). A quantitative analysis of all lesions was performed on the baseline images, from which patient-level features were extracted. The top four features with the highest concordance index to PFS were selected for training a multivariate linear regression model. This process was repeated with progressively larger training cohorts. The PFS was predicted on a 16-patient hold-out test population and on the training population (using Leave-One-Out cross-validation). Model classification performance was assessed using the root mean squared error (RMSE) and the area under the receiver operating characteristic curve (AUC).

RESULTS

The RMSE on the training cohort decreased from 59(CI=0,120) with 5 patients to 23(CI=18, 28) with 10 patients. From 10 patients onwards, the RMSE decreased monotonically, reaching 16 (CI=15, 17) when 65 patients were used for model training. On the other hand, the AUC increased pronouncedly from 0.73 (CI=0.45,0.95) with 5 patients to 0.89 (CI=0.80, 0.95) with 10 patients. From 10 patients onwards, the AUC also decreased monotonically, reaching 0.70 (CI=0.67, 0.73) when 65 patients were used for model training. The RMSE and AUC confidence interval range decreased substantially as the training cohort increased from 5 to 65 patients: from 120 to 2 for RMSE and from 0.40 to 0.06 for AUC. The predictions on the 16 patients hold-out population were constant with an average RMSE of 20 (CI=21,17.5) and AUC of 0.62 (CI=0.55, 0.70).

CONCLUSIONS

Our findings highlight the overestimation of predictive power in small patient cohorts and emphasize the importance of using larger and hold-out patient populations to improve model generalizability.

Given the relatively rare incidence of NETs, aggregating patient populations from multiple centers is crucial for developing accurate models. Future work will focus on collaboratively expanding patient cohorts to understand the applicability of PFS prediction models for NET patients.

ABSTRACT ID 33461



B-13

Claudin 18.2 in pancreatic neuroendocrine tumors: a potential therapeutic target

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BACKGROUND

There remains an unmet need for treatment options for advanced pancreatic neuroendocrine tumors (PanNETs). Claudin 18.2 (CLDN18.2) is a tight junction molecule of gastric epithelium, which becomes exposed on tumor cell surface following malignant transformation, making it a viable target for cancer therapy. Clinical trials with Zolbetuximab and other novel CLDN18.2 targeting therapeutic agents in several cancers are currently ongoing. Given CLDN18.2 is ectopically expressed in pancreatic adenocarcinoma, we sought to examine CLDN 18.2 as a potential biomarker in PanNETs.

METHODS

Paraffin embedded tissue microarrays (TMAs) with PanNET specimens from 110 patients were immunostained with anti-CLDN18.2 mAb (Abcam, ab314690). CLDN18.2 expression was quantified in each core by measuring the average intensity value, classified as low (0-84/1+), medium (85-170/2+), or high (171-255/3+). For patients noted to have high CLDN18.2 expression, we examined tumor grade (G) and SSTR2 expression. We then screened available PanNET cell lines (BON, QGP, NT-3) for CLDN18.2 expression using Western blot assay and assessed binding of Zolbetuximab (anti-CLDN18.2 mAb) with flow cytometry. The difference in CLDN18.2 positivity between QGP and BON cells was determined by a two-tailed unpaired t-test, with $p < 0.05$ considered statistically significant.

RESULTS

Immunostaining of TMAs confirmed high membranous CLDN18.2 expression in 14% ($n = 15/108$) of PanNET specimens. Two CLDN 18.2 positive specimens were later noted to be G1 small bowel liver metastasis and G1 gastric primary. G1, G2 and G3 represented 67% ($n=10$), 27% ($n=4$) and 6% ($n=1$) of PanNET patients. SSTR immunostaining was available in 16 patients, and positive in all except one patient with G3 PanNET. All three of the screened PanNET cell lines exhibited CLDN18.2 levels detectable by Western blot with QGP cells displaying the greatest positivity. Flow cytometry further confirmed CLDN18.2 expression in BON and QGP cell lines. QGP cells exhibited 2-fold greater percentage of live CLDN18.2-positive cells than BON ($p = 0.0025$) with a 1.27 fold difference in median fluorescence intensity ($p < 0.0001$).

CONCLUSIONS

CLDN 18.2 is a promising biomarker in PanNETs. Further studies are needed to assess CLDN 18.2 expression in gastrointestinal NETs and explore possible CLDN 18.2-targeted therapies in NETs.

ABSTRACT ID 33488

NANETS 2025 Symposium Abstracts

B-14

Advanced 3D preclinical models of pancreatic neuroendocrine tumors: from bioprinting to precision-cut tumor slices

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BACKGROUND

Current pancreatic neuroendocrine tumors (PanNETs) in vitro models struggle to accurately replicate the tumor's biology and microenvironment, limiting insights into disease mechanisms and drug response. This project aims to develop: 1) 3D bioprinted PanNETs models that replicate tumor-stroma interactions and support studies on tumor biology and 2) precision-cut tumor slices for personalized drug testing.

METHODS

Bioprinted models were generated using PanNET cell lines and HUVECs (human umbilical vein endothelial cells), embedded in a hydrogel-based bioink. Both simple (mono-culture) and complex (co-culture) models were generated, and cultured under static or dynamic (100 μ L/min flow rate) conditions. Immunofluorescence was used to assess morphology, viability, and functional marker expression. PanNET slices (350 μ m in thickness) were obtained from surgical specimens (n=15) using a vibratome. Viability, tissue architecture, and drug responses to Everolimus and Sunitinib were assessed.

RESULTS

- 1) Both simple and complex bioprinted scaffolds remained viable for up to 21 days. PanNET cell lines and HUVEC retained physiological morphology and marker expression (PanNET: CgA, SYN; endothelial cells: CD31). Homo- and hetero-cellular crosstalk was observed, including aggregation of PanNET cells into islet-like structures, cobblestone-like morphology and network formation by endothelial cells, and direct interactions between the two cell types. Distinct in vitro behaviors were observed depending on the aggressiveness of the PanNET cell lines, mirroring their in vivo characteristics.
- 2) Around 40 PanNET slices per patient were generated. The slices remained viable for up to 10 days post-vibratome cutting, assessed through metabolic assay. Histologically, PanNET slices retained the tissue original architecture and the cellular complexity and heterogeneity of the tumour and

tumor microenvironment during the culture period. Specifically, tumor slices retained key cellular populations, including tumor cells, endothelial cells, fibroblasts, and immune cells. PanNETs slices displayed distinct responses to each drug tested.

CONCLUSIONS

3D bioprinting is a feasible and effective method for generating PanNETs models potentially replicating tumor and microenvironment, on which to perform functional studies. Patient-derived vibratome slices demonstrated to be a valid and promising approach for tailored drug testing.

ABSTRACT ID 33407

C-1

An ongoing phase 1 trial of obixtamig in patients with extrapulmonary neuroendocrine carcinomas with high or low DLL3 expression

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BACKGROUND

Delta-like ligand 3 (DLL3) is highly expressed in neuroendocrine carcinomas (NEC). Obixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager that targets DLL3-positive tumors. NCT04429087 is an ongoing, phase 1, dose-escalation trial of obixtamig in patients with DLL3-positive pulmonary and extrapulmonary NEC (epNEC) who failed to respond to standard treatment.

METHODS

Obixtamig was given intravenously in 4 dose-escalation regimens (R): RA (fixed dose every 3 weeks [q3w]); RB1 (fixed dose weekly [qw]); RB2 (step-up dose, then qw); and RB3 (step-up dose, then qw for 3 weeks, then q3w). Efficacy was assessed through objective response rate (ORR) and disease control rate (DCR) using RECIST v1.1. Results are reported for patients who received obixtamig RB2 or RB3, categorized as having high versus low DLL3, using a threshold of $\geq 50\%$ of tumor cells stained with an investigational antibody for DLL3 (SP347, Roche Diagnostics).

RESULTS

As of June 21, 2024, 60 patients with epNEC were included (gastroenteropancreatic: 45.0%, genitourinary: 30.0%, other/unknown primary site: 25.0%); 30 each DLL3-high and DLL3-low. Mean age: 63.9 years (DLL3-high), 59.1 (DLL3-low). Baseline characteristics were well-balanced across DLL3 groups. All patients had received prior systemic therapy; 30.0% of DLL3-high and 50.0% of DLL3-low patients had received >2 lines of prior treatment. Efficacy data are shown in the Table. After obixtamig treatment, patients with high DLL3 expression had greater ORR, DCR, and duration of response

(DoR) than DLL3-low patients. Responses were seen most frequently among patients with DLL3-high gastroenteropancreatic (50.0%) or genitourinary (60.0%) epNECs. Seven DLL3-high patients are still receiving treatment. Most treatment-related adverse events (TRAEs) were mild to moderate for both groups (**Table**).

	DLL3-high (n=30)	DLL3-low (n=30)
ORR, % (95% CI)	40.0 (24.6–57.7)	3.3 (0.6–16.7)
DCR, % (95% CI)	66.7 (48.8–80.8)	26.7 (14.2–44.4)
Median DoR (95% CI), months	7.9 (6.2–NC)	2.8 (NC–NC)
TRAEs, all grade/grade ≥3, (%)	100.0/23.3	90.0/20.0
Cytokine release syndrome, all grade/grade ≥3, (%)	70.0/3.3	60.0/3.3
Neurotoxicity, including immune effector cell-associated neurotoxicity syndrome*, all grade/grade ≥3, (%)	16.7/6.7	10.0/3.3

*Evaluated with a customized MedDRA query
 CI, confidence interval; NC, not calculable

CONCLUSIONS

Analyses showed greater obixtamig efficacy in patients with DLL3-high versus DLL3-low epNEC. The safety profile was manageable and comparable across both groups. The ORR of 40.0% and median DoR of 7.9 months in heavily pretreated epNEC tumors with high DLL3 expression are encouraging and support further development of obixtamig for this subgroup.

ABSTRACT ID 33400

C-2

Prognostic Significance of MEN1, ATRX, and DAXX Mutations in Pancreatic Neuroendocrine Tumors Treated with CAPTEM: Insights from a Multicenter Cohort

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BACKGROUND

Capecitabine and temozolomide (CAPTEM) show promising response rates of 30–70% in pancreatic neuroendocrine tumors (pNETs). With multiple treatment options available, selecting the optimal sequence is challenging. Prognostic and predictive biomarkers are needed to identify patients who will benefit most. Mutations in ATRX, DAXX, and MEN1 are key drivers of pNETs, but few studies have examined how these combined molecular profiles affect response to CAPTEM.

METHODS

We conducted a multicenter retrospective study across Johns Hopkins Hospital (JHH), Memorial Sloan Kettering Cancer Center (MSK), and Cedars-Sinai Medical Center (CSM) to evaluate the role of ATRX, DAXX, and MEN1 mutations. Patients with histologically confirmed pNET who received CAPTEM and had molecular NGS data available were included. Clinical data collected comprised age, sex, race, MSI status, stage, surgery, metastatic status, systemic treatments, and survival. Statistical analyses included two sample t-test and chi-squared tests to examine associations between patient characteristics and mutations, and Kaplan-Meier methods and Cox regression models to evaluate survival outcomes.

RESULTS

The cohort included 275 patients from CSM (24.0%), JHH (30.2%), and MSK (45.8%), with a mean age at the initiation of CAPTEM of 57.3 years (SD 13.5) and 61.1% male. Most were White (71.6%) and presented with metastatic disease at diagnosis (72.4%) and CAPTEM start (89.8%). Prior surgery was reported in 34.9%, and CAPTEM was first-line treatment for 43.3%. MSI-High was found in 6.9% and MMR-proficient in 74.5% of patients; TMB was low in 63.3%, intermediate in 10.5%, and high in 4.7%. Mutation prevalence was 37.8% for MEN1, 18.5% for DAXX, 13.1% for ATRX, and 30.2% for combined DAXX/ATRX. CAPTEM discontinuation was mainly due to progression (42.9%) or therapy completion (41.1%). MEN1 mutations were associated with longer time to treatment failure (TTF; 25 vs. 9.8 months; HR 0.55, P<0.001) and longer overall survival (OS) (median OS 84.4 vs. 51.6 months; P=0.002) and remained independently associated with longer OS in multivariable analysis (HR [95% CI]: 0.52 [0.34, 0.80], P=0.003). Those with DAXX and/or ATRX mutations also showed longer OS (median OS 83.5

vs. 62.0 months; P=0.057), reaching statistical significance in multivariable analysis (HR [95% CI]: 0.64 [0.42, 0.99], P=0.043).

CONCLUSIONS

This is the largest analysis of CAPTEM treatment and molecular profiling in pNET patients. MEN1 mutations are independently associated with significantly longer TTF and OS, while DAXX/ATRX mutations are independently associated with OS. These findings suggest that profiling ATRX, DAXX, and MEN1 may help guide treatment decisions and optimize therapeutic sequencing in pNET. Further prospective studies are needed to validate these biomarkers for clinical use.

ABSTRACT ID 33482

C-3

Investigator-Assessed Disease Progression in a Phase 2 Study of Paltusotine in Patients with Neuroendocrine Tumors and Carcinoid Syndrome

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BACKGROUND

Paltusotine is an oral, nonpeptide, selective SST2 receptor agonist. In a phase 2 study, treatment with once-daily paltusotine reduced the frequency and severity of carcinoid syndrome (CS) symptoms and was well tolerated. The anti-tumor effects of paltusotine were further explored.

METHODS

This study included an 8-week randomized treatment phase and a 102-week open-label extension phase (OLE; currently ongoing). Enrolled patients were adults with a stable documented grade 1 or 2 NET and CS. These patients were actively symptomatic and either untreated with somatostatin receptor ligand (SRL) therapy (average of ≥ 4 bowel movements [BMs] per day or >2 flushing episodes per day in ≥ 2 days over 2-week period) or washed out of SRL therapy (symptoms previously controlled on SRL), with demonstrated symptom worsening after washout. Patients had stable disease in the 6 months prior to study entry. Patients were randomized to once-daily paltusotine 40 mg or 80 mg; one optional uptitration of 40 mg (to 80 mg or 120 mg) was permitted. Patients who completed the randomized treatment phase were eligible to enter the OLE. Radiographic tumor assessments (CT or MRI) were conducted pretrial, at week 10, week 36, week 70, week 110, and at end of treatment. At each assessment, investigators reported (yes/no) whether imaging represented disease progression, and “investigator-assessed progression-free survival (PFS)” was based on the overall impression of imaging results. This preliminary analysis (data cutoff: May 21, 2025) assessed tumor progression per investigator’s assessment; the Kaplan-Meier method was used to calculate the PFS.

RESULTS

The patient in this case demonstrated a deep partial response with minimal side effects attributable to D/T. The patient experienced progression of disease after 17 months of treatment and proceeded to next-line therapy. The patient remains alive at the time of this report, over 21 months from the date of diagnosis. Available cohorts suggest a prevalence of BRAF V600E mutations in GEP-NENs to be between 5-15%. Other reported targetable alterations in GEP-NENs include *KRAS*, *ALK*, *BRCA1/2*, *ATM*, *NTRK*, *FGFR*, and *RET*.

CONCLUSIONS

The observed PFS rate (74%) after 1 year of treatment with paltusotine, in this preliminary analysis of a phase 2 study, is encouraging data and warrants further investigation in the ongoing CAREFNDR Phase 3 study.

ABSTRACT ID 33401

C-4

Multicenter Real-World Study of Treatment Patterns in Well-Differentiated Grade 3 (G3) Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

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BACKGROUND

The 2017 WHO classification established well-differentiated G3 NETs as a distinct pathologic entity. However, their rarity and heterogeneity have hindered the definition of standard treatment strategies. Hereby, we present a multicenter real-world experience from the Mayo Clinic to inform clinical practice.

METHODS

Clinical data were collected across the three Mayo Clinic sites (Minnesota, Arizona, and Florida) including patients (pts) with histologically confirmed GEP-NETs G3 between 2017 and 2025. Primary endpoints included ORR, DCR, PFS, and OS. Prognostic factors were analyzed with a multivariate Cox regression.

RESULTS

76 pts, median age 62 years (range, 23–83), with either ab initio (88%) or transformed (12%) G3 GEP-NETs. The most common primary sites were pancreas (60%), small bowel (17%) and rectum (5%). The median Ki-67 was 35% (range, 20–90). Most cases were non-functional (70%). Among functional tumors, carcinoid syndrome and hypoglycemia were the most common presentations (each 11.8%). Overall, median plasma 5-HIAA level was 35.5 ng/mL (range, 5–1394). 85% had de novo metastatic disease and 18% recurrent disease. Metastatic sites included liver (91%), lymph nodes (32%), bone (22%), lung and peritoneum (each 8%). The median number of metastatic sites was 1 (range, 0–5). The median number of systemic lines was 2 (range, 0–8). Across all lines, the most frequent treatments were CAPTEM (23%), PRRT with Lutetium-177 DOTATATE (14%), lanreotide (11%), octreotide (8%), carboplatin–etoposide (7%), sunitinib (5%), and everolimus (5%). Efficacy outcomes were reported in Table 1 for the three most common regimens based on radiology reports. At a median follow-up of 26.4 months, mOS of the overall population was 56.2 months (95% CI, 42.9–69.5). Insulin-producing tumors (HR 6.07, 95% CI 1.33–27.5; $p=0.02$) and ≥ 2 metastatic sites (HR 3.53, 95% CI 1.55–8.05; $p=0.003$) were independently associated with poor survival.

CONCLUSIONS

Overall survival for malignant insulinoma can be several years with appropriate therapy. Systemic treatment with PRRT, CAPTEM, or mTOR inhibitor is very effective for hypoglycemic control.

Table 1: Efficacy of the three most common regimens.

	CAPTEM	PRRT Lu-177	Lanreotide
Line of therapy, n (%)			
First	24 (61.5)	3 (12.5)	11 (57.9)
Second	7 (17.9)	9 (37.5)	8 (42.1)
Third or further	24 (61.5)	12 (50.1)	0 (0)
DCR	62.9	94.7	50
ORR	37.1	57.9	11.1
mPFS, months (95% CI)	6.7 (1.8-11.5)	11.2 (0-27.0)	3.4 (2.0-4.2)
mOS, months (95% CI)	50.6 (15.5-85.7)	76.1 (8.2-143.9)	NR

Pooled efficacy outcomes across treatment lines.

ABSTRACT ID 33418

C-5

PPM1D as a Potential Driver of Myeloid Malignancy Transformation in Neuroendocrine Tumor (NET) Pts: An Underrecognized Malignant CHIPPerpetrator?

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BACKGROUND

Building on our prior work showing high baseline CHIP prevalence and cytopenias in NET pts receiving PRRT, we used NANETS support to analyze a new cohort with matched pre- (pre-tx) and post-treatment (post-tx) peripheral blood (PB) samples (pre-post chemotherapy/ctx, PRRT, or both). This expanded dataset enabled a deeper investigation of CHIP-associated hematologic toxicity, mutation dynamics, and high-risk mutation acquisition to validate earlier results, identify putative targets and inform predictive models of tx-related toxicity.

METHODS

Following IRB approval at CCF and Roswell, PB from NET pts was analyzed for CHIP using a 63-gene myeloid NGS panel ($\geq 2\%$ VAF cutoff). Sequencing was performed via anchored multiplex PCR and Illumina technology ($>500\times$ coverage). Clinical associations were assessed using chi-square and Mann-Whitney U tests, with significance set at $p < 0.05$.

RESULTS

At baseline/pre-tx, 8 of 41 pts (19.5%) were CHIP+ and had significantly older age (72.8 vs. 58.7 yrs, $p = 0.002$), lower ALC (1.1 vs. 1.5, $p=0.044$) and lower Hb (12.4 vs. 13.7 g/dL, $p = 0.063$, trend), suggesting reduced immune and marrow reserves. No associations were seen with sex, race, ECOG, WBC, ANC, platelets, or prior radiation/ctx. Majority of CHIP+ pts (5/8; 62.5%) at baseline had no prior RT/ctx exposure. Post-tx (post ctx, PRRT), pts who were CHIP+ at baseline demonstrated significantly higher mutation burden on follow up sequencing (2.0 ± 1.3 vs. 0.6 ± 1.1 , $p = 0.005$), and greater clonal progression (88.9% vs. 10.0%, $p < 0.001$), compared to those who were CHIP-negative at baseline. Stable mutation profiles or clonal stability post-tx were more common in CHIP-neg pts (90.0% vs. 5.6%). Recurrent post-tx mutations included PPM1D, DNMT3A, TET2, and ASXL1, with PPM1D emerging in 31.7% (13 of 41) despite being present in only one patient at baseline. PPM1D mutations (PPM1Dm) were characterized by multiple clinically significant truncating variants that were strongly selected for following tx. CHIP+ status was associated with greater clonal expansion post-tx and worse survival. Detailed mutation dynamics post-specific treatments will be presented.

CONCLUSIONS

Contrary to prior assumptions, PPM1Dm emerged post-tx in 31% of patients regardless of baseline CHIP status highlighting its role in therapy-related CHIP independent of initial mutation status. These

findings underscore the need for serial sequencing and long-term follow-up to detect clonal evolution early and enable timely intervention. Given PPM1D's link to impaired DNA repair and poor outcomes in overt myeloid malignancy (Fandrei et al., Clin Cancer Res. 2025), we plan a larger longitudinal study to validate these findings in the precursor CHIP state, map co-mutations, and identify progression drivers to inform prevention strategies.

ABSTRACT ID 33455

C-6

TROP2 Expression in the Gastroenteropancreatic Neuroendocrine Tumors; An analysis of 179 patients

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BACKGROUND

Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane glycoprotein that exhibits overexpression in various gastrointestinal (GI) malignancies, including colorectal, gastric, pancreatic, and esophageal cancers. This overexpression has been correlated with increased tumor aggressiveness, enhanced proliferation, and unfavorable prognostic outcomes. TROP2 serves as a predictive and prognostic biomarker in several GI cancers, guiding targeted therapy and correlating with overall survival. However, there exists a notable absence of dedicated studies investigating TROP2 expression specifically in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) highlighting an unmet need. This report presents the first and most extensive prospective study examining TROP2 overexpression in GEP-NETs.

METHODS

Our single-center retrospective study evaluated adult patients with metastatic GI-NETs treated with alternating SSAs on first progression from January 2007 to December 2023. Clinical course and disease characteristics were assessed through chart review. After transitioning to the alternate SSA, disease progression was defined as radiographic evidence of progressive disease or serologic marker increase/clinical symptoms worsening, requiring a change in therapy.

RESULTS

Our analysis included a total of 179 GEP-NET samples, comprised of 106 small bowel neuroendocrine tumors (NETs) and 73 pancreatic neuroendocrine tumors (pNETs). There were 54 females and 52 males in the small bowel cohort, and 37 females and 36 males in the pancreatic cohort. Notably, TROP2 expression was observed in 50% of pancreatic samples and 30% of small bowel NET samples. Furthermore, TROP2 expression appeared to correlate with decreased survival in pNETs ($p=0.022$), whereas its expression in small bowel NETs may suggest improved patient outcomes, although this latter correlation did not achieve statistical significance ($p=0.37$). Further analyses are pending study completion and will be presented later.

CONCLUSIONS

This study highlights the critical role of TROP2 overexpression in GEP-NETs and its importance for patient prognosis. TROP2 overexpression correlates with decreased survival outcomes in pNETs relative to small bowel NETs. Additionally, the identification of TROP2 as a prognostic and predictive

biomarker presents opportunities for future research focused on therapeutic targeting. Additional studies may be needed for further validation as we finalize the current research.

ABSTRACT ID 33192

C-7

The Hidden Cost of Enzyme Therapy: Oxalate Nephropathy in a NET Patient with Pancreatic Insufficiency

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BACKGROUND

Pancreatic exocrine insufficiency (PEI) is an often overlooked cause of chronic diarrhea in patients with neuroendocrine tumors (NETs). When inadequately treated, PEI can lead to serious complications such as oxalate nephropathy (ON), which may result in kidney damage and impact the feasibility of oncologic therapies like peptide receptor radionuclide therapy (PRRT).

METHODS

We retrospectively reviewed the clinical course, imaging, laboratory values, and management strategy of a patient with metastatic NET who developed oxalate nephropathy in the setting of untreated PEI.

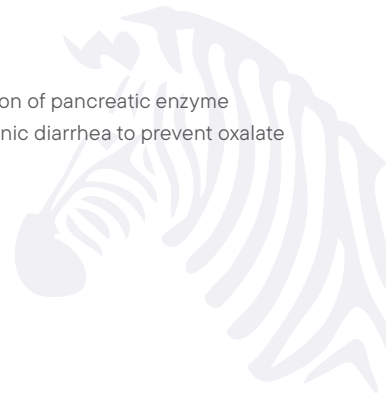
RESULTS

We present a 67-year-old male with a small bowel NET who developed persistent, uncontrolled diarrhea for several years. The diarrhea was attributed to multiple factors, including secretory NET (i.e. carcinoid syndrome), bile acid diarrhea, and PEI secondary to somatostatin analogue therapy. Due to financial constraints, the patient was unable to consistently take pancreatic enzyme replacement therapy (PERT). Years after the diagnosis of NET, the patient developed a new onset worsening of kidney function. Further work up including a kidney biopsy confirmed ON, which significantly limited subsequent treatment options, including PRRT.

CONCLUSIONS

Routine screening for pancreatic exocrine insufficiency and early initiation of pancreatic enzyme replacement therapy should be considered in all NET patients with chronic diarrhea to prevent oxalate nephropathy and preserve future treatment options.

ABSTRACT ID 33387



C-8

DAREON®-7: Phase I open-label dose-escalation/-expansion study of first-line obixtamig (BI 764532) plus chemotherapy in patients with DLL3-positive neuroendocrine carcinomas

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BACKGROUND

Delta-like ligand 3 (DLL3) is widely expressed in neuroendocrine carcinomas (NECs). Obixtamig is a DLL3/CD3 IgG-like T-cell engager that binds simultaneously to DLL3 on tumor cells and CD3 on T-cells. We report initial safety and efficacy data from the dose escalation part of the Phase I DAREON®-7 (NCT06132113) trial assessing obixtamig plus simultaneous chemotherapy (carboplatin plus etoposide) in patients with DLL3-positive NECs.

METHODS

Patients had locally advanced/metastatic DLL3-positive extrapulmonary NEC (epNEC), large cell NEC of the lung (LCNEC-L), or NEC of unknown primary site. Obixtamig was given as step-up dosing followed by target dose (3 dose levels), guided by a Bayesian Logistic Regression Model with overdose control. Carboplatin plus etoposide was given per label. Antitumor activity was assessed using RECIST v1.1 (investigator-assessed). The ongoing dose expansion part will assess obixtamig plus chemotherapy at the dose selected during dose escalation.

RESULTS

As of May 16, 2025, 27 patients were enrolled (epNEC: 78%, LCNEC-L: 7%, unknown primary site: 15%; median age: 67 years (range: 42–79); ECOG PS:0/1, 70%/30%). Overall, 26 patients received ≥ 1 dose of obixtamig plus carboplatin and etoposide; in these patients, median number of obixtamig cycles: 7 (range: 1–14); median treatment exposure: 4.4 months (range: 0.1–8.9). There were no dose-limiting toxicities; maximum tolerated dose was not reached. Most frequent adverse events (AEs) are shown in Table 1. No patients discontinued obixtamig due to AEs. One patient (4%) experienced a potential obixtamig-related neurotoxicity (grade [G]1 immune effector cell-associated neurotoxicity syndrome). One patient (4%) experienced G3 febrile neutropenia. Among 16 patients with cytokine release syndrome (CRS; 59%), most cases (n=13, 48%) were G1, with no cases $G \geq 3$. Confirmed objective response rate in evaluable patients (n=21): 76% (95% CI: 55–89; partial response 76%, stable disease 10%, progressive disease 10%); disease control rate: 86% (95% CI: 65–95). Confirmed median duration of response was not reached.

Most common AEs		
n (%)		
AEs (in n\geq10)	25 (93)	21 (78)
Neutropenia and/or neutrophil count decreased	17 (63)	16 (59)
CRS	16 (59)	0
Constipation	13 (48)	0
Anemia	12 (44)	9 (33)
Decreased appetite	10 (37)	1 (4)
Dysgeusia	10 (37)	0
Obixtamig-related AEs	23 (85)	1 (4)

CONCLUSIONS

Obixtamig plus chemotherapy was tolerable with no unexpected toxicities. The reported frequency/severity of AEs was consistent with the expected safety profile of the individual treatments, with no additional toxicities. Preliminary efficacy results were encouraging, warranting further development of the combination in this setting.

ABSTRACT ID 33390

C-9

Somatic genomic profiling of gastrointestinal neuroendocrine tumors: Implications for prognostication and therapeutic targeting

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BACKGROUND

The incidence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is rising, yet their biological heterogeneity and variable treatment response remain poorly understood. Comprehensive genomic characterization is needed to uncover somatic drivers and inform biomarker-driven therapeutic strategies.

METHODS

We performed next-generation sequencing (NGS) on tumor samples from 111 patients with confirmed GEP-NETs treated at Johns Hopkins Hospital between 2020 and 2022. Pathogenic and likely pathogenic mutations were identified using OncoKB, CHASmplus, and COSMIC databases. Mutational patterns were correlated with clinical characteristics and overall survival using univariate and multivariate analyses.

RESULTS

In this retrospective study of 111 patients with GEP-NETs, somatic pathogenic or likely pathogenic mutations were identified in 79% of cases. The most frequent alterations involved TP53 (19%), MEN1 (17%), and chromatin remodeling genes such as DAXX (9%) and ATRX (6%). Notably, 9% of patients harbored mutations typically associated with hematologic malignancies, a finding not widely reported in GEP-NETs. Distinct co-mutation patterns were observed between pNETs and non-pancreatic GI-NETs, including mutual exclusivity of MEN1 and TP53 mutations in pNETs. SHINYGO analysis revealed that GEP-NETs exhibit disrupted chromatin remodeling and DNA repair, with pancreatic primaries enriched for epigenetic modifiers and GI-NETs for Wnt signaling. Clinical correlation showed associations between poor tumor differentiation or high-grade disease and mutations in TP53 (P=0.02), KRAS (P=0.009), BRAF (P=0.01) and CDKN2A (P=0.03). Survival analysis demonstrated that mutations in KRAS (HR 7.45, P=0.009), the DAXX/ATRX group (HR 3.57, P=0.04) and hematologic malignancy-associated genes (HR 4.39, P=0.03) were independently associated with worse overall survival. These findings highlight distinct genomic and clinical correlates in GEP-NETs with implications for risk stratification and targeted therapy development.

CONCLUSIONS

This study reveals distinct somatic mutation patterns in GEP-NETs that are associated with tumor differentiation, grade, primary site, and survival. The identification of hematologic malignancy-associated mutations in a subset of GEP-NETs suggests possible shared molecular phenotypes with poor prognostic implications. These findings support incorporating genomic profiling into routine clinical evaluation to improve risk stratification and guide precision therapy in GEP-NETs.

ABSTRACT ID 33415



C-10

The Efficacy of Low-dose vs Standard-dose Everolimus in Patients with Advanced Neuroendocrine Tumors

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BACKGROUND

Everolimus is an oral mTOR inhibitor with significant anti-cancer activity in patients with gastroenteropancreatic and lung well-differentiated neuroendocrine neoplasms. Although 10 mg once daily has been approved by the FDA, in clinical practice this dose can lead to significant toxicity and requires dose modification in most patients. Previous data from phase 1 trial in solid tumors and multicenter real-world retrospective data in breast cancer and NETs evaluated everolimus at 5 and 10 mg daily and suggested comparable efficacy, but better safety of 5 mg. This study aimed to compare the efficacy and safety of 5 vs 10 mg everolimus in NET patients.

METHODS

This is a multicenter retrospective study aimed to compare the efficacy and safety of standard 10 mg (higher dose [HD]) vs 5 mg (lower dose [LD]) everolimus in patients with advanced NETs. A chart review of patients treated with everolimus at Mayo Clinic and University Hospitals Seidman Cancer Center from January 1st, 2015, to May 28th, 2025, was performed to obtain data points. Progression-free survival (PFS) and overall survival (OS) were measured from the start date of everolimus therapy. Analyses were performed on an intention-to-treat (ITT) basis. Treatment-related adverse events (TRAEs) were graded per CTCAE v4.03. Kaplan-Meier estimates and Cox regression were used to evaluate outcomes.

RESULTS

A total of 170 patients were eligible for the study including 49 (29%) treated with 5 mg daily and 121 (71%) treated with 10 mg daily. Median age at diagnosis was 59 years; 77 (45%) were male. There was no significant difference in OS between the 10 mg and 5 mg groups in multivariable analysis (HR = 0.70, 95% CI 0.39–1.26; p=0.24). Similarly, PFS did not significantly differ (HR = 0.78, 95% CI 0.50–1.22; p=0.27). In multivariable models, higher age at diagnosis (HR=1.05, p=0.0002), higher WHO grade (G3 vs G1: HR=3.15, p=0.0008), and more prior lines of therapy (HR=1.39, p=0.017) were significantly associated with worse outcomes. The 5 mg group experienced fewer TRAEs, including hyperglycemia (6% vs. 25%; p=0.005), hypercholesterolemia (2% vs. 15%; p=0.014), stomatitis (6% vs. 15%; p=0.19) and fatigue (47% vs. 54%; p=0.50). Grade 3–4 TRAEs occurred in 21 patients (17%) receiving 10 mg daily and in 7 patients (14%) receiving 5 mg daily.

CONCLUSIONS

These results suggest that LD everolimus may provide similar efficacy to the HD everolimus while reducing toxicity and having lower treatment cost. Prospective randomized trials are needed to confirm these findings.

ABSTRACT ID 33441



C-11

The useful combination of capecitabine and temozolomide (CAPTEM) in metastatic lung carcinoid tumors

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BACKGROUND

Capecitabine and temozolomide (CAPTEM) have been shown prospectively to have efficacy in pancreatic neuroendocrine tumors (NETs), however randomized controlled trials for CAPTEM in lung NETs have not been done¹⁻⁴. Despite this, there are guideline recommendations advocating for CAPTEM in lung NETs in certain circumstances. Additional data is needed to better understand responses, survival, and tolerability and to differentiate these findings between typical and atypical lung NETs.

METHODS

We identified adult patients with typical and atypical carcinoid (AC) tumors who have received CAPTEM under IRB approval at Vanderbilt-Ingram Cancer Center between 1/1/2019 and 3/15/2025. Variables including demographics, pathologic diagnosis, radiographic characteristics including somatostatin receptor positivity, treatment history, and outcomes including progression free survival (PFS), overall survival (OS) and disease control rate (DCR) were collected in Excel. Data analysis was conducted using R.

RESULTS

Twenty-seven patients were identified with a median age of 67 (55,72). The majority of patients were female (67%) and had AC tumors (81%). Treatment outcomes overall and by histology are listed in table 1.

Table 1			
	Overall (n=27)	Atypical (n=22)	Typical (n=5)
Median number of cycles ¹	12 (4, 19)	12 (4, 20)	12 (2, 18)
mPFS (months) ¹	13.8 (4.3, 26.5)	13.4 (4.2, 32.5)	12 (2, 18)
mOS (months) ¹	26.0 (12.3, 38.9)	26.6 (14.8, 48.0)	17.9 (10.8, 19.5)

Best Treatment Response			
CR ²	0 (0)	0 (0)	0 (0)
PR ²	2 (74)	1 (4.5)	1 (20)
SD ²	20 (74)	16 (73)	4 (80)
PD ²	4 (15)	4 (18)	0 (0)
Unknown ²	1 (3.7)	1 (4.5)	0 (0)
Disease control rate ²	22 (81)	17 (77)	
¹ Median (IQR) ² N, (%)			

In patients with somatostatin receptor positive avid disease on Octreoscan or ⁶⁸Gallium or ⁶⁴Copper DOTATATE-PET compared to those who had no avidity, there was a trend in improvement of PFS (16.7 months vs 7.8 months), however, OS (30.5 months vs 21.2 months) trended towards improvement in those with no avidity. DCR (100% vs 58%) was also improved in patients with avid disease (p=0.01). Drug related adverse effects resulting in hospitalization, dose reduction, and treatment discontinuation were 15%, 26%, and 19%, respectively.

CONCLUSIONS

CAPTEM results in a high disease control rate in both atypical and typical lung carcinoid tumors. Drug related adverse effects resulting in drug discontinuation were within the expected range and similar to rates in the ECOG-ACRIN E2211 trial. Ideally, randomized controlled trials studying CAPTEM in patients with lung NETs are needed to further elucidate safety and efficacy. Our study adds to the literature showing CAPTEM is a useful treatment in patients with metastatic lung NETs.

ABSTRACT ID 33476

C-12

Randomized Embolization Trial for NeuroEndocrine Tumors (RETNET)

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BACKGROUND

Transarterial bland and chemoembolization (TAE, TACE) have been employed for decades to treat liver-dominant neuroendocrine tumor (NET) metastases and are part of international guidelines without recommendation of a preferred technique. This international multicenter trial randomized patients to TAE, cTACE or DEB-TACE and evaluated efficacy, toxicities, and HRQoL.

METHODS

Patients with NET liver metastases of any histologic origin and grade that were progressive or symptomatic on somatostatin analog therapy or had >25% liver tumor burden were block randomized to bland embolization, lipiodol chemoembolization with a doxorubicin-based emulsion, or drug-eluting embolics with doxorubicin. Prior biliary intervention was an exclusion. Trial design was pragmatic with treatment according to each institutions' standard of care. Clinical, laboratory and imaging assessment was performed one month after completing liver-directed therapy, then every 3 months for 2 years. Toxicity was assessed by CTCAE and complications scored according to the SIR Classification. Blinded DSMB review was done at 10 and 30 patients per arm, then annually, with a 20% SAE rate as the stopping rule. Primary outcome was hepatic progression free survival (HPFS) by BICR. The study was powered for a hypothesized hazard ratio of 1.9 to detect a clinically meaningful difference.

RESULTS

The DEB-TACE arm was closed at the first safety review with an SAE rate of 40%. Between 2017-2022, 151 patients were randomized to TAE (n= 78) or cTACE (n=73) at 13 centers in North and South America and Europe. Primary sites of disease were midgut 54%, pancreas 36%, lung 4%, other/unknown 6%. Tumor grades 1/2/3/unknown were 36%, 56%, 3%, and 4%. 28% had prior liver resection or ablation. 76% had been on a somatostatin analog for an average of 3 years. Indications for embolization included tumor progression in 74%, high baseline tumor burden in 50%, symptom control in 44%, and downstaging in 6%. Baseline demographic and clinical parameters did not significantly differ between arms. SIR Class D-E complications occurred in 34 (44%) in the TAE arm and 21 (29%) in the cTACE arm. CTCAE G3-4 toxicities occurred in 42 (54%) in the TAE arm and 26 (36%) in the TACE arm. There was no statistically significant difference in HPFS by BICR for TAE vs cTACE, HR 1.40 [95% CI 0.80-2.46], p = 0.234 or in overall PFS, HR 1.43 [95% CI 0.90-2.26], p = 0.133.

CONCLUSIONS

DEB TACE has unacceptable toxicity in NETs. There is no significant difference in HPFS or PFS between TAE and cTACE. Serious toxicities and adverse events requiring elevated level of care occur more frequently with TAE.

ABSTRACT ID 33254

C-13

Safety and clinical implications of concurrent biopsy of neuroendocrine liver metastases at the time of liver-directed therapy

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BACKGROUND

Neuroendocrine tumor liver metastases (NETLMs) significantly affect patient prognosis. Tumor grade informs treatment and may evolve over time, suggesting a role for serial biopsy. As part of an ongoing prospective clinical research study, we obtained research and clinical biopsy samples of NETLMs at the time of liver-directed therapy (LDT). This study evaluates the safety of concurrent biopsy, determines the frequency of grade change compared to prior tissue samples, and assesses whether such results altered patient management.

METHODS

Patients with clinically diagnosed NETLMs were enrolled in a prospective cohort study for genetic, proteomic and metabolic characterisation of NETLMs at a single academic center from 2016–2024 (IRB#825782). 18G core biopsies were obtained using coaxial technique at the time of LDT. Primary outcomes included adverse event (AE) rates, using Society of Interventional Radiology guideline definitions. AEs requiring additional intervention and/or hospitalization were grouped as “major” and those requiring no therapy/receiving nominal therapy grouped as “minor”. Secondary outcomes included tumor grade change between biopsy samples and prior tissue samples and alterations in clinical management based on these results. Potential associations between clinical characteristics (biopsy location, number of cores, etc) and AEs were assessed by univariate analyses. Significance was set at $p < 0.05$.

RESULTS

Eighty-seven biopsies were performed in 77 patients were included in the primary analysis. The diagnostic biopsy rate was 92% (80/87). A mean of 8 core biopsies (SD 1.76) were taken from the same lesion per procedure. The median interval between baseline and research biopsy was 1.7 (IQR 0.7–3.6) years. Biopsy-related AEs occurred in 8% of cases (7/87); Major AEs occurred in 2% (2/87)

and included: 1) an arterioportal/arteriobiliary fistula resulting in hemobilia and a main portal vein thrombosis (PVT), and 2) perihepatic bleeding requiring an additional embolization procedure. Both patients fully recovered. Minor AEs included asymptomatic arterioportal (n=1) and arteriovenous (n=1) fistulas, subcapsular/perihepatic hematoma (n=2), and segmental PVT (n=1). No significant associations between AEs and clinical characteristics were identified. Among 63 patients eligible for grade change analysis, 27 (43%) exhibited a change in tumor grade: 8 (13%) decreased and 18 (30%) increased. Seven of 18 patients (39%) with increased grade consequently underwent changes in clinical management.

CONCLUSIONS

Concurrent biopsy of NETLMs at the time of LDT has an acceptable AE rate and yielded clinically actionable information regarding grade change in a significant proportion of patients. These findings suggest concurrent biopsy at the time of LDT should be considered in those lacking recent tissue sampling.

ABSTRACT ID 33410

C-14

Efficacy of ¹⁷⁷Lu-edotreotide vs everolimus in patients with grade 1 or grade 2 GEP-NETs: Phase 3 COMPETE trial (post hoc subgroup analyses)

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BACKGROUND

¹⁷⁷Lu-edotreotide is an innovative radiopharmaceutical therapy agent, assessed in COMPETE, a Phase III, multicenter, randomized, controlled and open-label trial comparing ¹⁷⁷Lu-edotreotide with a targeted molecular therapy (everolimus) in patients with WHO grade 1 or grade 2 gastroenteropancreatic-neuroendocrine tumors (GEP-NETs). Here, we focus on post hoc efficacy analyses of ¹⁷⁷Lu-edotreotide in clinically important subgroups.

METHODS

Eligible patients (aged ≥18 years) with inoperable, progressive, somatostatin receptor positive GEP-NETs (Ki-67 ≤20%) were randomized (2:1) to receive ¹⁷⁷Lu-edotreotide (4 cycles of 7.5 GBq/cycle every 12 weeks, or until disease progression) or everolimus (10 mg daily up to 30 months, or until disease progression). The primary endpoint was progression free survival (PFS) per RECIST v1.1 assessed by Blinded Independent Central Review (BICR). Key secondary endpoints were objective response rate (ORR) and overall survival (OS).

RESULTS

309 patients were randomized to ¹⁷⁷Lu-edotreotide (n=207) or everolimus (n=102). Median PFS was significantly prolonged by ¹⁷⁷Lu-edotreotide vs. everolimus (23.9 months vs. 14.1 months; p=0.0223; HR=0.673, 95% CI [0.477, 0.948]). Centrally assessed ORR was significantly higher with ¹⁷⁷Lu-edotreotide vs. everolimus (21.9% vs. 4.2%; p<0.0001). Preliminary median OS was numerically prolonged for ¹⁷⁷Lu-edotreotide vs. everolimus (63.4 months vs. 58.7 months; p=0.3230; HR=0.826,

95% CI [0.565, 1.208]). The subgroup analyses showed consistent improvements in PFS, ORR, and OS across subgroups, except for OS (immature data) reported in the treatment-naïve subgroup (Table).

Table: Subgroup analyses based on central (BICR) assessment

Subgroups	Median PFS	ORR	Median OS
	¹⁷⁷ Lu-edotreotide vs. everolimus (months)	¹⁷⁷ Lu-edotreotide vs. everolimus (%)	¹⁷⁷ Lu-edotreotide vs. everolimus (months)
Grade 1	24.5 (n=104) vs. 17.4 (n=63)	15.8 (n=101) vs. 3.3 (n=61)	NR (n=104) vs. NR (n=63)
Grade 2	21.6 (n=102) vs. 10.6 (n=37)	28.3 (n=99) vs. 3.1 (n=32)	56.7 (n=102) vs. 41.4 (n=37)
GE-NET	23.9 (n=88) vs. 12.0 (n=43)	6.0 (n=84) vs. 5.0 (n=40)	63.4 (n=88) vs. 58.7 (n=43)
P-NET	24.5 (n=119) vs. 14.7 (n=59)	33.3 (n=117) vs. 3.6 (n=55)	65.7 (n=119) vs. 49.3 (n=59)
Treatment-naïve (1st line)	NR (n=30) vs. 18.1 (n=17)	17.9 (n=28) vs. 5.9 (n=17)	57.4 (n=30) vs. NR (n=17)
Prior therapy (2nd line)	23.9 (n=177) vs. 14.1 (n=85)	22.5 (n=173) vs. 3.8 (n=78)	63.4 (n=177) vs. 43.3 (n=85)

n=total number of patients; NR=not reached

CONCLUSIONS

¹⁷⁷Lu-edotreotide demonstrated statistically significant improvements in PFS and ORR vs. everolimus. Despite the immature data, potential OS benefit was observed with ¹⁷⁷Lu-edotreotide vs. everolimus. The efficacy of ¹⁷⁷Lu-edotreotide was largely maintained across the subgroups (origin, grade, and prior treatment). These findings confirm the meaningful clinical benefit of ¹⁷⁷Lu-edotreotide vs. everolimus in GEP-NETs patients with high unmet needs.

ABSTRACT ID 33388



C-15

Long-term Follow-up of PRRT-Naïve Patients with GEP-NETs Treated with Targeted Alpha Therapy ^{212}Pb -DOTAMTATE in the Phase 2 ALPHAMEDIX 02 Trial

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BACKGROUND

Alpha-emitting radioisotopes efficiently induce double-stranded DNA breaks in tumors while aiming to spare healthy tissue, given their high linear energy transfer over short ranges. ^{212}Pb -DOTAMTATE (SAR447873) is a novel somatostatin receptor (SSTR)-targeted alpha therapy under clinical evaluation for patients with unresectable or metastatic SSTR+ gastroenteropancreatic neuroendocrine tumors (GEP-NETs) (ALPHAMEDIX 02 [NCT05153772]). Here we present a two-year landmark analysis of the efficacy and safety of ^{212}Pb -DOTAMTATE in patients with no prior exposure to peptide receptor radionuclide therapy (PRRT).

METHODS

ALPHAMEDIX 02 is a Phase 2, open-label, multicenter study evaluating the efficacy, safety, and tolerability of ^{212}Pb -DOTAMTATE in PRRT-naïve (cohort 1, N=35) and PRRT-exposed (cohort 2, N = 26) patients with histologically confirmed unresectable or metastatic GEP-NETs, positive somatostatin analogue imaging and at least 1 site of measurable disease. ^{212}Pb -DOTAMTATE was administered at 67.6 $\mu\text{Ci}/\text{kg}$ every 8 weeks for up to 4 cycles. Primary endpoints include ORR per RECIST1.1, and incidence and severity of adverse events (AEs). Secondary endpoints include progression free survival (PFS) and overall survival (OS).

RESULTS

As of 14 April, among 35 PRRT-naïve patients, the most common primary tumor sites were pancreas and small intestine (both n=15, 42.9%). The majority (n=31, 88.6%) had Grade 1/2 tumors. Twenty patients achieved a confirmed partial response (ORR 57.1%; 95% CI: 39.4–73.7); 13 (37.1%), stable disease; and 1 (2.9%), progressive disease (1 patient not evaluable). Fourteen of 20 patients with a confirmed response had a duration of response (DOR) ≥ 12 months; 2 patients had a DOR ≥ 24 months. Two-year PFS and OS rates were 71.3% and 88.2%, respectively. All patients experienced ≥ 1 treatment-emergent adverse event (TEAE). The most common Grade 3 or 4 TEAE was decreased lymphocyte count (25.7%).

CONCLUSIONS

With 2 years median follow-up, ^{212}Pb -DOTAMTATE (SAR447873) treatment continues to be associated with frequent, durable responses and survival in patients with advanced SSTR+ GEP-NETs. No new safety signals emerged with longer follow-up.

ABSTRACT ID 33414



C-16

Phase 2 Study of Targeted Alpha Therapy ^{212}Pb -DOTAMTATE in Patients with Advanced Gastroenteropancreatic (GEP)-NETs Previously Treated with PRRT

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BACKGROUND

Effective treatment options are limited for patients with unresectable or metastatic Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) whose disease progresses after peptide receptor radionuclide therapy (PRRT) with beta-emitting ^{177}Lu -labelled somatostatin analogs (SSA). ^{212}Pb -DOTAMTATE (SAR447873) is a novel SSTR-targeted alpha therapy under clinical evaluation for patients with SSTR+ NETs in a Phase 2 two-cohort trial (ALPHAMEDIX 02 [NCT05153772]). In PRRT-naïve patients (cohort 1), treatment was associated with a 54.3% overall response rate (ORR) and a manageable safety profile. Here we report the first efficacy and safety results in patients previously treated with PRRT (cohort 2).

METHODS

This is a Phase 2, open-label, multicenter study evaluating the clinical activity of ^{212}Pb -DOTAMTATE in PRRT-naïve and PRRT-exposed patients with histologically confirmed unresectable or metastatic GEP-NETs, positive SSA imaging and at least 1 site of measurable disease. PRRT-exposed patients had progressive disease after receiving ≤ 4 doses of ^{177}Lu -SSA and received their last dose ≥ 6 months prior to Day 1. ^{212}Pb -DOTAMTATE was administered at 67.6 $\mu\text{Ci}/\text{kg}$ every 8 weeks for up to 4 cycles. Primary endpoints include ORR per RECIST1.1, and safety. Secondary endpoints include progression free survival and overall survival.

RESULTS

Among 26 PRRT-exposed patients, the most common primary tumor sites were pancreas and small intestine (both $n=11$, 42.3%). The majority ($n=20$; 76.9%) had Grade 1/2 tumors. Eight patients (30.8%) achieved a confirmed partial response (PR); 17 (65.4%), stable disease (with 1 unconfirmed PR pending confirmation); and 1 (3.8%), progressive disease (96.2% disease control rate). Seven of 8 patients with a confirmed PR maintained their response at the time of data cutoff. All patients experienced at least one treatment-emergent adverse event (TEAE), with 9 (34.6%) having at least one Grade ≥ 3 TEAE. The most common Grade 3 or 4 TEAE was lymphocyte count decrease (15.4%).

CONCLUSIONS

In patients with unresectable or metastatic SSTR+ GEP-NETs previously treated with PRRT,²¹²Pb-DOTAMTATE (SAR447873) was associated with a clinically meaningful overall response rate of 30.8%. TEAEs were generally Grade 1 or 2 and manageable.

ABSTRACT ID 33429

C-17

61Cu-NODAGA-LM3 versus 68Ga-DOTATOC in the same patients with neuroendocrine tumors: Preliminary results of the Phase I/II COPPER-PET-in-NET Trial

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BACKGROUND

(Pre)clinical data suggest that somatostatin receptor (sstr) antagonists, when radiolabeled with gallium-68, offer superior imaging performance over agonists in patients with neuroendocrine tumors (NETs). ⁶¹Cu-NODAGA-LM3 is a novel PET tracer targeting sstr2 that may overcome key limitations of [⁶⁸Ga]-based tracers, including production capacity, image resolution, and logistics. Cyclotron-produced ⁶¹Cu and has a longer half-life compared to ⁶⁸Ga or ¹⁸F, supporting delayed imaging and easier logistics. Additionally, ⁶¹Cu has a higher positron fraction than ⁶⁴Cu, enhancing image quality per administered activity. We report first-in-human data on ⁶¹Cu-NODAGA-LM3 covering safety, biodistribution, dosimetry, pharmacokinetics, image quality, and lesion detection.

METHODS

In this ongoing, randomized, crossover, controlled, reader-blind, phase I/II PET/CT trial (NCT06455358), 23 patients with sstr2-positive, well-differentiated gastroenteropancreatic or bronchopulmonary NETs receive both ⁶¹Cu-NODAGA-LM3 (1h and 3h post-injection) and ⁶⁸Ga-DOTA-TOC PET/CT (1h post-injection) on the same scanner. Imaging is conducted within 28 days and, if applicable, 14±2 days post last somatostatin analogue injection. Co-primary endpoints are safety and sensitivity of ⁶¹Cu-NODAGA-LM3 with noninferiority of sensitivity against ⁶⁸Ga-DOTA-TOC using mixed-effects logistic regression. Biopsy and/or composite imaging during 2–7 months of follow-up serve as gold standard. Adverse events are monitored up to one day post-injection (p.i) (CTCAE v5.0). Secondary endpoints include biodistribution, pharmacokinetics, dosimetry, and lesion detection. Six patients undergo additional imaging at 18h p.i. for dosimetry, and 1h vs. 3h p.i. images are compared to define optimal imaging time.

RESULTS

To date, 20 patients completed imaging; 6 had full dosimetry. No clinically significant adverse events occurred. ⁶¹Cu-NODAGA-LM3 showed rapid biexponential blood clearance (median 234 mL/min [IQR: 139–365]; R²>0.99) and a short distribution phase (median α half-life: 34 min [IQR: 25–37]). Biodistribution was favorable, with similar bone marrow uptake at 1h p.i. (SUVmax Th6: 1.0 [IQR: 0.9–1.3] vs. 1.1 [IQR: 1.0–1.4] for ⁶¹Cu-NODAGA-LM3 vs. ⁶⁸Ga-DOTA-TOC), but significantly lower liver (3.1 vs.

6.4) and spleen (9.0 vs. 24.0) uptake ($p < 0.001$ and 0.002). Median tumor SUVmax at 1h p.i. for the three hottest matched lesions was 12% higher with ^{61}Cu -NODAGA-LM3 (19.6 vs. 16.9), enhancing lesion detection and tumor-to-background contrast. Median effective dose was 5.0 mSv [4.2–5.7]. In blinded review, image quality was rated superior with ^{61}Cu -NODAGA-LM3 in 16 of 20 cases and equivalent in the remaining 4.

CONCLUSIONS

These preliminary data support ^{61}Cu -NODAGA-LM3 as a safe, effective sstr2-targeting tracer with favorable pharmacokinetics, biodistribution, dosimetry, with logistical and diagnostic advantages over ^{68}Ga -labeled somatostatin receptor agonist-based imaging in patients with NETs.

ABSTRACT ID 33431

C-18

Patient Characteristics and Treatment Patterns With [177Lu]Lu-DOTA-TATE (177Lu-DOTATATE) In the US: A Real-World Assessment

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BACKGROUND

¹⁷⁷Lu-DOTATATE is a radiolabeled somatostatin analog (SSA) approved for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) by the US Food and Drug Administration in January 2018 and has recently been indicated as first-line treatment. ¹⁷⁷Lu-DOTATATE is administered every 8 weeks for a total of 4 cycles. Phase III trials have demonstrated that ¹⁷⁷Lu-DOTATATE significantly improves clinical outcomes versus standard of care in patients with GEP-NETs. The aim of this study is to describe real-world ¹⁷⁷Lu-DOTATATE treatment patterns in the US.

METHODS

This was a real-world study of patients treated with ¹⁷⁷Lu-DOTATATE using data from the open-source IQVIA Longitudinal Prescription and Patient Centric Medical Claims databases between 1 July 2017–28 February 2025. Demographics and clinical characteristics were assessed 6 months prior to index date (¹⁷⁷Lu-DOTATATE initiation). Treatment patterns, including number of ¹⁷⁷Lu-DOTATATE cycles, treatment discontinuation, treatment switch/addition, treatment extension (>4 cycles), and ¹⁷⁷Lu-DOTATATE retreatment (following progression) were assessed from index date until the end of follow-up. Results were evaluated descriptively.

RESULTS

In total, 3,410 patients treated with ¹⁷⁷Lu-DOTATATE, with a mean (standard deviation) age of 64.9 (12.3) years, were included. Common comorbidities included hypertension (38.4%), liver, gallbladder and pancreatic diseases (29.0%), and diabetes (24.4%). Patients at ¹⁷⁷Lu-DOTATATE initiation had liver (67.0%), gastrointestinal (16.5%), lymph node (19.7%), lung (4.6%) and brain (1.1%) metastases. Prior systemic treatments were received by 67.6% of patients (SSAs [62.1%], chemotherapy [7.5%], targeted therapy [6.2%], immunotherapy [0.2%]). Patients received a median (range) of 4 (1–8) ¹⁷⁷Lu-DOTATATE cycles with median (range) time between cycles being 8.1 (0.1–221.3) weeks. Among patients with <4 cycles, 29.3% discontinued treatment within a median (range) of 16.0 (8.0–41.0) weeks. Patients who switched treatment (n=200; 5.9%) mostly switched to chemotherapy (54.0%) or targeted therapy (34.5%). Furthermore, 89 (2.6%) patients extended ¹⁷⁷Lu-DOTATATE treatment (>4 cycles), with a median (range) of 2 (1–4) additional cycles, while 241 (7.1%) patients received ¹⁷⁷Lu-DOTATATE retreatment after progression, with a median (range) of 3 (1–7) cycles following the progression event.

CONCLUSIONS

These data show that real-world use of ^{177}Lu -DOTATATE has high patient adherence, with most patients receiving 4 cycles of treatment at 8-week intervals, consistent with the label indication. Patients are receiving retreatment with ^{177}Lu -DOTATATE in clinical practice, and some patients are receiving >4 cycles. Additional research is necessary to assess the outcomes of these patients in the real world.

ABSTRACT ID 33412



C-19

[²¹²Pb]VMT-alpha-NET for advanced SSTR+ NETs: safety and preliminary efficacy results from cohorts 1 and 2 of the dose escalation phase

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BACKGROUND

Somatostatin receptor subtype 2 (SSTR2) is expressed in neuroendocrine tumors (NETs), and it is an important target for both diagnosis and therapy. [²¹²Pb]VMT-alpha-NET is an alpha therapy agent targeting SSTR2-expressing NETs. Here, we report the results of a prospective, open-label, Phase I/IIa clinical trial evaluating the safety, tolerability, pharmacokinetics, and preliminary efficacy of [²¹²Pb]VMT-alpha-NET [NCT05636618].

METHODS

Adults with well-differentiated unresectable or metastatic SSTR2-expressing NETs, who are peptide receptor radionuclide therapy (PRRT) naïve, and who progressed on at least one prior line of systemic therapy, are eligible. The study design follows a Bayesian dose-finding algorithm. Participants receive up to four doses of [²¹²Pb]VMT-alpha-NET on 8-weeks intervals at the assigned dose level. Efficacy is assessed by investigators according to RECIST criteria v1.1.

RESULTS

As of 30-Apr-2025, nine participants were enrolled for dose-limiting toxicity (DLT) observation into cohort 1 (n=2) and cohort 2 (n=7) at dose levels of 92.5 MBq [2.5 mCi] and 185 MBq [5 mCi], respectively. Thirty-three (33) additional patients were enrolled into cohort 2 to further evaluate safety and efficacy at the selected dose. Safety was assessed for all participants treated (n=42), while efficacy was evaluated for the nine participants enrolled for DLT-observation. Among all participants treated with [²¹²Pb]VMT-alpha-NET (n=42), no DLTs, no grade 4 or 5 adverse events (AEs), no treatment-related discontinuations, no serious renal complications or myelosuppression, and no dysphagia were observed. Four out of seven participants (57%) enrolled for DLT-observation in cohort 2 achieved an objective response with a median follow-up time of 52 weeks (range: 6,64). Three objective responses were confirmed, while one was pending confirmation at the time of data cut-off (DCO). Overall, seven of the nine participants (78%) enrolled for DLT-observation both in cohort 1 and 2 were without progression as of the DCO, with a median follow up time of 56 weeks (range: 6,77). Cohort 3, at a dose level of 222 MBq [6 mCi], has recently been opened for enrollment. Safety data for all treated participants and efficacy results for a mature subset will be presented at the congress.

CONCLUSIONS

[²¹²Pb]VMT-alpha-NET is a well-tolerated therapy for patients with advanced NETs, and it has shown promising clinical benefit at the dose level of 185 MBq [5 mCi]. The study is ongoing and open for enrollment in cohort 3.

ABSTRACT ID 33440



C-20

Multi-center NCI-sponsored phase 1 study of triapine in combination with 177Lu-dotatate in patients with progressive well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

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BACKGROUND

177Lu-Dotatate is an FDA-approved somatostatin receptor-targeted radiopharmaceutical shown to improve progression-free survival (PFS) in patients with progressive well-differentiated neuroendocrine tumors (NETs). Benchmark NETTER-1 trial established a median PFS of 28.4 months and an objective response rate (ORR) of 14% for Lu-177 dotatate. Triapine, an oral ribonucleotide reductase inhibitor, is a potent radiation sensitizer. This phase 1 study evaluated the safety and efficacy of combining triapine with 177Lu-Dotatate in patients with progressive NETs.

METHODS

ETCTN 10388 is a multi-center, investigator-initiated, NCI-sponsored phase 1 trial conducted at six academic institutions in the United States. Eligible patients had metastatic, progressive, well-differentiated GEP-NETs and had progressed on at least one prior line of therapy. The study included a dose-escalation phase (Part A, n=15) utilizing a Bayesian Optimal Interval (BOIN) design, followed by a dose-expansion phase (Part B, n=16). All patients received 177Lu-Dotatate 200 mCi on Day 1 of each 8-week cycle, along with oral triapine (50–200 mg) on Days 1–14, for a total of four cycles.

RESULTS

Thirty-one patients received study treatment. The most common treatment-related adverse events were anemia (94%), lymphopenia (88%), and thrombocytopenia (81%), which were largely transient and resolved within two weeks without impacting treatment continuity. Dose-limiting toxicities (DLTs) were observed in nine patients across dose levels. Based on integrated safety and pharmacokinetic data, the recommended phase 2 dose (RP2D) of triapine was established at 150 mg. Among 28 patients evaluable for efficacy, the confirmed ORR was 21.4%, and the median PFS was 38.03 months. In the RP2D cohort, median PFS has not yet been reached and may exceed 40 months.

CONCLUSIONS

Triapine in combination with 177Lu-Dotatate was well tolerated and demonstrated encouraging signs of clinical activity in patients with progressive well-differentiated GEP-NETs. The 177Lu-Dotatate (200

mCi) plus triapine (150 mg) regimen has been selected for further evaluation. A randomized phase 2 trial (ETCTN 10558) comparing the combination to standard ^{177}Lu -Dotatate monotherapy is currently enrolling at 14 sites across the United States.

ABSTRACT ID 33403



C-21

Single institution experience with [¹³¹I]MIBG for pheochromocytoma and paraganglioma: Long-term outcomes and dosimetry

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BACKGROUND

I-131 high-specific activity MIBG ([¹³¹I]MIBG) is the only FDA-approved radiopharmaceutical for metastatic pheochromocytoma/paraganglioma (PHEO/PGL). We present our institution's long-term efficacy, safety, and dosimetry data.

METHODS

A retrospective review of patients with metastatic PHEO/PGL who received [¹³¹I]MIBG was performed. Radiographic response was assessed using RECIST 1.1 criteria, and toxicities were graded using CTCAE v5.0. Demographics, clinical presentation, lab values, and outcomes were assessed. Dosimetry was used to estimate absorbed dose to the kidneys, liver, and lungs, and reduce activity when necessary. Median progression-free survival (PFS) was estimated using the Kaplan-Meier method.

RESULTS

Between 2020–2024, seven patients with metastatic PHEO (n=4) or PGL (n=3) were treated with [¹³¹I]MIBG. Median age was 63.7 years (range: 31–69); and mean follow-up was 27.7 months (range: 5.6 – 60.3). Three patients had SDHB mutations, one had a RET mutation. Five received 2 cycles and two received 1 cycle. Best responses included complete response (n=1), partial response (n=2), stable disease (n=2), and progressive disease (n=2), yielding an objective response rate of 42.9% and disease control rate of 71.4%. Only PHEO patients had objective responses. At last follow-up, 2/7 patients had died. Overall median PFS was 35.3 months. The median PFS and OS for patients with PGL were 2.5 months and 9.6 months, respectively. 2/3 (67%) patients with PGL experienced progression and death within 1 year, compared to 0/4 (0%) with progression or death in the PHEO group. Only 1/4 (25%) with PHEO progressed during the study period. Average organ dose per 1000 mCi was 23.2 Gy (range: 15.5–42.9) to kidneys, 21.8 (8.8–51.4) to liver, and 21.8 (14.6–57.7) to lungs. Post-progression therapies included [¹⁷⁷Lu]Lu-DOTATATE (n=2), chemotherapy (n=1), and external beam radiation (n=1). Transient G3/G4 anemia occurred in 2/7 (29%), leukopenia in 2/7 (29%), and G4 thrombocytopenia in 1/7 (14%). None developed G3/G4 nephrotoxicity.

Table 1: Patient Outcomes

Patient	Tumor	Best Response	PFS (months)
P1	PHEO	PR	19.1*
P2	PGL	PD	0.90
P3	PGL	SD	52.1
P4	PGL	PD	2.5
P5	PHEO	CR	35.3
P6	PHEO	SD	21.7*
P7	PHEO	PR	15.7*

* PFS Censored: No progression at last imaging.

CONCLUSIONS

[¹³¹I]MIBG therapy resulted in prolonged disease control in metastatic PHEO/PGL with limited toxicity. Median PFS exceeded 35 months, with better outcomes in PHEO versus PGL. The most common toxicity was marrow suppression. These real-world findings support [¹³¹I]MIBG as an important option in select patients.

ABSTRACT ID 33501



C-22

Systematic Literature Review and Radiomics Quality Assessment for Lung, Adrenal, Thyroid and Pituitary Neuroendocrine Tumors

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BACKGROUND

Radiomic analysis has been an emerging diagnostic tool in tumor classification and treatment prediction with a growing volume of radiomics research studying neuroendocrine tumors (NETs). Current reviews have highlighted numerous issues in radiomics research leading to the development of the radiomics quality scoring (RQS) system. Literature summarizing radiomics work in the NET space has concentrated on gastroenteropancreatic NETs. This work will provide a review of the topic of radiomics, summarize the radiomics research studying non GEP-NET subtypes, and provide an analysis of radiomics workflows using RQS metrics.

METHODS

This IRB-approved multicenter NET registry uses REDCap (Research Electronic Data Capture) to collect over 200 variables for patients treated at Memorial Sloan Kettering Cancer Center (MSK) or the University of California, San Francisco (UCSF). Patients with a diagnosis of advanced NET and previous or current treatment with ¹⁷⁷Lu-DOTATATE are eligible. Registry sections include: demographics and baseline clinicopathologic data, prior treatment history, radiologic results, and collection of data related to ¹⁷⁷Lu-DOTATATE treatment (dosing, total cycles administered, treatment-related toxicities, radiologic response assessment). Data are continually updated.

RESULTS

A systematic literature review was conducted by extracting articles from PubMed, Scopus, and Embase database using unique search terms and boolean operators. Inclusion criteria (1) non GEP-NET and (2) radiomics workflow were used to extract articles of interest. Once the unique articles were identified the RQS questionnaire was used to evaluate the RQS score based on the radiomics workflow used in the study.

CONCLUSIONS

While research in radiomic analysis of non GEP-NETs has not been as extensive as those in GEP-NET, promising models have been developed. Future radiomic research in non GEP-NETs should focus on creating large multicenter prospective studies, implementing multimodal imaging strategies, using standardized segmentation/extraction techniques, and emphasizing external model validation to improve the quality of the resultant studies.

ABSTRACT ID 33190

C-23

Efficacy and safety of [¹⁷⁷Lu]Lu-edotreotide ([¹⁷⁷Lu]Lu-DOTATOC) for the treatment of neuroendocrine tumors (NETs) – a systematic literature review (SLR) and meta-analysis

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BACKGROUND

[¹⁷⁷Lu]Lu-edotreotide represents a promising radiopharmaceutical therapy (RPT) currently undergoing clinical evaluation for its efficacy in the management of patients with advanced NETs. No meta-analysis of data has previously been published for [¹⁷⁷Lu]Lu-edotreotide in this clinical setting.

METHODS

PubMed, EMBASE, Cochrane databases, and abstracts from select congresses were searched for eligible [¹⁷⁷Lu]Lu-edotreotide studies (PROSPERO 2024 CRD42024518028). Meta-analyses were performed using fixed and random-effects models. The primary outcome was the objective response rate (ORR; complete + partial response) in the subgroup of patients with gastroenteropancreatic NETs (GEP-NETs) and in those with any NETs, irrespective of origin (All-NETs). Secondary outcomes included disease control rate (DCR; best overall response of complete response + partial response + stable disease), median progression-free survival (mPFS), and median overall survival (mOS). Safety/tolerability data for [¹⁷⁷Lu]Lu-edotreotide were reviewed but not analyzed. Unpublished/updated data were requested from the authors where needed, to permit additional analyses.

RESULTS

Of 591 unique publications identified in the searches, eight studies were eligible for inclusion, all in the advanced disease setting (5/8 included patients with progressive NETs). Updated data were included from 4/8 studies (maximum n=294 GEP-NETs; n=489 All-NETs). Most patients had grade 1/2 NETs (grade 1: 11%–63%; 2: 30%–79%; 3: 4%–11%). The response was assessed using RECIST-based criteria in 4/8 studies. There was high heterogeneity ($I^2 >70%$) across meta-analysis outcomes/patient

populations, therefore, results from the more conservative random-effects model were prioritized. Patients with GEP-NETs had better RPT efficacy outcomes than those with All-NETs (Table). Safety/ tolerability data were inconsistently reported, but grade 3/4 hematological, renal and hepatic toxicities were rarely noted during [¹⁷⁷Lu]Lu-edotreotide treatment. No secondary malignancies were reported in patients receiving RPT with [¹⁷⁷Lu]Lu-edotreotide alone.

Meta-analysis efficacy results (random-effects model)

	GEP-NETs	All-NETs
ORR, % (95% CI)	34 (17–54) [n=222]	19 (8–32) [n=423]
DCR, % (95% CI)	78 (60–92) [n=222]	57 (33–79) [n=423]
mPFS, months (95% CI)	24.9 (17.6–32.2) [n=294]	18.6 (12.5–24.8) [n=267]
mOS, months (95% CI)	44.8 (36.8–52.8) [n=256]	39.1 (25.1–53.0) [n=408]

CI = confidence interval; n = number of patients in analysis

CONCLUSIONS

Overall, these results show favorable efficacy for [¹⁷⁷Lu]Lu-edotreotide in patients with advanced NETs, especially in those with GEP-NETs. Response and PFS outcomes were encouraging in relation to recent phase 3 [¹⁷⁷Lu]Lu-edotreotide data from COMPETE. The safety/tolerability profile of [¹⁷⁷Lu]Lu-edotreotide also appears to be good and in line with the findings in COMPETE.

ABSTRACT ID 33271



C-24

First-line Treatment with [¹⁷⁷Lu]Lu-edotreotide ([¹⁷⁷Lu]Lu-DOTATOC) in patients with NETs: a SwissNET Registry Analysis

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BACKGROUND

SwissNET registry, founded in 2008, is a continuous, systematic prospective data collection from patients diagnosed with NETs in Switzerland who consented to participation. There is limited real-world data available regarding first-line ¹⁷⁷Lu-edotreotide treatment. Therefore, the purpose of this analysis was to determine the effectiveness of ¹⁷⁷Lu-edotreotide in a systemic first-line treatment setting in adult patients with metastatic, well-differentiated, and somatostatin receptor-positive NETs.

METHODS

¹⁷⁷Lu-edotreotide was prepared on-site as a “magistral preparation” in accordance with GMP regulations and national Swiss laws. Patients were required to be naïve to anti-cancer systemic therapy, or with less than six months use of somatostatin analogs, without progression documentation. The primary endpoint was real-world progression-free survival (rwPFS), defined as time from start of treatment with ¹⁷⁷Lu-edotreotide (i.e., date of the first administration) until the date of first objective report of tumor progression (defined as radiological progression or change of treatment modality) or death, whichever occurred first. Secondary endpoints included overall survival (OS), real-world objective response rate (rwORR; response was determined by composite radiological, biochemical, and clinical judgement), real-world duration of response (rwDoR), real-world disease control rate (rwDCR), and real-world duration of disease control (rwDDC).

RESULTS

There were 104 patients reported with first-line treatment, with a mean age of 63.3 (±13.2) years (28-86 years, 50 female/54 male), with data collected up to July 2024. Patients were followed for 4.1 years on average. The distribution of tumor origin was: 48% GI-NET, 4% lung NET, 33% pancreatic NET, 14% unknown primary NET, 2% other NET, with 29, 66, and 9 patients having tumor grade G1, G2 and G3, respectively. 84% of the patients had liver metastases. 37% had functional NETs (62% non-functional, 2% unknown).

Treatment Data and Efficacy Results

Median rwPFS	23.1 (15.5-32.0) months
Median OS	75.8 (60.3-87.4) months
rwORR	29.6% (20.8%-39.7%)
Median rwDoR	27.3 (9.2-not estimable) months
rwDCR	83.7% (74.8%-90.4%)
Median rwDDC	26.8 (15.9-42.2) months
Median number of ¹⁷⁷ Lu-edotreotide cycles	4 (1-5 cycles)
Median interval between cycles (minimum interval)	10.0 (7.3) weeks
Median activity per cycle	7.12 (3.70-7.47) GBq

Of 98 patients with a response assessment, a complete response was observed in seven, a partial response in 22 patients. OS was generally longer in patients with non-functional tumors.

CONCLUSIONS

This is the first report of first-line treatment with ¹⁷⁷Lu-edotreotide in a real-world population. First-line therapy with ¹⁷⁷Lu-edotreotide can be considered a promising treatment option for patients with metastatic, somatostatin receptor positive, well-differentiated NETs of different origins.

ABSTRACT ID 33277

C-25

Safety of Transarterial Liver Directed Therapy for Metastatic Neuroendocrine Tumor for Patients with Carcinoid Heart Disease

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BACKGROUND

Transarterial liver directed therapies such as bland embolization, transarterial chemoembolization and Yttrium-90 radioembolization help control tumor burden for patients with neuroendocrine tumor liver metastases. Functional neuroendocrine tumors secrete vasoactive substances that can lead to carcinoid heart disease. The purpose of this study is to evaluate the safety of liver embolotherapy and risk of cardiac adverse events (AEs) in the setting of carcinoid heart disease.

METHODS

This study was a retrospective analysis at two institutions of patients with well-differentiated neuroendocrine tumor liver metastases and carcinoid heart disease who underwent embolotherapy from 2000 to 2023. The incidence of cardiac adverse events was reported, and the severity of AEs was graded based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Significant associations between the prevalence of cardiac adverse events with ECOG status and severe tricuspid regurgitation were estimated with the Chi-Square Test of Independence. Overall survival was estimated using the Kaplan-Meier method.

RESULTS

Twenty-nine patients (15 men, 14 women, mean age 59 years) underwent 79 embolotherapies (35 bland embolization, 31 conventional TACE, 11 radioembolization). All patients had echocardiography confirmed tricuspid (n=24) and/or pulmonic valve (n=20) thickening, regurgitation or prior valve replacement (n=7). Valvular regurgitation ranged from none to severe, with 16 patients (55.2%) demonstrating severe tricuspid regurgitation and 4 patients (13.8%) having severe pulmonic regurgitation. Sixteen patients had Grade 1 neuroendocrine tumor, 12 had Grade 2, and 1 had Grade 3. Primary tumor sites were small bowel (n=23), large bowel (n=3), and pancreas (n=3). Cardiac AEs occurred following 7 of 79 procedures (8.9%) in 7 patients. Five AEs characterized by heart failure necessitated hospitalization (CTCAE Grade 3 and above), including one ICU admission. AEs requiring hospitalization started 1-39 days following treatment (median 17 days). Hospital stay ranged from 2-14 days (median 4 days). All hospitalized patients were medically managed and discharged. Two AEs were managed as outpatients. The prevalence of cardiac AEs was not significantly associated with ECOG

performance status ($P=0.712$) nor the presence of severe tricuspid regurgitation ($P=0.321$). Overall survival following embolotherapy at 1 year, 3 years and 5 years was 85.7%, 70.4% and 43% respectively.

CONCLUSIONS

Transarterial liver directed therapies for patients with carcinoid heart disease was associated with 8.9% prevalence of cardiac adverse events, which all improved with medical management. Larger studies to further elucidate the relative risk of cardiac toxicities for patients with carcinoid heart disease are warranted.

ABSTRACT ID 33393



C-26

Clinical outcomes following salvage PRRT in patients with metastatic neuroendocrine tumors

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BACKGROUND

Peptide receptor radionuclide therapy (PRRT) with ¹⁷⁷Lu-DOTATATE prolongs survival in metastatic, well-differentiated, somatostatin receptor subtype 2 (SSTR2)-positive gastro-entero-pancreatic neuroendocrine tumors (NETs). Disease progression after initial PRRT remains a clinical challenge. PRRT retreatment has emerged as a potential strategy, with real-world data supporting its efficacy and tolerability. This study evaluated clinical outcomes following PRRT retreatment, including progression-free survival (PFS), overall survival (OS), and treatment-related toxicity.

METHODS

We retrospectively analyzed patients with metastatic, well-differentiated NETs who received PRRT retreatment after progression following initial PRRT at Mayo Clinic sites between 2016 and 2025. Patients were eligible for retreatment if they had previously benefited from PRRT with good tolerance and had DOTATATE-avid, potentially treatable disease. Clinical records, imaging (Ga-68 DOTATATE PET/CT), and laboratory results were reviewed. Toxicities were graded using CTCAE v5.0. Survival outcomes were estimated using the Kaplan-Meier method and Cox regression in RStudio, with multivariable adjustment for key clinical variables.

RESULTS

Fifty-six patients underwent PRRT retreatment, receiving a median of 6 cycles in total (4 during initial therapy, 2 during retreatment). Most had small bowel (50%) or pancreatic (33.9%) primaries; 87.5% had a Krenning score of 4. The median interval between first cycle of initial PRRT and retreatment was 41.7 months. Over half received systemic therapies between PRRT courses. Median PFS and OS after retreatment were 14.5 and 31.8 months, respectively. The most common toxicities were Grade 1–2 thrombocytopenia (25%) and neutropenia (5.4%); no Grade ≥3 hematologic toxicities occurred. Three patients developed delayed hematologic events, including evolving myelodysplastic syndrome (n=1), acute myeloid leukemia (n=1), and prolonged myelosuppression (n=1). One patient experienced Grade 1 acute kidney injury.

In multivariable analysis, higher tumor grade and shorter time between PRRT courses were significantly associated with shorter PFS. Small bowel primary tumors and better ECOG performance status were associated with longer OS. Intervening therapies were not significantly associated with survival outcomes.

Five of the 56 patients in this cohort received an additional two cycles after progression from retreatment (total of 8 cycles). No acute toxicities were observed. Three progressed within 8 months; two remained progression-free at last follow-up (10.3 and 17.0 months)

CONCLUSIONS

PRRT retreatment was well tolerated and associated with clinically meaningful PFS and OS in select patients with progressive, well-differentiated NETs.

ABSTRACT ID 33402



C-27

Efficacy and Safety of Peptide Receptor Radionuclide Therapy Retreatment (r-PRRT) Practices in Progressive Neuroendocrine Tumors (prog-NETs): Systematic Review and Meta-Analysis

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BACKGROUND

In patients with prog-NETs, PRRT can prolong survival with low toxicity. r-PRRT is being increasingly utilized for prog-NETs, especially in patients with sustained responses to initial PRRT (i-PRRT) and limited alternative treatment options. While we eagerly await results from a prospective r-PRRT study (NET RETREAT, NCT05773274), to better understand the efficacy and safety of r-PRRT in patients with prog-NETs, we conducted a systematic review and meta-analysis of global r-PRRT practices.

METHODS

A systematic search of PubMed, Embase, and CENTRAL databases and a manual search of key conference abstracts were performed to identify studies published between 2020–2024, in adult patients with prog-NETs previously treated with PRRT and retreated with ¹⁷⁷Lu-, ⁹⁰Y-, or α-emitting PRRT. Eligible studies were those with ≥10 patients, in which the time gap between i-PRRT and r-PRRT was specified or indicated. Efficacy and safety outcomes were investigated, including progression-free survival (PFS), overall survival (OS), response rates, hematotoxicity, and nephrotoxicity. Outcomes were summarized descriptively, with pooled median PFS weighted by sample size, and pooled disease control rate (DCR) estimated from a meta-analysis using a random effects model in R.

RESULTS

Of 1709 studies screened, 12 studies were included along with four studies identified through manual searches (n=16; 1149 patients). i-PRRT included ¹⁷⁷Lu- and/or ⁹⁰Y-, or unspecified PRRT, with ¹⁷⁷Lu-DOTATATE being the most common. r-PRRT included ¹⁷⁷Lu- and/or ⁹⁰Y-, or unspecified PRRT and ²²⁵Ac-DOTATATE. Most studies (n=14) reported ≥12 months (mean or median) from i-PRRT completion to r-PRRT, with one study inexplicitly reporting ≥6 weeks and another ≥6 months. Median r-PRRT follow-up ranged from 6.5–25.8 months (n=9). Following r-PRRT, the pooled median PFS weighted by sample size was 18.2 months (n=14). Only four studies reported median OS ranging from 7.0–27.7 months. The pooled DCR (95% CI), defined as stable disease, complete response, or partial response with RECIST v1.1, reported at any time (n=11) was 61.6% (55.5–67.5%), with no significant heterogeneity (P=.09). Hematotoxicity was mainly transient, low-grade anemia, with only one study reporting myelodysplastic syndrome or acute myeloid leukemia (0.243 per 100 person-years). Nephrotoxicity was mostly low

grade, with only one study reporting one patient (10.0%) with grade ≥ 3 nephrotoxicity. Overall, r-PRRT was well-tolerated and comparable to i-PRRT with no unexpected or new safety signals.

CONCLUSIONS

These data suggest that r-PRRT is well-tolerated and effective in patients with prog-NETs. Clinically meaningful PFS benefit without additional safety concerns supports r-PRRT as a promising treatment in these patients warranting further randomized data.

ABSTRACT ID 33411



C-29

Liver-directed therapy for metastatic neuroendocrine carcinoma and grade 3 well-differentiated neuroendocrine tumors

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BACKGROUND

Lu177-DOTATATE has been used to treat GEP-NETs since 2018, however a strong correlation between dosimetry results and hematopoietic and nephrological toxicities has not yet been established. This study aims to investigate the relationship between these toxicities and absorbed dose for patients treated with Lu177-DOTATATE at a single institution.

METHODS

Post-therapy dosimetry was performed on 11 patients using quantitative SPECT/CT acquisitions. Ten patients had imaging at 4-, 24-, 48-, and 72-hours post-injection, and one patient had imaging at 4- and 72-hours. Absorbed doses to the kidneys and representative regions of lumbar bone marrow were calculated using organ-level dosimetry (MIM Software Inc., Cleveland, OH). Dosimetry was performed due to re-treatment (7 patients) or due to reduced kidney function (4 patients). Total dose was estimated using the calculated mGy/GBq and the cumulative treatment activity. Pre-therapy baseline lab results were compared to blood labs at an average of 32 days after treatment and kidney labs at an average of 115 days after treatment. Spearman's rank correlation coefficient with Bonferroni correction was used to assess dose-response relationships.

RESULTS

Table 1: Summary Statistics: Administered Activity and Absorbed Dose to the Bone Marrow and Kidneys (Gy/GBq)

Parameters	Range	Mean	Standard Deviation
Cycle 1 Administered Activity (GBq)	3.78 - 7.58	6.91	1.17
Bone Marrow Dose (Gy/GBq)	0.02 - 0.17	0.06	0.04
Kidney Dose (Gy/GBq)	0.25 - 1.21	0.47	0.26

Average bone marrow dose was 0.06 Gy/GBq (range: 0.02 – 0.17 Gy/GBq), and average kidney dose was 0.47 Gy/GBq (range: 0.25 - 1.21 Gy/GBq). Conservative toxicity limits were exceeded for cumulative bone marrow dose (2 Gy) in two patients, and cumulative kidney dose (23 Gy) in four retreatment patients.

Significant correlations were found between bone marrow dose and both white blood cell count reduction ($r_s = -0.86$, $p < 0.01$) and platelet count reduction ($r_s = -0.89$, $p < 0.001$). No significant relationships were found for serum creatinine or hemoglobin.

CONCLUSIONS

Although accepted tolerance doses were exceeded for bone marrow (n=2) and kidneys (n=4), no treatment emergent G3/G4 toxicities were observed. A significant relationship was found between absorbed dose to the bone marrow and both platelet and white cell count reduction at ~1 month after treatment. No relationship was found between kidney dose and serum creatinine; however, the follow-up period may have been too short to see long-term effects.

ABSTRACT ID 33437



C-30

DISCO: Safety, Tolerability and Diagnostic performance of ⁶⁴Cu-SARTATE compared to ⁶⁸Ga-DOTATATE in patients with known or suspected neuroendocrine tumors.

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BACKGROUND

Diagnostic imaging is critical in the diagnosis, staging, management, and follow-up of neuroendocrine tumors (NETs). Characteristics of ⁶⁴Cu-SARTATE may provide advantages over existing imaging, including ⁶⁸Ga-DOTATATE, because of its longer half-life and potential to detect additional disease.

METHODS

This Phase I/II study assessed the safety and efficacy of ⁶⁴Cu-SARTATE (200 MBq) in participants with known or suspected gastroenteropancreatic (GEP)-NETs. Participants were assessed with ⁶⁸Ga-DOTATATE PET/CT within 35 days prior to ⁶⁴Cu-SARTATE administration, with the ⁶⁴Cu-SARTATE PET/CT performed at 4 ± 1 hrs (same-day) and 20 ± 4 hrs (next-day) post-injection. Scans were assessed by 2 independent blinded central readers. Discordant lesions (lesions present on only one scan, either ⁶⁴Cu-SARTATE or ⁶⁸Ga-DOTATATE) were subsequently evaluated by an independent assessor against the standard of truth (biopsy and/or conventional imaging, collected during a follow-up period of up to 12-month). Per-lesion sensitivity, specificity, and lesion detection rate of both ⁶⁴Cu-SARTATE timepoints were compared to ⁶⁸Ga-DOTATATE among those with discordant findings. Safety was assessed via vital signs, laboratory tests, physical examinations, ECGs and adverse event (AE) reporting.

RESULTS

45 participants were enrolled, 41 with known NETs and 4 with suspected NETs, across 4 sites in Australia. The number of lesions detected across readers ranged from 393-488 with ⁶⁴Cu-SARTATE (both timepoints) and 186-265 for ⁶⁸Ga-DOTATATE. 93.5% of 230-251 discordant lesions identified were detected on ⁶⁴Cu-SARTATE, while only 6.5% of discordant lesions were identified on ⁶⁸Ga-DOTATATE. Average lesion-level sensitivity of evaluable discordant lesions was 94.7% (95% CI 65.1, 99.5) for ⁶⁴Cu-SARTATE (across both timepoints) compared to 5.4% (95% CI 0.5, 34.9) for ⁶⁸Ga-DOTATATE. Average sensitivity on same-day ⁶⁴Cu-SARTATE PET/CT was 95.1% (95% CI 80.1, 98.6) and 94.3% (95% CI 65.1, 99.5) on next-day PET/CT. Average specificity was 62.5% (95% CI 3.1, 99.5) for ⁶⁴Cu-SARTATE (across both timepoints) and 37.5% (95% CI 0.5, 96.9) for ⁶⁸Ga-DOTATATE, this was impacted by the low number of discordant lesions identified by ⁶⁸Ga-DOTATATE. Seven (15.6%) participants experienced ⁶⁴Cu-SARTATE-related AEs; 8 were Grade 1, 1 was Grade 2, mostly resolving within 2 days. No serious treatment-emergent AEs were observed.

CONCLUSIONS

⁶⁴Cu-SARTATE was found to be safe and well-tolerated. In participants with known or suspected GEP-NETs, ⁶⁴Cu-SARTATE lesion detection outperformed that of ⁶⁸Ga-DOTATATE. The improved diagnostic performance of ⁶⁴Cu-SARTATE has important clinical implications for the identification of GEP-NET lesions to inform treatment pathways. A phase III study of ⁶⁴Cu-SARTATE in NETs is being planned to build on these results.

ABSTRACT ID 33463

C-32

Incidence of Peripheral Inserted Central Line Complications with Administration of ¹⁷⁷Lutetium Dotatate

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BACKGROUND

¹⁷⁷Lutetium dotatate is a radioligand therapy that can be used to treat somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs). The package insert does not specify which type of line is required for administration. VUMC uses peripherally inserted central catheters (PICCs) for administration, however, other facilities use peripheral intravenous catheters (PIVs). Current data on extravasation risk of radionucleotide therapy is sparse. We sought to determine the incidence of complications in patients who received a PICC.

METHODS

This is a retrospective cohort quality improvement project in patients at VUMC who received ¹⁷⁷lutetium dotatate from 4/1/2018 to 2/28/2025. All patients who received ¹⁷⁷lutetium dotatate were included. Data was collected from the electronic health record. All patient data was analyzed using descriptive statistics. The primary endpoint is the incidence of complications due to ¹⁷⁷lutetium dotatate administration via PICC. Secondary endpoints include cost associated with complications of receiving a peripheral or central line for administration of treatment.

RESULTS

There were a total of 1,059 PICC placements during the defined time period. Fifty percent of patients were male and the median age was 65. The small intestine was the primary disease site in 37.8% of patients, followed by pancreas in 24.3% of patients. PICC complications occurred in 46 (4.3%) of PICC placements. Specifics on complications are shown in table 1.

Complication	n=46
Bleeding	14 (32.6)
Clot	3 (7.0)
Irritation	2 (4.7)
Itching	2 (4.7)
Pain	12 (28.0)
Syncopal episode	7 (16.3)
Other	6 (14.0)
n(%)	

Other complications included numbness, mispositioning, hematoma, heart palpitations, pinching, and swelling.

Thirty patients received PICC but did not receive treatment due to lab parameters not being met, issues with obtaining a dose, or symptom burden. Three patients had unsuccessful PICC placement and thirteen required additional imaging to confirm placement. A financial analysis of these complications is ongoing.

CONCLUSIONS

This study shows that patients receiving ¹⁷⁷lutetium dotatate through a PICC had complications in 4.3% of line placements. The most common complications from PICC placement and administration of treatment included bleeding, pain, and syncopal episodes. There were patients who received PICCs and required removal of the line without a dose of ¹⁷⁷lutetium dotatate and/or additional imaging to rule out complications, increasing costs to both the health care system and to the patient. Given the number of complications and increased cost of PICC line placement compared to PIV it is reasonable to administer ¹⁷⁷lutetium dotatate via PIV. Future directions include a comparison of complications and cost in patients who received treatment through a PIV line compared to PICC line.

ABSTRACT ID 33479

C-33

Somatostatin receptor expression on ⁶⁸Ga-Dotatate imaging among patients with poorly differentiated extra-pulmonary neuroendocrine carcinomas: a prospective study

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BACKGROUND

Limited data are available regarding somatostatin receptor (SSTR) expression in poorly-differentiated neuroendocrine carcinoma (NEC). Some retrospective series report strong SSTR expression in as high as 40% of patients with NEC. However, these figures may be influenced by selection bias, such as imaging of patients with lower ki-67 index or uncertainty about pathologic tumor differentiation.

METHODS

In this prospective study, ⁶⁸Ga-Dotatate PET was compared with FDG PET in patients with metastatic extrapulmonary NEC and at least one measurable site of metastasis. The primary endpoint was proportion of patients with tumors showing uniform dotatate-avidity (uptake > normal liver) tumors. Secondary endpoint was the proportion of patients with completely negative SSTR expression or a heterogeneous pattern of expression.

RESULTS

The study enrolled 30 patients, who underwent ⁶⁸Ga-Dotatate PET imaging; 28 patients also had FDG PET imaging within a prespecified 2 month-interval from ⁶⁸Ga-Dotatate PET. Primary tumor sites included pancreatic (7), colorectal (6), uterine (2) and unknown (9). Histologic subtype included small cell (15), large cell (6), and mixed or unspecified (9). All patients had anatomically measurable metastases at time of scanning, although metabolic uptake on FDG PET may have been attenuated, in some cases, by prior chemotherapy administration. Only 3 patients (10%) had evidence of avid (Krenning grade 3 or 4) uniform dotatate avidity indicating strong SSTR expression with corresponding uptake on FDG/PET and/or anatomic imaging. Nine patients had disease characterized as completely negative on Dotatate PET, another 9 had mostly dotatate PET negative disease with a few weakly avid lesions, eight had heterogeneous avidity patterns, and 1 patient had weakly avid lesions on dotatate PET.

CONCLUSIONS

A small proportion, approximately 10%, of patients with metastatic poorly-differentiated extrapulmonary NEC exhibit strong and uniform somatostatin receptors expression, indicating their suitability for peptide receptor radionuclide therapy.

C-34

Outcomes of Peptide Receptor Radionuclide Therapy in Patients with Pheochromocytoma and Paraganglioma: A Center of Excellence Experience

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BACKGROUND

Pheochromocytomas (PCs) and paragangliomas (PGs) are rare neuroendocrine tumors with variable 5-year survival outcomes and limited treatment options. Peptide Receptor Radionuclide Therapy (PRRT) is a relatively novel treatment option that can be administered systemically to treat patients with advanced somatostatin-positive PCs and PGs. This study aims to evaluate the safety and efficacy of PRRT in patients with metastatic/inoperable PCs and PGs.

METHODS

This is a single-center retrospective case series. Records of patients with metastatic or inoperable PCs or PGs treated with PRRT were selected based on participation in the Iowa NET registry. Patient characteristics, adverse events, biochemical response, blood pressure response, and imaging response based on RECIST 1.1 criteria were abstracted. Statistical analyses were performed using RStudio. P-values were calculated using Fisher's exact test for categorical variables and t-test for continuous variables.

RESULTS

A total of 11 patients received PRRT, including 2/11 (18.2%) with PC and 9/11 (81.8%) with PG. Among patients on first restaging imaging, 3/11 (27%) demonstrated partial response (PR), 6/11 (55%) had stable disease (SD), and 2/11 (18%) had progressive disease (PD). Both PC patients exhibited SD on restaging. Among patients with PG, 3/9 (33%) demonstrated PR, 4/9 (44%) with SD, and 2/9 (22%) with PD. Of the patients with non-functional tumors, 1/4 (25%) had PD and 3/4 (75%) had SD. Among functional tumor cases, 3/7 (43%) achieved PR, 3/7 (43%) SD, and 1/7 (14%) PD. No significant difference in likelihood of partial response was observed between functional and non-functional tumor groups ($p = 0.24$). Median progression-free survival (PFS) and overall survival (OS) were not reached at a median follow-up of 11 months. PRRT was well tolerated overall, with the most common adverse effect following PRRT being nausea (2/11, 18.2%). No grade 3 or 4 toxicities were reported. Changes in systolic blood pressure (SBP) were -4.5 mm Hg in patients with PC and +5.9 mm Hg in those with PG ($p=0.40$). Diastolic blood pressure (DBP) changes were -8.0 mm Hg and +0.7 mm Hg, respectively ($p=0.21$). The median change in chromogranin A (CgA) after PRRT was -8.5 (n=6, IQR: -84.75 to 298; $p = 0.41$).

CONCLUSIONS

PRRT demonstrated tolerability and efficacy for the treatment of patients with advanced PCs and PGs. Our findings are consistent with the existing literature. Future prospective randomized controlled studies are needed to further assess the efficacy of PRRT in treating this challenging patient group.

ABSTRACT ID 33493



C-35

Care of Neuroendocrine Tumors: the Collaborative of Surgical Teams for NeuroEndocrine Tumors (CUTNETs)

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BACKGROUND

Despite the importance of surgical management, most data on NETs surgical care come from single-center studies, limiting generalizability. To address these challenges and improve NETs surgical care, a worldwide Collaborative of Surgical Teams for NeuroEndocrine Tumors (CUTNETs) was created.

METHODS

A cross-sectional survey was conducted to profile CUTNETs centres and surgeons, assess expertise, and document general clinical practices. The survey was self-administered online by CUTNETs centers. Descriptive analysis was used.

RESULTS

In 27 centres in 11 countries, on 2 continents, 2–15 surgeons were involved in NETs care, with strong representation in hepato-pancreato-biliary (88.0%) and surgical oncology (76.0%). Surgeons were involved in initial assessment (92.3%), delivery of systemic therapy (34.6%), and follow-up (80.8%). Specialized NETs multidisciplinary tumor boards existed in 84.6% of centres. Most services estimated seeing over 11 new NETs consultations (76.9%) and performing over 6 NETs operations (65.4%) monthly. Most centres were engaged in research, with 80.8% maintaining a NET registry and 71.4% a biobank, and 69% training graduate students in NETs research. Variability across reported practices was observed for hepatic cytoreduction, resection of asymptomatic primary in stage IV small intestine NETs, use of preoperative systemic therapy, and resection of advanced neuroendocrine carcinomas.

CONCLUSIONS

CUTNETs is an international initiative to enhance NETs surgical care. This survey revealed a strong foundation in clinical expertise and research, with NETs-specific expertise and volume, surgeon-led care, multidisciplinary tumor boards, biobanks, and clinical registries. CUTNETs is poised to leverage these strengths to address key clinical questions to advance NETs surgical care.

ABSTRACT ID 32944

C-36

The Natural History of Small Bowel Neuroendocrine Tumor (SBNET) Metastases

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BACKGROUND

Small bowel neuroendocrine tumors (SBNETs) have a strong propensity to metastasize, with stage IV (M1) disease present in >50% of cases at diagnosis. Most patients develop liver metastases, but the frequency of metastases to other sites is less well documented. We set out to define these sites, identify risk factors and outcomes associated with metastases, and determine how many patients presenting with M0 disease developed metastases in follow-up.

METHODS

Review of a single institution database identified patients from 2005-2024 with a histopathologic diagnosis of SBNET who underwent surgical intervention (primary/nodal resections with/without metastatic cytoreduction). Demographics, disease characteristics, treatments, and outcomes were abstracted. Overall survival (OS) was estimated by Kaplan-Meier Method and compared by Log Rank Test. Multivariate regression (MR) was utilized to identify variables associated with metastatic disease at presentation.

RESULTS

396 SBNET patients were included in the study and rate of metastatic disease (over their entire disease course) was 77%, with the most common sites being liver (74.5%), peritoneum (30.1%) and bone (20.2%; Table). 288 (72.7%) presented with metastatic disease. The frequency of preoperative functional imaging (DOTA-PET, Octreoscan) was 66.9% (83.2% in past 5 years). Patients presenting as M1 had higher T stage, grade, and neuroendocrine biomarker levels; on MR, higher grade, T stage and elevation of neuroendocrine markers were independently associated with increased risk of presenting with metastatic disease. 20/108 (18.5%) patients presenting with M0 disease developed metastases (at median of 59 months) with the most common sites being liver (95%) and peritoneum (25%). There was no difference in OS between long-term M0 patients (median 169 months) vs. M0 patients who later developed metastases (median not reached; p=0.60) and both groups had better OS than patients presenting as M1 (median 119 months; p<0.01). Patients who progressed to M1 disease underwent more additional treatments than long-term M0 patients, with 35% undergoing reoperation.

Sites of Metastases	Overall n = 396 (%)
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CONCLUSIONS

Most patients with SBNETs at our institution presented with metastatic disease, predominantly in the liver, peritoneum, and bone. One-fifth of M0 patients developed metastases at a median of 59 months after resection. Despite this, most patients with metastatic SBNETs have extended survival with surgical and medical therapy, and these results highlight the importance of long-term follow-up in SBNET patients.

ABSTRACT ID 28667



C-37

International expert consensus on perioperative management of carcinoid crisis.

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BACKGROUND

Carcinoid crisis is a critical concern for patients with neuroendocrine tumors (NETs) undergoing invasive procedures. Guidance is needed to standardize and optimize perioperative care for patients at risk of carcinoid crisis. We aimed to develop consensus based expert recommendations for the perioperative management of carcinoid crisis.

METHODS

We used a modified Delphi approach with 4 rounds of voting to reach expert consensus on statements about perioperative management of carcinoid crisis. A multidisciplinary international panel of 44 experts was formed, and 3 patient partners were engaged. An initial survey round identified items to cover in the statements. Statements addressing preoperative, intraoperative, and post-operative considerations were created. Panelists rated statements on a Likert scale (1 to 7). Three additional rounds of iterative rating and feedback were completed anonymously. Consensus was defined with median score between 5-7 and <13 panelists rating outside the score category containing the median. Dissent analyses (bipolarity and stakeholder-group comparison) were conducted to understand the robustness of the consensus results. The level of evidence and grade of recommendation was based on the Oxford Centre for Evidence-Based Medicine. Open community feedback was obtained over 2 weeks via an online survey.

RESULTS

Final consensus was reached on 41 statements. Of these, 12 focused on preoperative work-up and optimization, 27 on intraoperative management including monitoring, prophylaxis and treatment of crisis, and 2 on postoperative management. Statements stated that somatostatin analogs are not necessary for prophylaxis prior to operation or on the day of operation, and treatment in case of carcinoid crisis should start with vasopressors with short-acting somatostatin analogs used as an adjunct. No dissent was identified. Open feedback was provided by 43 participants and 80% agreed with the statements presented.

CONCLUSIONS

Using modified Delphi methodology, we developed recommendations to guide the perioperative management of carcinoid crisis. Considering the importance of carcinoid crisis on the management and outcomes of patients undergoing surgical resection for NETs, this guidance can help standardize

care and optimize outcomes. Future work should focus on implementation in clinical practice, monitoring of outcomes, and furthering understanding of carcinoid crisis to update recommendations.

ABSTRACT ID 32914



C-38

Association of Surgical Intervention with 30-Day Re-admission and Outcomes in Patients Hospitalized for Small Bowel Neuroendocrine Tumor-Related Obstruction

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BACKGROUND

Small bowel neuroendocrine tumors (SBNETs) are associated with a significantly increased risk small bowel obstruction (SBO). Although an effective treatment strategy, recurrence of SBO after surgical resection is common and data to guide the timing of surgical resection are limited. We sought to investigate the association of surgery during index admission for SBO with 30-day readmission and outcomes among patients with SBNETs.

METHODS

This retrospective study used the 2019-2021 National Readmission Database to identify and include adult patients with an ICD-10 diagnosis of SBNETs who were admitted for SBO. Readmission was defined as the first admission to any hospital for any non-trauma diagnosis within 30 days of the index admission. We analyzed rates of 30-day readmission, 30-day overall mortality rates, and resource utilization. Multivariate regression analysis was performed to identify independent risk factors for 30-day readmissions. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 11,214 patients with SBNETs were identified, of which, 1,048 (9.3%) (mean age= 66 years, females=52%) presented with SBO. A total of 554 (53%) patients underwent surgical management during index admission and 451 patients (45%) were managed conservatively. On average, 30-day readmission rate was significantly lower for patients who underwent surgical management during index admission compared to those who were managed conservatively (5.4% vs 20.8%, p=0.005). On multivariate cox regression analysis, surgical management during index admission was associated with significantly lower (OR=0.52, 95% CI- 0.38-0.82), while higher Charlson comorbidity index was associated with significantly higher odds of 30-day readmission (OR=1.22, 95% CI 1.02-1.47). Surgical management during index admission was also associated with significantly lower 30-day overall mortality rate compared to conservative management (3.6% vs 6.6%, p<0.01). No differences in average hospitalization cost (p=0.67) and length of stay (p=0.48) were noted.

CONCLUSIONS

In this retrospective analysis of patients with SBNETs presenting with small bowel obstruction, surgical management during the index admission was associated with significantly lower 30-day readmission rates and overall mortality compared to conservative management. Despite these benefits, no

differences were observed in hospitalization costs or length of stay between the two groups. These findings highlight the potential benefit of early surgical intervention in selected patients with SBNETs and SBO.

ABSTRACT ID 33000

C-39

Primary Tumor Resection Is Associated With Improved Survival in Metastatic GI-NETs: A Retrospective Study in the Bronx, NY

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BACKGROUND

Neuroendocrine tumors (NETs) present distinct clinical outcomes depending on the age at diagnosis, differentiating early-onset (EO, <50 years) from late-onset (LO, ≥50 years) cases. Although surgical removal of the primary tumor is a key component of treatment for localized NETs, its impact on survival in metastatic disease—particularly in the absence of metastasectomy—remains unclear. This study aims to explore survival-related factors in EO versus LO NET patients, with a focus on the role of primary tumor resection.

METHODS

A retrospective cohort of 240 patients diagnosed with gastrointestinal (GI) NETs was identified through an IRB-approved study. The analysis included variables such as disease stage (localized vs. metastatic), tumor grade (G1–G3), five-year survival, primary tumor resection status, and race/ethnicity.

RESULTS

Among all the 240 patients, 18% identified as Hispanic (44), 23% as Non-Hispanic Black (54), 32% as Non-Hispanic White (78), 13% as other (31) and 14% for which the information was not available (33). Among all the patients, 201 were classified as G1/G2. Among LO patients, 76.6% (n = 154) were G1/G2, among which 68.8% (n = 106) were metastatic. Among EO patients, 23.34% (n = 47) were G1/G2, among which 78.7% (n = 37) were metastatic. In the LO group with G1/G2 tumors, the 5-year survival rate was 27.8% (n = 42) for metastatic disease and 23.38% (n = 36) for localized disease. For EO WITH g1/g2 tumors, the 5 year survival rate was 42.5% (n = 20) for metastatic disease and 19.15% (n = 9) for localized disease. In the EO G1/G2 group, 12 of the 37 patients with metastatic disease had primary tumor removal without metastasectomy with 75% 5-year survival rate. In the LO G1/G2 group, 14 of the 106 metastatic patients had primary tumor removal without metastasectomy with 58.33% 5-year survival rate. Fisher exact test was performed independent of age at diagnosis between >5 year/< 5 year survival and surgery vs no surgery amongst metastatic individuals and we obtained a p-value of 5.34x10⁻⁶ with Odds Ratio of 6.25 meaning that surgery for metastatic patients (with no metastasectomy) had a higher odds of 5-year survival as compared with no surgery patients.

CONCLUSIONS

Primary tumor resection in patients with metastatic GI NETs, even without metastasectomy, was significantly associated with improved 5-year survival. This association was observed across the entire cohort, regardless of age at diagnosis. These findings suggest that primary tumor surgery may confer a survival benefit in metastatic GI-NETs and should be considered as part of treatment planning in patients.

ABSTRACT ID 33471



C-40

Short-term post-operative outcomes after surgery for entero-pancreatic neuroendocrine tumors (NETs): a population-based analysis

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BACKGROUND

Surgery is a cornerstone of management for neuroendocrine tumors (NETs), but outcomes vary. It is critical to understand the real-world morbidity profile of surgery to optimize patient selection and outcomes. We examined short-term outcomes after resection for entero-pancreatic NETs.

METHODS

We performed a population-based retrospective cohort study of adults with entero-pancreatic NETs (2000–2023). The outcome was 90-day major morbidity (MM – Clavien-Dindo 3–5) and 90-day days-at-home after surgery (90-DAH). Logistic regression examined factors associated with outcomes for each type of surgery.

RESULTS

Of 3,536 patients operated for entero-pancreatic NETs, 40.1% had pancreatic primary and 57.4% had metastases. Surgery occurred at median 2 months after diagnosis (IQR: 0–75). 90-day MM was 24.4% after all surgeries, including 26.9% after hepatectomy, 30.3% after pancreatectomy, 21.3% after enterectomy, and 30.4% after combined resection (hepatectomy with enterectomy or pancreatectomy). 90-day mortality was 3.4% overall, with 4.0%, 1.7%, and 4.1% after hepatectomy, pancreatectomy, and enterectomy, respectively. Median LOS was 7 days (IQR: 5–10) overall, with 26.9% having prolonged LOS (>75th percentile). Combined resection (OR 1.44; 95%CI 1.08–1.94) and pancreatoduodenectomy (OR 2.35; 95%CI 1.77–3.12), as well as age (OR 1.21; 95%CI 1.14–1.29) and higher comorbidity burden (OR 1.56; 95%CI 1.21–2.01) were independently associated with increased odds of 90-day MM. Median DAH-90 was 89 (IQR: 88–89) overall and did not differ by surgery type. Enterectomy (OR 0.98; 95%CI 0.97–0.99) and pancreatoduodenectomy (OR 0.98; 95%CI 0.96–0.99), increasing age (OR 0.97; 95%CI 0.97–0.98), and higher comorbidity (OR 0.95; 95%CI 0.92–0.98) were independently associated with fewer 90-DAH.

CONCLUSIONS

Approximately 1 out of 4 patients experienced 90d-MM after surgery for NETs and mortality below 5%, with increased risk for combined and pancreatoduodenectomy. Most patients spent the majority of time at home after surgery for NETs. This information is important to counsel patients, inform

ABSTRACT ID 32943

C-41

Survival outcomes after surgery for 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 in Ontario, Canada. 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) NET (66.5% metastases) and 1,107 had P-NETs (37.5% metastases). Median follow-up was 6 years (IQR 3-10), and 1,144 patients (32.4%) died during follow-up. 10-year OS was 65.8% (95%CI 64.0-67.7%) after surgery overall, 67.1% (95%CI 65.0-69.4%) for SB-NETs and 59.9% (95%CI 56.3-63.6%) for P-NETs, after adjustment for age, sex, comorbidity burden, and year of surgery. In those with metastases, 10-year adjusted OS was 62.5% (95%CI 60.0-65.1%) for SB-NETs and 43.1% (95%CI 38.0-48.9%) for P-NETs. Advancing age, metastatic disease, and higher comorbidity burden were independently associated with inferior OS overall and for SB-NET and P-NETs, 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 P-NETs.

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 32975

C-42

Risk Factors and Prognosis of Peritoneal Metastases in Small Bowel Neuroendocrine Tumor Patients

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BACKGROUND

Small bowel neuroendocrine tumors (SBNETs) demonstrate indolent growth despite 25-50% of patients presenting with metastases at diagnosis. Surgical resection and cytoreduction may improve survival even with metastatic disease. The peritoneum is the second most common metastatic site after the liver, and while studies suggest that peritoneal metastases (PM) are associated with worse overall survival (OS), limited data exist on risk factors and outcomes of these patients post resection.

METHODS

A single-institution review of a prospective database identified patients from 2005-2024 with histopathologic diagnosis of SBNET who underwent surgical intervention (primary resection and/or metastasis cytoreduction). Demographics, disease characteristics, treatments, and outcomes were abstracted. The Lyon staging system defined the extent of PM when available. Primary outcome measures were OS and progression-free survival (PFS), estimated by Kaplan Meier Method and compared by Log Rank Test. Cox multivariable analysis was performed to identify variables independently associated with PM.

RESULTS

396 patients were included in the study with rates of metastatic disease and PM of 71.7% and 30.1%, respectively. 21 (5.3%) of patients developed PM after their initial surgery at a median time of 54 months. Presence of liver metastases, female sex, higher T stage and elevated pancreaticatin levels were associated with increased risk of PM. By Kaplan-Meier analysis, patients with PM had worse OS (109 vs. 169 months, $p=0.01$) and PFS (42 vs. 75 months, $p<0.01$) than those without PM. On multivariable analysis, these factors were not independently significant. Patients who received cytoreduction of PM had higher rates of major complications (i.e. Clavien Dindo 3 or 4) than those who did not (11.2% vs 2.0%, $p<0.01$) and had higher rates of postoperative bowel obstruction (at any time point after initial surgery; 22.7% vs 3.6%, $p<0.01$). A contributing factor may be the increased use of peptide receptor radionuclide therapy (PRRT) in this population (36.1% PM vs 19.9% no PM, $p<0.01$), as the rate of bowel obstruction in PM patients who received PRRT was 44.2%.

CONCLUSIONS

Peritoneal metastases occur in 30% of patients with SBNETs and are more common in patients with liver metastases and higher T stage. Despite PM, patients can still have good long-term survival

after cytoreduction. Although there is an increase in complication rate, these findings validate that aggressive surgical management of SBNET patients with PM are warranted when feasible.

ABSTRACT ID 33396



C-43

Mapping the evidence for surgical care of gastro-entero-pancreatic neuroendocrine tumors: a scoping review

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BACKGROUND

Surgical management remains the cornerstone in the management of gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs), yet indications and procedures are often inconsistent. To inform the development of a research agenda to strengthen the evidence in NETs surgical care, we conducted a scoping review to map the existing literature on surgery for GEP-NETs.

METHODS

The scoping review was conducted following the expanded framework of Arksey and O'Malley. A literature search was run on MEDLINE, Embase, and Scopus in October 2024 for studies published since 2000 reporting on any surgical intervention, performed under general or loco-regional anesthesia on adults with GEP-NETs at any stage. We excluded interventions performed with endoscopy or interventional radiology.

RESULTS

Among the 15,191 studies screened, 260 were included. Most publications were from the US, Italy and Germany. Publications included a majority of reviews, with 96 narrative reviews and 30 systematic reviews/meta-analyses covering a broad range of topics including management of functional vs non-functional NETs, perioperative therapies, liver transplantation, and minimally invasive surgery. Of the 118 original investigations, 97.5% were retrospective cohort studies and 67% were single-centre. The only 3 prospective cohort studies that examined surveillance of small pancreatic NETs (n=2) and assessment of nodal metastases in pancreatic NETs (n=1). Most publications addressed pancreatic NETs (Table). Of all publications included, the most common topics were observation of small pancreatic NETs, treatment of liver metastases, safety of minimally invasive surgery, and prognostication. Of original investigations, the majority compared surgical approaches, followed by examination of lymph node harvest, prognostic factors, and defining size cut-off for observation of pancreatic NETs.

Table. Distribution of included publications by extent of disease, stratified by primary NET site.

	Locoregional disease (n=110)	Metastatic disease (n=43)	Combined locoregional and metastatic disease (n=97)	All (n=250)
Gastro-enteric NETs	14 (12.7%)	6 (14.0%)	30 (30.9%)	50 (20.0%)
Pancreatic NETs	85 (77.3%)	8 (18.6%)	43 (44.3%)	136 (54.4%)
Mixed NETs	11 (10.0%)	28 (65.1%)	22 (22.7%)	61 (24.4%)
Other NETs	0 (0%)	1 (2.3%)	2 (2.1%)	3 (1.2%)

CONCLUSIONS

This scoping review highlights limitations and gaps in the evidence supporting surgical care for GEP-NETs. A considerable part of the literature is made of narrative reviews. Very few original investigations report prospective or multi-institutional data, and examination of pancreatic NETs dominate the literature. Gaps to target include: prospective data collection, multi-institutional studies, non-pancreatic NETs studies, focus on stage-specific and primary-site specific data, interventional studies of the value of surgery compared to other therapies and of perioperative therapies combined with surgery.

ABSTRACT ID 33439



C-44

Resection of Primary Pancreatic Neuroendocrine Tumors in the Metastatic Setting

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BACKGROUND

Surgical resection is the standard of care for small bowel neuroendocrine tumors (NETs) and is associated with improved survival, even in the presence of metastatic disease. Benefits of resection of primary pancreatic NETs (pNETs) in the metastatic setting are uncertain due to a lack of clinical data and the morbidity associated with pancreatic surgery. Herein, we report updated results of progression and overall survival of a cohort of metastatic pNET patients who underwent resection of their primary tumor compared to those that remained unresected.

METHODS

The healthcare systems database was searched to find primary pNET patients with metastases and at least 2 years of follow up. Patients were divided based on whether they underwent primary tumor resection or not, then further subdivided into those with synchronous or metachronous metastatic lesions. Unresected patients were analyzed using modified NCCN pancreatic adenocarcinoma surgical guidelines and categorized as "resectable," (surgery possible at diagnosis) "borderline resectable," or "locally advanced" (surgery not indicated at diagnosis). Primary outcomes included overall survival (OS) and progression-free survival (PFS), estimated by Kaplan-Meier curves. Results were compared using the log rank test. Demographics, additional treatments, tumor grade, resection type, and treatment-related adverse events were recorded.

RESULTS

284 patients with primary metastatic pNETs were analyzed. 155 underwent resection and 129 did not. 31% of resected patients had a perioperative complication and 70% developed long-term morbidities including new/worsening diabetes or exocrine insufficiency.

The median OS for the resected vs unresected group was 190 vs 45.6 months, respectively (HR 5.59, $p < 0.0001$). The median PFS of the resected vs unresected group was 38.1 vs 8.5 months (HR 2.38, $p < 0.0001$).

Among patients with synchronous metastases, the median OS for the resected, resectable (but not resected) and locally advanced groups was 142 months (95% CI 122-162 mo), 63 months (42-84 mo) and 50 months (40-60 mo), respectively. Survival was significantly better among resected patients, HR 0.31 (95% CI 0.18-0.51), $p < 0.0001$, whereas potentially resectable patient who were not operated on had similar survival to the unresectable group, HR 0.96 (0.55-1.67).

CONCLUSIONS

Resection of the primary pNET in the metastatic setting is associated with improved overall and progression free survival but also with frequent perioperative complications and long-term morbidity.

ABSTRACT ID 33454

C-45

Improving Outcomes for Neuroendocrine Patients: 25 year review of 1699 NET Surgical Cytoreduction Patients at a Single Institution

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BACKGROUND

Surgical cytoreduction for neuroendocrine tumors (NETs) remains a standard of care treatment strategy. Patient selection and long-term expectations of survival have relied on relatively small series of primarily abdominal tumors; however, a better understanding of cytoreductive outcomes is important for patients as treatment paradigms have evolved. The objective of this study was to evaluate the value of surgery from a large cohort of patients at a single institution with strong surgical experience, robust clinical variables that support patient selection, and long term follow up data on survival. It also clarifies the potential to improve outcomes in cases that are outside standard selection criteria, including higher grade tumors and metastatic bronchopulmonary NETs.

METHODS

Records of patients with NETs who underwent surgical cytoreduction at our institution from 1999 to present were reviewed. From 5290 NET pts, 1699 were identified to have documented grade, primary site and overall survival data. Length of follow up was calculated from date of index surgery to date of either death or last documented encounter. Kaplan Miere curves were constructed and median overall survival (mOS) and % OS were calculated. Survival was computed based on clinical records and cross reference with social security master death lists using Lexis Advance software.

RESULTS

Amongst the 1699 patients, 898, 673, and 128 pts were G1/G2/G3 respectively. Of the 1699 patients, complete demographic data was identified in 1472 (F:821 (55.8%) , M:651 (44.2%). Mean age of diagnosis was 56 ± 13.2 years. Average follow up was 8.1 ± 5.6 years. Median overall survival (mOS) of all G1/G2/G3 NETs were 230 months, 148 months, and 109 months respectively ($p < 0.01$), exceeding previously published data. G1/G2/G3 small bowel NETs ($n = 531/327/36$) had a mOS of 18.5, 16.3, and 9.6 years, again exceeding previously published data. Interestingly, G1/G2/G3 PNET patients ($n = 97/129/41$) had a 10/15 year % OS of 69.8% and 57.9% for G1 vs over 50% for G2 vs 18.1% and 0% for G3. Furthermore, G1/G2 bronchopulmonary primary NETs ($n = 36/30$) had a 5/10 year % OS of 83.9% and 80.0% for G1 vs 50% and 47.8% for G2.

CONCLUSIONS

Surgical cytoreduction remains an important treatment option in NETs patients with long-term

survival data showing increasingly improved outcomes over 25-year follow-up, including in G3 well-differentiated tumors and metastatic bronchopulmonary NETs. Our data underscores the merits of care at a high-volume center with standard methods of patient selection and cytoreduction endpoints.

ABSTRACT ID 33458



C-46

Evaluating the role of postoperative long-acting somatostatin analogue therapy in patients with metastatic neuroendocrine tumors undergoing surgical debulking

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BACKGROUND

The optimal timing of postoperative somatostatin analogue (SSA) resumption in patients with metastatic gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) after surgical debulking is unknown and varies between institutions. We hypothesized that SSA resumption can be safely deferred post-debulking in select patients.

METHODS

We performed a retrospective cohort study of patients with well-differentiated GEP-NETs with liver metastases who underwent liver debulking, synchronously or metachronously with primary tumor resection at an academic referral center (2019-2023). Clinicopathologic characteristics and progression-free survival (PFS) were compared between patients who resumed SSA within 90 days of surgery and those who did not (never resumed or resumed > 90 postoperative days).

RESULTS

Of 83 patients, 56 (68%) had small bowel NETs, while 27 (32%) had pancreatic NETs. Twenty-seven (33%) resumed SSA within 90 days of debulking. The SSA resumption group had higher frequency of pancreatic NETs (52% vs 23%, $p=0.01$), extrahepatic metastases (70% vs 36%, $p=0.005$), and higher Ki-67 index (median 4% vs 2%, $p=0.03$). SSA resumption was associated with worse PFS (median 13 vs 21 months, $p=0.048$). Pancreatic location (HR=2.2, $p=0.003$) and osseous metastases (HR=2.0, $p=0.04$) were independent predictors of shorter PFS after debulking. Among patients who did not immediately resume SSA, small bowel NETs had longer PFS (median 34 vs 16 months, $p=0.02$).

CONCLUSIONS

Patients with small bowel NETs without osseous metastases undergoing surgical debulking experience long PFS and might therefore benefit from delaying postoperative SSA resumption. Our findings provide foundational data for a prospective trial.

ABSTRACT ID 33474

C-47

Role of Surgery in Patients with G1-G2 Pancreatic Neuroendocrine Tumors and Synchronous Liver Metastases

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BACKGROUND

The liver represents the most common site of metastatic involvement in patients with pancreatic neuroendocrine tumors (PanNET). While surgery remains the cornerstone of treatment for localized disease, its role in the metastatic setting is still debated. Notably, there is a lack of robust comparative data evaluating the outcomes of surgical intervention versus systemic therapy in patients with metastatic PanNETs. The aim of this study was to compare progression-free survival (PFS) and overall survival (OS) in patients with G1-G2 PanNENs and liver metastases (LMs) who underwent either surgical or medical treatment.

METHODS

This is a retrospective cohort study that included patients with histologically confirmed G1-G2 PanNENs and synchronous LMs treated between 2010 and 2024 at San Raffaele Hospital (Italy). Patients were divided into two groups based on initial treatment strategy: surgery versus systemic treatment. A propensity score matching (PSM) was performed to minimize baseline differences between the groups.

RESULTS

Overall, 82 patients were included. Of these, 48 (58%) underwent surgical resection and 34 (42%) received medical treatment as first-line therapy. A higher proportion of females was observed in the surgical group (60%) compared to the medical treatment group (32%) ($p=0.012$). The surgical group had also a significantly longer follow-up, with a median of 62 months, compared to 23 months in the non-surgical group ($p<0.001$). After a median follow-up of 44 months, disease progression occurred in 56 patients (68%), and 18 patients (22%) died during the study period, with 17 deaths attributed to PanNET progression. A trend towards a longer PFS in the medical treatment group was observed ($p=0.119$), whereas OS was comparable between the two groups ($p=0.419$). After PSM (based on gender and follow-up duration), the medical treatment group exhibited a significantly longer PFS compared to the surgical group: 20 months vs. 9 months, respectively ($p=0.033$). No statistically significant difference in OS between the two groups ($p=0.567$) was confirmed after PSM.

CONCLUSIONS

The present study demonstrated that patients with G1-G2 PanNENs and LMs who were managed

with medical therapy experienced longer PFS compared to those who underwent surgery. Also, no significant OS benefit was observed in the surgically treated group. These findings suggest that the role of surgery in the metastatic setting is uncertain and likely restricted to highly selected cases, especially when complete oncological clearance cannot be reached. Further prospective, ideally randomized, trials are needed to define optimal treatment strategies and identify subgroups of metastatic patients that may benefit the most from surgery.

ABSTRACT ID 33475

C-48

Pancreatic Neuroendocrine Tumors with Intraductal Growth: Unraveling a Rare Entity

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BACKGROUND

Main pancreatic duct (MPD) dilation has been recognized as a predictor of disease aggressiveness in patients with pancreatic neuroendocrine tumors (PanNETs). Most PanNETs that cause MPD dilation tend to grow near or around the MPD. On the other hand, tumor growth within the pancreatic ductal system itself has been poorly investigated so far. This study aims to describe the frequency of PanNETs with intraductal growth and assess its association with other pathological features of aggressiveness, as well as its impact on survival outcomes.

METHODS

All consecutive patients who underwent pancreatic resection for a well-differentiated non-functioning (NF-) PanNET at San Raffaele Hospital (Milan, Italy) between January 1997 and December 2023 were included.

RESULTS

A total of 465 patients were included in the study. Intraductal tumor growth was observed in 18 cases (4%). The most common clinical presentations in patients with intraductal growth were acute pancreatitis, exocrine insufficiency, and the onset or worsening of diabetes. The median BMI was significantly lower in these patients compared to the remaining study cohort (21.4 versus 25.0 kg/m², $p=0.005$). The Ki67 proliferative index was significantly higher in patients with intraductal tumor growth compared to the other subjects (11% versus 2%, $p < 0.001$). After a median follow-up of 55 months, 114 patients (25%) experienced disease progression or recurrence, and 50 patients (11%) eventually died. The 3-year progression-free survival (PFS) rate for patients with intraductal tumor growth was 44%, compared to 81% in those without intraductal growth ($p=0.001$). After propensity score matching, the PFS difference between these two groups was no longer statistically significant ($p=0.629$).

CONCLUSIONS

Intraductal tumor growth is a histological finding that occurs more frequently than expected, being present in 4% of patients undergoing surgery for PanNETs. This growth pattern seems to be associated with more aggressive histological features, in particular with a higher proliferative index. These findings reinforce the well-established principle that surgical intervention is essential for all PanNETs with any form of MPD involvement.

ABSTRACT ID 33481

C-49

Differential Expression of GLUT-1 and FASN Across Histological Grades of Pancreatic Neuroendocrine Neoplasms

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BACKGROUND

Pancreatic neuroendocrine tumors (PanNETs) are a heterogeneous group of tumors that exhibit variable clinical behavior. Understanding metabolic alterations across tumor grades may reveal diagnostic and therapeutic opportunities. In this study, we examined the expression of two critical metabolic proteins, glucose transporter 1 (GLUT-1) and fatty acid synthase (FASN), in various histological grades of PanNETs and metastatic lesions.

METHODS

Seventeen formalin-fixed, paraffin-embedded PanNET samples were selected retrospectively from the Huntsman Cancer Institute (University of Utah) and classified using the current World Health Organization (WHO) grading criteria. The samples were classified as follows: grade 1 (n = 7), grade 2 (n = 8), grade 3 (n = 1), and metastatic (n = 1). Immunohistochemistry for GLUT-1 and FASN was performed using an automated Leica Bond platform. Staining quantification was carried out using QuPath software with a compartment-specific analysis. GLUT-1 staining was defined as both cytoplasmic and membranous, while FASN staining was defined as exclusively cytoplasmic. Five representative regions per tumor were analyzed, and data were subjected to statistical comparison using the Kruskal-Wallis and Dwass-Steel-Critchlow-Fligner post-hoc tests (Jamovi v2.3.28.0), with $p < 0.05$ considered significant.

RESULTS

GLUT-1 expression was limited to the islets of adjacent normal pancreatic tissue, whereas the neoplastic areas exhibited diffuse cytoplasmic and membranous staining. Grade 3 tumors showed markedly lower GLUT-1 expression (8.5%) and lower staining intensity (0.11) than grades 1 (56.1%, intensity 0.30) and 2 (61.3%, intensity 0.26). Significantly, higher GLUT-1 expression was observed in grades 1 and 2 compared to grade 3 ($p < 0.05$ for both comparisons). A similar pattern was observed for staining intensity, however, a statistically significant difference was found only between grades 1 and 2 ($p < 0.05$). FASN exhibited strong, diffuse cytoplasmic staining in both normal pancreatic tissue and

neoplastic tissue, with relatively lower expression in normal islets. In neoplastic cells, FASN expression remained high across most groups, with over 93% of cells staining positive in grades 1 and 2 and metastatic tumors, but staining positivity decreased to 65.6% in grade 3 tumors. The mean staining intensity was highest in grade 1 tumors (0.65), followed by metastatic tumors (0.60) and grade 2 tumors (0.51). It was lowest in grade 3 tumors (0.33). While the percentage of FASN-positive cells did not differ significantly among the groups, staining intensity was significantly higher in grades 1 and 2 than in grade 3 ($p < 0.05$ for both comparisons).

CONCLUSIONS

GLUT-1 expression is markedly reduced in well-differentiated (grade 3) PanNETs, suggesting impaired or altered glucose uptake pathways in high-grade tumors. In contrast, FASN remains highly expressed across tumor grades, although staining intensity progressively decreases in grade 2 and 3 well-differentiated tumors, but increases in the metastasis. These findings underscore the distinct metabolic profiles across PanNET grades and suggest that GLUT-1 downregulation may be a marker of aggressive behavior. Further studies in larger cohorts are necessary to validate these biomarkers for clinical application.

ABSTRACT ID 33489



C-50

Preoperative Predictors of New-Onset Diabetes Mellitus Following Distal Pancreatectomy for Non-functioning Pancreatic Neuroendocrine Tumours

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BACKGROUND

Non-functioning pancreatic neuroendocrine tumours (NF-PanNETs) are typically indolent neoplasms with a rising incidence. Distal pancreatectomy (DP) remains the standard treatment for localized tumours in the pancreatic body/tail. Given the favorable long-term prognosis, accurate assessment of postoperative morbidity, particularly postoperative new-onset diabetes mellitus (PONO-DM), is critical. Aims of the study were to identify preoperative predictors of PONO-DM in patients undergoing DP for NF-PanNETs and to develop a predictive model for individualized risk assessment.

METHODS

All consecutive patients who underwent curative DP for localized NF-PanNETs at San Raffaele Hospital (Milan, Italy) between 2015 and 2022 were included. Exclusion criteria included pre-existing diabetes and follow-up <24 months. Clinical and radiological data, including body composition and pancreatic measurements, were evaluated.

RESULTS

A total of 65 patients were included. After a median follow-up of 58 months, 27/65 patients (41%) developed PONO-DM. PONO-DM was significantly associated with elevated BMI ($p=0.016$), pancreatic atrophy ($p=0.044$), increased total ($p=0.014$) and visceral fat area ($p=0.021$), and a greater percentage of resected distal pancreatic parenchyma (HPP, $p=0.046$). On Cox regression, higher BMI (HR 1.187; $p=0.001$), elevated HbA1c (HR 1.169; $p=0.001$), and greater proportion of distal HPP (HR 1.030; $p=0.018$) were identified as significant risk factors of PONO-DM. A nomogram and online risk calculator (<https://net-distal-pancreatectomy.shinyapps.io/postoperative-diabetes-risk-calculator/>) were developed to predict individual risk at 1, 3, and 5 years after surgery, with good discriminatory performance (AUC 0.766; $p<0.001$).

CONCLUSIONS

PONO-DM occurred in 41% of patients undergoing DP for NF-PanNETs. Elevated BMI, HbA1c and percentage of resected distal HPP emerged as significant risk factors of PONO-DM. The developed nomogram and web-based calculator may support preoperative counseling and guide tailored prehabilitation or parenchyma-sparing strategies in high-risk patients.

P-1

Quality of Life and Care Experiences in a U.S. Multi-Institutional Neuroendocrine Tumor Cohort

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BACKGROUND

Neuroendocrine tumors (NETs) are uncommon, heterogeneous neoplasms associated with prolonged survival and substantial symptom burden. However, patient-reported outcomes (PROs) across NET subtypes remain poorly characterized, particularly in real-world settings.

METHODS

The Neuroendocrine Tumors–Patient Reported Outcomes (NET-PRO) study is a prospective, multi-institutional U.S. cohort funded by the Patient-Centered Outcomes Research Institute (PCORI), conducted across 14 sites. Adults aged ≥18 years with incident small intestinal (SI-NET), pancreatic (pNET), gastroenteropancreatic (GEP), or lung NETs diagnosed from January 2018 through September 2024 were enrolled using a validated EMR-based computable phenotype. Baseline surveys assessed health-related quality of life (HRQoL), symptoms, care experiences, and clinical characteristics using validated instruments. Descriptive statistics and standardized mean differences (SMDs) compared responses by NET site and time since diagnosis.

RESULTS

Among 2,367 participants (mean age 57.8 years; 57.3% female), 1,974 had GEP-NETs (659 SI-NET, 555 pNET) and 393 had lung NETs. Fatigue (mean 33.0), insomnia (32.5), and diarrhea (25.7) were the most burdensome symptoms. Lung NET patients reported worse dyspnea (SMD = 0.58, $p < 0.001$) and lower physical, role, and global QoL scores than those with GEP-NETs. Patients with pNETs reported better functioning and lower symptom burden. Diarrhea worsened over time, especially in SI-NETs. Most rated care highly (75.3%) and reported good coordination, but concerns about treatment side effects (80.4%), costs (60.7%), and travel burden (58.8%) were common.

CONCLUSIONS

This large U.S. cohort highlights substantial, persistent symptom burden among NET patients, with variation by tumor site and disease duration. Findings support longitudinal assessment of HRQoL in this growing patient population.

ABSTRACT ID 33433

P-2

Racial and ethnic disparities in US neuroendocrine tumor clinical trial enrollment over the past quarter century.

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BACKGROUND

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms originating from neuroendocrine cells, with considerable variation in behavior and clinical presentation. The rising incidence of NETs has driven advancements in drug development; however, it remains unclear whether all demographic groups have equal access to novel therapeutic trials. Previous oncologic epidemiological studies have identified race-specific disparities in overall and disease-specific survival. This study aimed to assess whether similar racial and ethnic disparities exist in the enrollment of patients in NET clinical trials.

METHODS

We collected data from all completed NET clinical trials involving adult patients conducted in the United States over the past 25 years (1/1/2000 to 1/1/2025) as reported on clinicaltrials.gov. Therapeutic interventional trials were included while observational, non-interventional or non-therapeutic trials were excluded. Key study variables included race, ethnicity, sex, tumor type, and year of study. To assess enrollment patterns, we calculated the enrollment ratio for each racial and ethnic group, defined as the percentage of enrollees from each group divided by their proportion among the overall NET patient population.

RESULTS

We analyzed 64 NET trials, comprising 5,020 participants total. The gender distribution was similar, with 2,455 women and 2,565 men. Racial demographic data were reported in 60.9% (39/64) of the trials, while ethnicity data were provided in 42.2% (27/64). The reporting of race increased markedly, rising from 16.7% during 2008–2011 to 78.3% in 2020–2024. The comparison of enrollment ratios revealed that Black participants were significantly underrepresented compared to White participants (0.292, $p < 0.001$), and Hispanic participants were significantly underrepresented compared to Non-Hispanic participants (0.536, $p < 0.001$).

Table 1: Demographic Representation and Enrollment Ratios in NETs Clinical Trials

	Black	White	Hispanic	Non-Hispanic
NETs Patient Demographics	16.1%	74.0%	10.4%	89.6%
NETs Clinical Trial Enrollee Demographics	5.33%	83.5%	5.69%	91.3%
Enrollment Ratio	0.331	1.13	0.546	1.02
Relative Enrollment Compared with White	0.292 ($p < 0.001$)	1.00	-	-
Relative Enrollment Compared with Non-Hispanic	-	-	0.536 ($p < 0.001$)	1.00

CONCLUSIONS

Black and Hispanic Americans are significantly underrepresented in NET clinical trials. Clinical trials are critical for developing effective treatments and understanding how interventions perform across populations. The lack of representation hinders our ability to evaluate how NET therapies affect different racial and ethnic groups, potentially worsening existing health disparities. Enhancing the inclusion of underrepresented minorities in NET clinical trials is vital to promoting equitable care and improving health outcomes for all patients.

ABSTRACT ID 33487

P-3

Higher composite Social Determinants of Health scores predict worsened survival for early-stage small bowel Neuroendocrine Tumors

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BACKGROUND

Patients with early stage well-differentiated small bowel neuroendocrine tumors (sbNETs) typically have favorable overall survival with timely diagnosis and treatment. However, the influence of social determinants of health (SDH) and care at Minority-Serving Hospitals (MSH) on survival in sbNETs patients remain scarce. This study examines the combined impact of SDH factors and hospital type on long-term survival, offering insight into health disparities in patients with early stage sbNETs.

METHODS

The 2010-2020 National Cancer Database was queried to include adult patients with G1 and G2 sbNETs, diagnosed with Stage I or II disease who underwent complete surgical resection. Exclusion criteria included G3 NETs, stage III or IV disease, neuroendocrine carcinoma, duodenal NETs, and patients with incomplete follow-up data. The SDH score was developed using a composite of four Sociogeographic factors: (1)low income, (2)low education, (3)distance travelled for treatment (>250 miles), and (4)rurality. Patients were categorized into SDH+ (0-1 score) and SDH- (2-4) cohorts. Hospitals in the top decile of Black and Hispanic patient representation were classified as MSHs. KM curve and Cox regression analyses assessed survival outcome.

RESULTS

Of 2688 sbNET patients, the median age was 64 (54-73) years, with 48% female and 57% classified as SDH-. Overall survival rates at 5, 10, and 15 years were 79%, 62%, and 49%. Stratified by SDH and hospital type, SDH+ patients at MSHs had a 5-year survival of 82%, while SDH- patients dropped to 63%. Non-MSH hospitals showed similar results: 82% for SDH+ and 77% for SDH-. Median survival for SDH- patients was 11 years at MSHs, compared to 12 years at non-MSHs, with minimal SDH impact on survival at non-MSHs (Figure). In the regression analysis, SDH score was a significantly associated with worse survival for the SDH- group (HR 1.24, p<0.001). Treatment at non-MSH hospitals was linked to significantly better survival (HR 0.41, p<0.001). Black patients had a 20% higher risk of mortality compared to White patients (HR 1.20, p=0.002), while there was no significant difference for Hispanic patients(HR 0.87, p=0.2). Other significant factors included age, sex, and insurance status.

CONCLUSIONS

A higher composite SDH score and hospital type were associated with worsened survival for early

stage sbNETs. Recognizing SDH factors, such as income, education, and geographic barriers, is crucial in improving cancer outcomes, particularly for populations treated at MSHs. Future studies examining interventions aimed at reducing sociogeographic disparities are needed for patients with sbNETs

ABSTRACT ID 33056

P-4

Survival of colorectal small cell carcinoma and comparison with colorectal adenocarcinoma

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BACKGROUND

Colorectal small cell carcinoma (SCC), comprising fewer than 1% of colorectal cancers, is associated with a poor prognosis. However, detailed survival information is limited due to its rarity. In this study, we performed a survival analysis using Survival, Epidemiology, and End Result (SEER) database (2000-2022) and compared outcomes with colorectal adenocarcinoma.

METHODS

All patients with SCC or adenocarcinoma with colon or rectal primaries were extracted from SEER database. AJCC stage was calculated based on 8th edition TNM classifications. Stage-by-stage median overall survival (mOS) was calculated by Kaplan-Meier method. The mOS were compared between SCC and adenocarcinoma and between colon SCC and rectal SCC using log-rank test. Univariate and multivariate Cox regression, including AJCC stage, surgery, radiation, and chemotherapy variables, was used to model survival trends.

RESULTS

761 colorectal SCC cases were extracted. Median age was 65 (24-89) and median follow-up was 108 months (95% CI: 65 – 129). While no significant mOS difference was observed between colon and rectal SCC for stages I-III, a significantly longer mOS was observed in stage IV rectal SCC when compared with stage IV colon SCC (7 months vs 2 months, $p < 0.0001$; Table 1). When compared with cohorts of patients with colon and rectal adenocarcinoma, more SCC cases were diagnosed at stage IV. Patients with SCC of both colon and rectum had significantly shorter mOS than adenocarcinoma across different stages except for stage II colon, for which only numerically shorter mOS was observed with SCC (Table 1). In Cox regressions, surgery and chemotherapy were significantly associated with improved survival for both primaries ($p < 0.001$), while radiation was not significant for either primary.

Table 1. Survival analysis.

mOS (months)	Colon SCC (n/mOS)	Colon Adenocarcinoma (n/mOS)	Colon: SCC vs Adenocarcinoma P-value	Rectal SCC (n/mOS)	Rectal Adenocarcinoma (n/mOS)	Rectal: SCC vs Adenocarcinoma P-value	Colon SCC vs Rectal SCC P-value
Stage I	19/32	114,213/144	<0.0001	27/23	54,702/160	<0.0001	0.99
Stage II	17/38	121,757/106	0.4	17/16	38,417/106	<0.0001	0.065
Stage III	40/14	104,793/82	<0.0001	50/19	46,687/107	<0.0001	0.48
Stage IV	245/2	83,542/13	<0.0001	260/7	36,652/17	<0.0001	<0.0001

CONCLUSIONS

Colorectal SCC is an aggressive subtype of colorectal malignancy with poor prognosis. Most patients present with stage IV disease. When compared with stage IV colon SCC, stage IV rectal SCC has significantly longer mOS, whereas there were no significant mOS differences between early-stage colon and rectum SCC. Further research should continue exploring early diagnosis and effective therapies for this rare, aggressive malignancy.

ABSTRACT ID 33434

P-5

Treatment Decision Concerns: A Latent Class Analysis in Young-Onset Neuroendocrine Tumors

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BACKGROUND

With the increasing incidence of neuroendocrine tumors (NETs), patients often face multiple worries about treatment decisions, including side-effects, costs, and disruptions to daily life. This study aimed to identify distinct worry profiles and examine their associations with sociodemographic and clinicopathological factors.

METHODS

Baseline survey data were analyzed from patients, diagnosed between January 2018 and September 2024, in a multi-institutional U.S. cohort study - Neuroendocrine Tumors-Patient Reported Outcomes (NET-PRO), funded by the Patient-Centered Outcomes Research Institute (PCORI). The latent class analysis included five binary indicators reflecting whether participants reported being "at least a little worried" versus "not worried" about the following: (1) treatment side effects, (2) treatment costs, (3) time away from family, (4) time away from work, and (5) transportation to treatment facilities. We selected a three-class model that showed the best statistical fit and clear separation between classes.

Multivariable multinomial logistic regression was used to examine associations between patient characteristics and worry profile membership.

RESULTS

Among 2,198 participants (57.2% female) who completed five worry items, 261 (11.9%) were younger adults (aged 18–39 years at diagnosis). Classes identified were: (1) low-worry (10.8% overall [n=238]; 6.5% younger [n=17] vs 11.4% older adults [n=221]), characterized by consistently low responses across items; (2) moderate-worry (52.6% overall [n=1156]; 34.9% younger [n=91] vs 55.0% older adults [n=1065]), marked by concerns primarily about treatment side-effects (84.8%) and time away from family (58.4%); and (3) high-worry (36.6% overall [n=804]; 58.6% younger [n=153] vs 33.6% older adults [n=651]), characterized by widespread worry across all domains. In multivariable multinomial logistic regression, Being female, having an advanced cancer stage, lower household income, greater distance to treatment, lower perceived quality of care, employer-sponsored or Medicaid coverage, limited health literacy, having carcinoid syndrome, and tumor location in the pancreas, lung, or unknown primary were all significantly associated with higher odds of belonging to the moderate- to high-worry latent classes ($P < 0.05$). The association between advanced disease stage and higher worry was stronger among younger individuals, who had significantly higher odds of belonging to the moderate- to high-worry latent classes compared to older individuals (interaction $P < 0.001$).

CONCLUSIONS

Higher levels of worries about decision-making were associated with key sociodemographic and clinicopathological factors. Younger adults may face unique challenges and greater levels of worry when navigating treatment decisions in the context of advanced disease. Routine assessment of treatment-related worries may facilitate supportive care and help reduce decisional distress in this growing population.

ABSTRACT ID 33435



P-6

Contemporary epidemiology of gastro-entero-pancreatic neuroendocrine neoplasms

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BACKGROUND

While rise in incidence of gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs) was described in the early 2000s, awareness and diagnostics have changed. Continued understanding trends in NEN epidemiology is crucial to inform practices and health system planning, but contemporary data are lacking. We examined GEP-NENs incidence and overall survival (OS) after diagnosis in the last 20 years.

METHODS

We conducted a population-based study of incident GEP-NENs from 2000 to 2023. Yearly incidence per 100,000 people were computed. Multivariable Poisson regression examined factors associated with incidence over time. OS was computed with Kaplan-Meier methods and factors associated with OS assessed with multivariable Cox regression.

RESULTS

Of 12,877 GEP-NENs identified, 26.7% had metastases at diagnosis. The overall incidence increased 3-fold, from 1.83 to 7.46 per 100,000, over 2000-2023. As of 2023, the incidence was highest among small intestine NENs, followed by pancreas, rectum, appendix, stomach and large intestine NENs. The increase in incidence over 2000-2023 was largest for gastric (5.6-fold) and pancreatic NENs (4.6-fold). The rise in incidence was mostly driven by that of non-metastatic NENs (absolute difference 4.81 per 100,000 for 6.5-fold increase), with little change for metastatic NENs (absolute difference 0.9 per 100,000 for 1.2-fold increase). No change in incidence was observed for neuroendocrine carcinoma. Advancing age and rural residence (rate ratio – RR 3.23, 95%CI 3.01-3.46) were associated with larger increase in incidence, and female sex (RR 0.91, 95%CI 0.88-0.95) and metastases (RR 0.44, 95%CI 0.42-0.46) with a smaller increase. 5-year OS was 76% (95%CI 75-77%) overall, with 88% (95%CI 87-89%) without metastases and 56% (95%CI 54-57%) with metastases at diagnosis. OS was best for gastric neuroendocrine tumors and worst for colon NENs, with 93% (95%CI 91-94%) and 51% (95%CI 48-54%) at 5 years, respectively. Advancing age, lower socio-economic status, metastases at diagnosis (hazard ratio – HR 3.6, 95%CI 3.3-3.8) and carcinoma histology (HR 2.0, 95%CI 1.9-2.2) were independently associated with worse OS, while female sex (HR 0.83, 95%CI 0.78-0.88) was associated with better OS.

CONCLUSIONS

The incidence of GEP-NENs continued to rise over the past two decades, driven by non-metastatic NENs and neuroendocrine tumors. Combined with larger increases observed for gastric and

pancreatic NENs, this suggests increased detection as a likely mechanism. OS is favourable after GEP-NEN diagnosis, with worse prognosis for older patients and those with metastases and neuroendocrine carcinoma. Further work will examine the correlation between diagnostic testing use and changes in incidence, and assess changes in OS over time.

ABSTRACT ID 33436



P-7

Germline Pathogenic Variants Among Participants with Neuroendocrine Tumors in the Healthy Nevada Project

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BACKGROUND

The genetic drivers of neuroendocrine tumors (NET) remain incompletely defined, with emerging evidence suggesting potential links to hereditary cancer syndromes. The Healthy Nevada Project (HNP), a large, population based genomic screening initiative offers a unique opportunity to explore the prevalence of pathogenic germline variants associated with NETs.

METHODS

We evaluated germline genomic data from 98 participants enrolled in the HNP with a diagnosis of NET on a set of internal clinical sources that includes, but is not limited to, the problem list and medical history. Pathogenic or likely pathogenic variants were identified based on curated evidence in a panel of 74 genes previously associated with cancer risk, hereditary cancer syndromes, or of potential relevance to NET biology.

RESULTS

Of the 98 individuals with a diagnosis of a NET, 15 (15%) carried pathogenic or likely pathogenic germline variants according to ClinVar or VEP annotations for novel variants. The variants identified were in the following genes: *MUTYH*, *BRCA2*, *LZTR1*, *MBD4* each with 2 carriers and singletons in the following genes: *MITF*, *MSH3*, *MSH6*, *RAD51C*, *RET*, *SDHD*, and *TSC1*. Notably, several of these genes (such as *RET*, *SDHD*, and *TSC1*) are implicated in syndromes associated with increased NET risk.

CONCLUSIONS

A considerable subset (15%) of HNP participants with NETs were found to have germline pathogenic variants, including alterations in genes relevant to NET predisposition. These findings highlight the potential value of population level genomic screening for identifying individuals at elevated risk for NETs and defining specific germline risks for various NET phenotypes. Expanding these findings across broader genomic screening programs has potential to demonstrate the importance of integrating germline testing into NET risk assessment and management strategies. Further studies are warranted to determine the clinical significance of these and more variants in NET development, progression, and outcomes.

ABSTRACT ID 33443

P-8

Clinical details of early-onset neuroendocrine neoplasms differ by race and ethnicity and overall differ from typical-onset

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BACKGROUND

The epidemiology of neuroendocrine neoplasms (NENs) in younger adults is complex, and it is unclear who presents with which distinct clinical features. Expanding upon our prior work demonstrating a rising incidence of early-onset (EO) NENs overall and differences by race and ethnicity (RE), we characterize detailed clinical features of EONENs by patient demographics in the diverse California population.

METHODS

All patients with malignant NENs diagnosed from 1992-2019 in the population-based California Cancer Registry were identified by histology (ICD-O-3 code 8013, 8041-5, 8150-5, 8240-9). Patients diagnosed by age 49 were designated as EO, and from age 50 as typical-onset (TO). Proportions and age-adjusted incidence rates were calculated for comparisons. Patient demographics, tumor, and other clinical characteristics were compared by onset age. Clinical details of EONENs were compared by patient demographics. Comparisons used Kruskal-Wallis or Pearson chi-squared tests, multivariable logistic regression, and incidence rate ratios.

RESULTS

There were 12,266 EONEN patients identified. Compared to the 107,860 TONEN patients, statistically significantly more of the EONEN patients were women (55% vs 49%), Hispanic (28% vs 12%), or Asian/Pacific Islander (API) (10% vs 7%). More had localized-stage (50% vs 27%), appendiceal primary (12% vs 1%), or rectal primary (15% vs 6%). Fewer of the EONENs were distant-stage (29% vs 52%), or large-cell or small-cell (LSSC) lung NEN (16% vs 49%). Temporal trends in EONENs were similar to TONENs, both showing increasing proportions of patients over time who presented with localized, low-grade, or gastrointestinal primaries, and fewer with metastatic, high-grade, or pulmonary NENs. Furthermore within the EONENs group itself, statistically significant clinical differences were seen across patient demographics. The Hispanic population presented with the most locoregional-stage EONENs (69%; an 18-84% higher odds than other REs), followed by API (67%). The highest incidence rates of small bowel (0.30/100,000 person-years; 177-609% higher than other REs) and extra-gastroenteropancreatic/extra-pulmonary primary (0.39/100,000; 133-155% higher) were among the non-Hispanic (NH) Black population; highest of colon (0.33/100,000; 121-316% higher) and appendix (0.26/100,000; 157-418% higher) among NH White.

CONCLUSIONS

We found differences in the clinicopathologic features of EONENs by demographics and compared with TONENs in California. The increasing proportion of localized disease over time may reflect improvements in diagnostic methods and increased awareness of NENs. Younger patients were much less likely to present with LC/SC lung NENs, which may reflect declining smoking rates. Further research is underway to better understand the mechanisms driving differences in EONENs.

ABSTRACT ID 33485

P-9

Demographic and Survival Outcomes in Early-Onset Pancreatic Neuroendocrine Tumors: A National Cancer Database Study

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BACKGROUND

Pancreatic neuroendocrine tumors (pNETs) have been observed in younger adults, though epidemiologic trends remain poorly defined. This study aimed to characterize demographic predictors, treatment patterns, and survival disparities in early-onset pNET (EOPNET) using national data.

METHODS

We analyzed the National Cancer Database (2012–2021) for patients with pNET. EOPNET was defined as diagnosis at age < 50. Multivariable logistic regression and Cox models assessed predictors of EOPNET and all-cause mortality among patients with pNET, adjusting for demographics, tumor features, treatment, and socioeconomic factors. Trends in diagnosis and survival by income and urbanicity were examined using chi-square and trend tests.

RESULTS

Among 4,576 pNET cases, 953 (20.8%) were EOPNET, with a median age of 42 (IQR 35–46). The proportion of EOPNET was stable over time. Compared to late onset pNET, EOPNET patients were more likely to be female (49.7% vs. 43.5%), Black (16.9% vs. 10.7%), Hispanic (11% vs. 6.2%), and have private insurance (73.2% vs. 40.9%) or Medicaid (13% vs. 5.8%) (all $p < 0.001$). They had fewer comorbidities (Charlson–Deyo 0–1: 95% vs. 89.5%, $p < 0.0001$) and higher rates of surgical resection (82.7% vs. 72.1%, $p < 0.001$). There were no differences in tumor grade, stage, or receipt of chemotherapy/radiation. In multivariable analysis of patients with pNETs, diagnosis at an early age (EOPNET) was independently associated with improved overall survival (HR 0.56, 95% CI 0.45–0.70). In contrast, Medicaid (HR 1.71, 95% CI 1.32–2.22), Medicare (HR 2.04, 95% CI 1.76–2.37), and uninsured status (HR 1.65, 95% CI 1.10–2.47) — all compared to private insurance — as well as grade III disease (HR 4.01, 95% CI 3.30–4.87), increasing clinical T stage (HR 1.69–2.80 for cT2–cT4 vs. cT1, 95% CI 1.42–3.59), and N stage (HR 1.67–4.22 for cN1–cN2 vs. cN0, 95% CI 1.42–10.35) were significantly associated with worse survival. 10-year overall survival for patients with neuroendocrine EOPC was 81.7% (95% CI 75.9–85.7%) compared to late onset pNET 60.1% (95% CI 57.0%–63.1%), $p < 0.001$.

CONCLUSIONS

EOPNET constitutes a distinct clinical subgroup marked by younger age, greater racial and ethnic diversity, and higher rates of surgical intervention. Despite comparable tumor characteristics, early-

onset disease is independently associated with improved survival, highlighting the importance of age-specific approaches to pNET management.

ABSTRACT ID 33486

P-10

Racial and Gender Disparities in Neuroendocrine Tumors – A Retrospective Study Using a Single Institutional Database

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BACKGROUND

Neuroendocrine tumors (NETs) have increased in incidence over the past several years and occur more frequently in black Americans for unknown reasons. There are notable survival differences in NETs among racial, ethnic, gender, and socioeconomic groups which may reflect the effect of socioeconomic status on healthcare delivery broadly.

METHODS

Patients diagnosed with any stage NET (ICD-0-3/WHO 2008 histology recode: "8150-8157;8240-8249) of any primary site were identified from 2009 to 2017 using a tumor registry of an NCI-designated Comprehensive Cancer Center. The baseline patient characteristics were examined, and overall survival (OS) was estimated using the Kaplan-Meier method and Cox proportional hazards model with an index date of tumor diagnosis until death. A chi square test of independence was performed to examine the relationship between race and primary site of NET.

RESULTS

784 patients were identified, including 641 white patients and 143 black patients. There was a significant difference in distribution of primary site by race as determined by chi square analysis. Black patients were significantly more likely to have a rectal primary compared to white patients, and less likely to have a pancreatic or lung primary, $X^2(41.73, N=784) = 41.17, p = <.001$. In Cox regression analysis of a subset of 294 patients with lung, pancreatic, small intestinal, or colorectal primary, female gender was associated with longer OS (HR 0.5, 95CI: 0.3-0.8). Pancreatic primary was associated with longer OS compared to small intestine or lung primary (HR: 2, 95CI 1-5).

CONCLUSIONS

In this single institution cohort, black patients had a different distribution of primary site compared to white patients. Female gender and pancreatic primary site were associated with longer OS. Future research should examine for an association between area deprivation index, genomic mutations, or clinical treatment history with survival to further define the reason for survival differences between racial and gender groups.

ABSTRACT ID 33677

O-1

Distinct Sociodemographic, Symptom, and HRQoL Profiles in Early-Onset Neuroendocrine Tumors: Insights from the NET-PRO Study

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BACKGROUND

The incidence of neuroendocrine tumors (NETs) has increased over the past four decades, particularly among young individuals (age <50 years). Data from other malignancies have demonstrated that earlier onset may be associated with distinct disease biology and unique care needs; however similar data among patients with early-onset NETs (EO-NETs) are lacking. We sought to investigate differences in sociodemographic and clinicopathological profiles, HRQoL and symptoms among patients with EO-NETs compared to average-onset NETs (AO-NETs) using a large multi-institutional cohort.

METHODS

The Neuroendocrine Tumors–Patient Reported Outcomes (NET-PRO) study is a prospective, multi-institutional U.S. cohort funded by the Patient-Centered Outcomes Research Institute (PCORI). Adults aged ≥18 years with incident gastroenteropancreatic or lung NETs diagnosed from January

2018 through September 2024 were enrolled. Age at diagnosis was categorized (i) as a continuous variable and (ii) dichotomously using a single cut-point: EO (< 50 years) versus AO (≥ 50 years). Effect sizes were quantified with standardized mean differences (SMDs), and between-group significance was tested. Spearman correlations described how each score of HRQoL or symptoms changed with increasing age.

RESULTS

Among 2340 participants, 617 (26.4%) were EO-NETs and 1721 (73.5%) were AO-NETs (mean age 31.5 years and 61.2 years, respectively). Patients in the EO-NETs cohort were more likely to be female (69% vs 53.5%, $p < 0.001$), Hispanic (6.5% vs 1.6%, $p < 0.001$), Non-Hispanic Blacks (4.4% vs 3.8%, $p < 0.001$) and have localized disease at diagnosis (40.6% vs 38.3%, $p = 0.01$). Younger patients also showed significantly lower mean cognitive functioning (74.4 vs 81.1; SMD = 0.29; $p < 0.001$), emotional functioning (68.0 vs 78.8; SMD = 0.47; $p < 0.001$), physical functioning (86.5 vs 82.4; SMD = 0.20; $P < 0.001$) and social functioning (75.2 vs 79.5; SMD = 0.15; $p < 0.001$) compared to their AO counterparts. Notably, patients in the EO-NETs cohort also experienced significantly higher mean financial burden (30.1 vs 15.8; SMD = 0.48; $p < 0.001$). Younger patients had greater symptom burden across domains, including pain, nausea/ vomiting, insomnia, appetite loss and diarrhea ($p < 0.05$). Spearman correlations were consistent with these findings.

CONCLUSIONS

To our knowledge, this is the first and largest analysis analyzing characteristics, symptom burden and HRQoL among EO-NETs. We found that younger patients with NETs have a unique clinicopathological profile and have notably worse symptom burden and HRQoL across various domains. Recognizing these differences underscores the importance of age-tailored supportive care and ongoing assessment in EO-NETs patient population.

ABSTRACT ID 33490

O-2

Analysis of patient selection for germline testing in early-onset gastroenteropancreatic neuroendocrine neoplasms (GEPNENs) at a single institution

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BACKGROUND

In our previous work, we found a high rate of pathogenic/likely pathogenic germline mutations (PGM) in patients with early-onset GEPNENs (EO-GEPNENs) at UCSF, particularly in pancreatic primaries. However, germline testing practices in EO-GEPNENs have not been standardized. Testing has historically been driven by clinical factors, patient preference, and insurance coverage, but the process is prone to bias and relies on subjective provider assessment. This study characterizes the clinicodemographic features of EO-GEPNEN patients who underwent testing versus those who did not.

METHODS

In this IRB-approved study, we identified 252 EO-GEPNEN patients (age 18–49 at diagnosis, any stage/grade) from 2011–2023. Group differences in categorical and continuous variables were assessed using the Chi-squared and Wilcoxon tests.

RESULTS

Of 252 patients with EO-GEPNENs, 109 (43%) underwent germline testing. Among them, 29 (27%) had a PGM. Tested patients had a median age of 42 years at diagnosis, 55% female, 47% locoregional disease, and 92% well-differentiated tumors. Additional clinicodemographic features are in Table 1:

Characteristic	Not Tested (n=143, 56.7%)	Tested (n=109, 43.3%)	P Value
Age (median [IQR])	42.00 [36.00, 46.00]	43.00 [35.00, 47.00]	0.914
Sex			1
Female	78 (54.5)	60 (55.0)	
Male	65 (45.5)	49 (45.0)	
Race			0.074
White	86 (66.7)	82 (78.1)	
Non-White	43 (33.3)	23 (21.9)	
Suspected genetic syndrome	10 (9.2)	21 (19.3)	0.052
Other cancers besides NEN	14 (10.3)	18 (17.1)	0.173

Primary Tumor Site			
GI	70 (49.0)	50 (45.9)	0.721
Pancreas	73 (51.0)	59 (54.1)	
Grade at Diagnosis			
G1/G2 NET	108 (75.5)	82 (75.2)	0.036
G3 NET	3 (2.1)	12 (11)	
G3 NEC	8 (5.6)	6 (5.5)	
Unknown	24 (16.7)	9 (8.3)	
Metastatic Disease	79 (56.4)	82 (75.2)	0.003

CONCLUSIONS

EO-GEPNEN incidence is rising, but its association with PGMs is unclear. At UCSF, 43.3% of patients underwent germline testing, with 26.6% harboring a PGM. The tested population was enriched for G3 and stage IV disease, with no significant differences in age, sex, site, second cancers, or race, though our data suggest more suspected genetic syndromes in tested patients and more non-White patients in the non-tested group. Clinicodemographic features by PGM status will be presented. Further work is needed to define testing indications and assess downstream implications.

ABSTRACT ID 33483

O-3

Clinical Features and Outcomes of Small and Very Small Pancreatic Neuroendocrine Tumors

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BACKGROUND

Pancreatic neuroendocrine tumors (PNETs) are being detected with increasing frequency. Incidental PNETs are often stage I lesions defined by a size less than 20mm. Data are limited regarding optimal diagnostic, surveillance, and treatment pathways, particularly for incidental lesions <10mm in size. The aim of this study is to describe the clinical features of patients who present with stage I PNETs and compare clinical features and outcomes of small (11-20mm) and very small (\leq 10mm) lesions.

METHODS

Patients with localized neuroendocrine tumors \leq 2cm in size were retrospectively identified using ICD-O-3 topographical (C25.0-4,C25.7-9) and histology (8150-8153,8155,8240,8241,8246) codes from a single cancer center database from 1992 to 2022. Tumors were characterized as very small (\leq 10mm) and small (11-20mm). Univariate analysis was performed to compare lesion characteristics and clinical outcomes.

RESULTS

330 patients were identified including 116 (35.2%) \leq 10mm and 214 (64.8%) 11 to 20mm in size with significant increase in incidence over the study period. There was no significant difference in Ki67 scores in very small (median 2.0%, IQR 1.2-3.5%) and small (median 2.0%, IQR 1.0-3.5%) lesions ($p=0.674$). The proportion of moderately to poorly differentiated lesions was significantly higher in lesions 11 to 20mm in size than 0 to 10mm (29.9% vs. 19.0%, $p = 0.031$). 5 (1.5%) poorly differentiated tumors were seen with clinical details highlighted in Table 1. 5-year survival was similar (93.1% small vs. 90.1% very small, $p=0.335$), however very small lesions were associated with a lower 10-year survival (90.3% vs 81.3%, $p = 0.026$). Of the 21 patients with very small lesions deceased by 10 years, only 1 (4.8%) was related to underlying PNET. Cause of death was related to non-index malignancy in 7(33.3%) patients and non-cancer related in 13(61.9%).

Table 1. Clinical features of poorly differentiated lesions \leq 20mm in size

Size	Presentation	Imaging	Management	Status
10mm	Unknown	Unknown	Unknown	Alive
15mm	Unknown	Unknown	Unknown	Unknown
17mm	Hypoglycemia	Hyperenhancing mass	Surgery	Alive
17mm	MEN1 with multiple lesions	Multiple hyperenhancing mass lesions	Surgery	Alive
18mm	Pancreatitis	Hyperenhancing mass, Irregular Borders, PD obstruction	Surgery, Chemotherapy	Deceased at 1 year

CONCLUSIONS

Small and very small PNETs are being diagnosed with increasing frequency. Very small lesions are unlikely to harbor aggressive histology or impact survival, particularly in asymptomatic patients without hereditary disease.

ABSTRACT ID 33406

O-4

Real World Outcomes with Chemotherapy and Immunotherapy in Metastatic Poorly Differentiated Gastroenteropancreatic Neuroendocrine Carcinomas

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BACKGROUND

Gastroenteropancreatic poorly differentiated neuroendocrine carcinomas (GEP-NECs) are aggressive cancers where cytotoxic chemotherapy (chemo) is the backbone of management. While the addition of immune checkpoint inhibitors (IOs) to chemo is recommended for lung NEC, evidence regarding IO efficacy in GEP-NECs is limited. We explore outcomes with systemic therapies in patients with metastatic GEP-NECs.

METHODS

Cases of metastatic GEP-NECs from 2018 and 2021 were identified within the USA's National Cancer Database (NCDB). Overall survival (OS) was analyzed using Kaplan-Meier estimations and Cox proportional hazards regression.

RESULTS

2,280 cases of metastatic GEP-NECs treated with chemo with survival data available were identified. Of these, 1748 (76.7%) received chemo alone, and 532 (23.3%) received chemo plus IO (ChemoIO). Patients treated with chemoIO had prolonged OS versus chemo alone (10.51 months [m] vs. 8.31 m; HR, 0.77; 95% CI, 0.69 – 0.85; $p < 0.001$). The association was significant in all histologies (small cell, $p < 0.001$; large cell, $p = 0.04$; others, $p = 0.01$) and in some primary site subgroups (colorectal&anal, $p < 0.001$; gastroesophageal, $p = 0.02$; others&unknown, $p = 0.01$; biliary, $p = 0.78$; pancreas, $p = 0.48$; small intestine, $p = 0.73$). The association was significant on multivariable analysis with select clinicopathological variables and comorbidity index ($N = 2,235$; Table).

Table: Multivariable Cox regression – select results

	HR (95% CI)	p-value
Chemo+IO (vs. Chemo alone)	0.71 (0.64 – 0.80)	<0.001
Age	1.004 (1.0003 – 1.008)	0.03

Primary (Ref: Colorectal&Anal)		
Gastroesophageal	0.86 (0.76 – 0.98)	0.02
Biliary	0.65 (0.53 – 0.80)	<0.001
Small Intestinal	0.65 (0.48 – 0.89)	<0.001
Pancreas	0.75 (0.66 – 0.85)	<0.001
Others (& Unknown)	1.00 (0.80 – 1.26)	0.97
Bone Mets (vs. Absent)	1.00 (0.80 – 1.26)	0.005
Liver Mets (vs. Absent)	1.37 (1.22 – 1.54)	<0.001
Lung Mets (vs. Absent)	1.24 (1.10 – 1.41)	<0.001
Primary Surgery (vs. No Surgery)	0.64 (0.55 – 0.73)	<0.001

CONCLUSIONS

Despite the limitations of the NCDB, combination chemoIO showed improved survival vs. chemo in metastatic GEP-NECs. Results of ongoing trials (NCT05058651) are awaited.

ABSTRACT ID 33419

O-5

Recurrent Tympanic Paragangliomas: An Overview of Institutional Experience

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BACKGROUND

Tympanic paragangliomas (TPGLs) are rare and mostly slow growing head and neck tumors of the lateral skull base. TPGLs are neuroendocrine tumors arising from neural crest-derived cell clusters. Recurrence rates in the literature have been reported at 0 to 15%, depending on cohort size and mean follow up time.

METHODS

Single-institution chart review of tertiary care hospital from 2009-2025.

RESULTS

Among the cohort of 43 patients diagnosed with TPGLs from 2009 to 2025, all patients had a unilateral TPGL, 40 (91%) were women and 8 had recurrent TPGLs (18%). The primary TPGLs were diagnosed from 1994 to 2019, and the recurrent TPGLs were diagnosed between 2010 and 2024. The mean age at the primary TPGL diagnosis was 51.5 years (range 18 to 76 years). The mean age at the recurrence was 62.5 years (range 19 to 83 years). The mean interval of recurrence was 11 years (range 1-20 years). Among this cohort, one patient with recurrent TPGL had an additional pheochromocytoma diagnosed at the same time as the TPGL, and one patient without recurrent TPGL had multiple additional HNPGLs including a facial nerve, bilateral carotid and bilateral vagal PGLs. All patients underwent surgery for their primary TPGLs. For recurrent TPGLs, six patients (75%) had surgical resection while two patients opted for observation. Among the six patients who underwent surgical resection, three required tympanoplasty due to adherent tumor, two required an extensive skull base approach due to expansile tumor growth requiring an infratemporal fossa approach with a fat graft, and one underwent a radical mastoidectomy with closure of the external auditory canal due to extensive recurrent tumor and cholesteatoma. Among the eight patients with recurrent TPGLs, four had genetic testing and one had SDHD mutation. Two recurrent TPGLs were considered biochemically active with either elevated metanephrines or catecholamines. Surgery remained the definitive treatment for both primary and recurrent TPGLs.

CONCLUSIONS

The current practice at our institution has evolved to have all patients with TPGLs go for genetic and biochemical evaluation. We also have weekly multidisciplinary meetings to discuss the management. Given the high rate (18%) and long interval (mean 11 years) of recurrence, we believe that TPGLs require long-term follow-up.

ABSTRACT ID 33438

NANETS 2025 Symposium Abstracts

O-6

Effect of GLP-1 receptors agonists on progression free survival in patients with well differentiated neuroendocrine tumors treated with lanreotide

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BACKGROUND

The use of GLP-1 receptor agonists (GLP-RA) is steadily increasing in the US, especially for diabetes and weight loss management, yet their effects on neuroendocrine tumors (NET) remain unclear. Considering that diabetes and cancer become more prevalent in older population, understanding the relationship between GLP-RA with NET also becomes more relevant given multiple potential biochemical interactions. While GLP-RA are currently contraindicated patients with medullary carcinoma of the thyroid, preclinical studies have suggested that other primary NETs with high GLP1R expression may have increased growth in response to GLP-RA. This study explores GLP-RA use amongst patients with NETs in a retrospective data set.

METHODS

A retrospective cohort study was conducted at a large cancer center in New York City to evaluate NET patients with and without GLP-RA exposure. The study was IRB-approved, and patients were identified by chart review between January 2023 and March 2024. Exclusion criteria included high-grade neuroendocrine carcinoma, poorly differentiated neuroendocrine carcinoma, pheochromocytoma, and paragangliomas.

RESULTS

A total of 588 patients were included. 58.5% were females and 62% identified as white race. The mean age was 62.19 ±13.60. Of the 48 individuals (8.16%) exposed to GLP-RA, 63% initiated treatment after their NET diagnosis. 57% of the patients on GLP-RA had localized disease with grade 1 tumors and 72% did not have functional hormonal syndrome. They were started on GLP-RA mostly for diabetes control (67%). 29 individuals (59%) in the exposed group were treated with lanreotide and had a median [95% CI] progression free survival of 781 days [357; 1218].

CONCLUSIONS

Of our total 588 patients with NET in this study, only a small percentage (8.16%) had been treated with GLP-RA, which is likely due to the lack of data in its use in these patients. More research needs to be done in the safety and efficacy of GLP-RA use in this patient population.

ABSTRACT ID 33442

O-7

Treatment Sequence in Advanced Small Bowel Neuroendocrine Neoplasms: A Simulation Study

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BACKGROUND

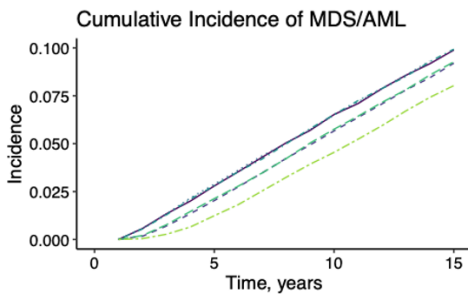
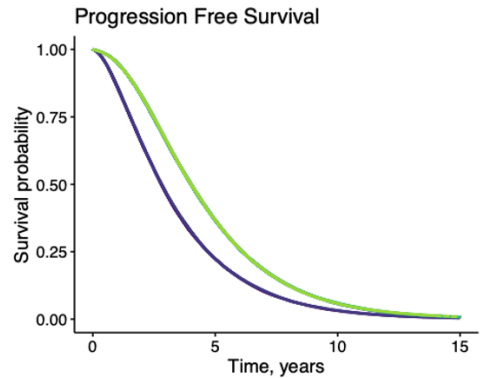
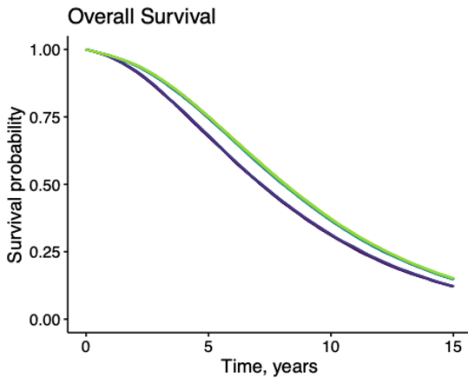
Patients with small bowel neuroendocrine neoplasms (SBNENs) typically receive somatostatin analogues as first-line therapy. Upon progression, options include Peptide Receptor Radionuclide Therapy (PRRT) followed by Everolimus (Eve) or the reverse sequence. However, PRRT increases the risk of life-limiting acute myeloid dysplasia/myelodysplastic syndrome AML/MDS. In May 2025, the FDA approved Cabozantinib (Cabo) for previously treated SBNENs. The optimal sequencing of these therapies remains a subject of clinical debate.

METHODS

We conducted a clinical decision analysis comparing six strategies in patients with SBNENs who progress after first-line treatment: i) no access to Cabozantinib (PRRT→Eve and Eve→PRRT); ii) Cabozantinib at the third line (PRRT→Cabo→Eve and Ev→Cabo→PRRT); iii) Cabozantinib at the fourth line (PRRT→Eve→Cabo and Eve→PRRT→Cabo). We compared the treatment strategies using a discrete event simulation model designed to reflect real-world patient demographics (50% female; mean age of 63 years, standard deviation of 9 years). Patients who experience progression on all lines of therapy are assumed to receive salvage treatment and may ultimately die from disease progression. In any strategy, patients initiating PRRT are at risk of developing and dying from AML/MDS. All patients have sex- and age-specific risks of mortality from other causes. Incidence functions were derived from published literature and supplemented by expert opinion.

RESULTS

Figure 1 presents overall survival (OS), progression-free survival (PFS), and 5-year cumulative incidence of MDS/AML for the six treatment strategies. Incorporating cabozantinib increases PFS by approximately 1.2 years and OS by about 0.9 years on average. Delaying PRRT lowers the risk of MDS/AML, with the Eve→Cabo→PRRT strategy showing the lowest incidence (0.018). However, MDS/AML risk has minimal influence on overall survival. Among strategies including cabozantinib, the difference in PFS and OS between early (second-line) and delayed (fourth-line) PRRT use is less than two months



Strategy	MDS/AML IR, 5y	Median PFS	Median OS
#1 PRRT-Eve	0.035 (0.034-0.037)	2.80 (2.77-2.82)	7.13 (7.07-7.19)
#2 Eve-PRRT	0.027 (0.026-0.029)	2.81 (2.79-2.84)	7.17 (7.11-7.23)
#3 PRRT-Eve-Cabo	0.036 (0.034-0.038)	4.00 (3.97-4.03)	8.04 (7.98-8.11)
#4 PRRT-Cabo-Eve	0.035 (0.034-0.037)	4.01 (3.98-4.04)	8.07 (8.02-8.13)
#5 Eve-PRRT-Cabo	0.028 (0.026-0.029)	4.03 (4.00-4.06)	8.07 (8.01-8.13)
#6 Eve-Cabo-PRRT	0.018 (0.017-0.019)	4.01 (3.98-4.04)	8.15 (8.09-8.22)

Strategy — #1 PRRT-Eve #3 PRRT-Eve-Cabo #5 Eve-PRRT-Cabo
 — #2 Eve-PRRT #4 PRRT-Cabo-Eve #6 Eve-Cabo-PRRT

CONCLUSIONS

Adding cabozantinib improved survival outcomes, increasing PFS and OS by over a year. Sequencing PRRT earlier or later had minimal survival impact. Delaying PRRT reduced MDS/AML risk, with the Eve→Cabo→PRRT strategy offering the best overall balance of efficacy and safety.

ABSTRACT ID 33452



O-8

Symptom burden and outcomes among patients with early-onset and average-onset neuroendocrine neoplasms.

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BACKGROUND

The incidence of neuroendocrine neoplasms (NENs) is rising, particularly among younger individuals. However, data comparing clinical features and outcomes between early-onset NENs (EO-NENs) and average-onset NENs (AO-NENs) remain limited. Using a large national hospitalizations database, we aimed to compare patient characteristics, symptom burden, and clinical outcomes between these groups.

METHODS

We identified all hospitalizations involving patients with neuroendocrine neoplasms (NENs) in the National Inpatient Sample (NIS) from 2016 to 2020 using ICD-10 codes. Hospitalizations were stratified into an early-onset cohort (age < 50 years) and a late-onset cohort (age ≥50 years). Demographic characteristics, symptom burden, treatment interventions, and clinical outcomes were extracted and compared between cohorts. Independent sample t-tests were used for continuous variables, and chi-squared tests were used for categorical variables. A p-value of < 0.05 was considered statistically significant.

RESULTS

There were 22,555 hospitalizations with EO-NENs (median age 42.0) and 149,470 with AO-NENs (median age 67.0), respectively. The EO-NENs cohort had more females (55.3% vs. 49.3%, $p < .001$), a lower Charlson Comorbidity Index (CCI) (6.3 vs. 9.7, $p < .002$), and a greater likelihood of private insurance as primary payer (59.3% vs 28.3%, $p < .001$). Hospitalizations for EO-NENs were more commonly associated with tumors of intestinal and thymic origin ($p < .001$). EO-NENs hospitalizations experienced a substantially higher symptom burden, including more nausea/vomiting (8.6% vs. 4.7%, $p < .001$), constipation (13.9% vs. 10.8%, $p < .001$), abdominal pain (1.9% vs 1.3%, $p < .001$) and anxiety (18.3% vs. 14.0%, $p < .001$). However, AO-NENs hospitalizations had higher rates of acute complications (heart failure, liver failure, sepsis) and in-hospital mortality (6.2% vs. 4.0%, $p < .001$). Early-onset hospitalizations underwent more chemotherapy (6.1% vs. 4.2%, $p < .001$) and surgical resection.

CONCLUSIONS

We demonstrate significant clinical differences between EO- and AO-NENs, notably a higher symptom burden and relatively favorable outcomes. These data add to a growing body of literature indicating that EO-NENs characterize a clinically distinct subset. These findings underscore the need for age-adapted care pathways and further research into the unique biology that underpins the distinct clinical features of EO-NENs.

ABSTRACT ID 33465



Neuroendocrine neoplasms diagnosed in the setting of inflammatory bowel disease: An appraisal of published literature and proposed management algorithm.

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BACKGROUND

Patients with inflammatory bowel disease (IBD) are at higher risk of developing malignancies, including neuroendocrine neoplasms, but the exact specifics of that are not well known. We reviewed the existing literature to better map the evidence surrounding this phenomenon.

METHODS

We performed a PubMed search from inception to September 2024 for patients with gastrointestinal neuroendocrine neoplasms (NENs) and either Crohn's disease (CD) or ulcerative colitis (UC). Eligible studies included abstracts, case reports, case series, and data from larger retrospective IBD cohorts. We extracted demographic and clinical information, including tumor grade, location, metastatic status, and mode of detection.

RESULTS

We identified 67 case studies with data available for a total of 108 patients (61.1% male), ranging from 14 to 87 years of age. The median duration from IBD diagnosis to NEN detection was 13 years. Fifty-five (50.9%) patients had Crohn's disease (CD) and 53 (49.1%) had UC. UC patients were older at initial NEN diagnosis (mean: 48.7 years) than CD patients (mean: 40.1 years) and had a higher metastatic rate (39.6% vs. 18.2%). In general, most NENs were low-grade (69.4%), while 20.4% were high-grade and 8.3% were mixed. The most common tumor locations were the rectum (29.6%) and appendix (27.8%), with rectal and colonic NENs more prevalent in UC and small bowel or appendiceal NENs more common in CD. At diagnosis, 71.3% of patients had localized disease. For high-grade NENs, 86.4% of cases were metastatic, compared to 9.3% for low-grade tumors. Only 10.2% of NENs were detected via endoscopic surveillance.

CONCLUSIONS

Our findings reinforce the need for increased awareness and tailored surveillance strategies in IBD, particularly given the distinct tumor locations in UC versus CD and the high metastatic potential of high-grade tumors. Surveillance may be most beneficial after 10 years of IBD or around 44 years of age, focusing on rectal lesions in UC and appendiceal or small bowel lesions in CD. Future studies are needed to solidify optimal imaging protocols and elucidate mechanisms by which chronic inflammation fosters NEN development.

O-10

Expanding Access to Neuroendocrine Tumor Care: Early Impact of the University of Utah NET Destination Care Program

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BACKGROUND

Neuroendocrine neoplasms (NENs) are rare cancers that require multidisciplinary management, yet access to specialized care remains limited—particularly in rural and frontier regions. These disparities can delay diagnosis, hinder coordinated care, and limit access to clinical trials. In 2022, the University of Utah launched the NET Destination Care Program to address these barriers through centralized referrals, integrated care delivery, and regional clinician engagement.

METHODS

Data on new and follow-up visits for patients with NENs were extracted from the University of Utah's Enterprise Data Warehouse using ICD-10 codes. Referrals were tracked using a disease-specific EPC dashboard from January 2019 through December 2024. All data were de-identified before access and analysis. Patient ZIP codes were used to calculate travel distance, and virtual visit volumes were collected starting in 2020. Demographic data were analyzed to evaluate equity in access.

RESULTS

Since program implementation, NET referrals and follow-up visits have increased substantially. Comparing pre-program years (2019–2021) to post-implementation years (2022–2024), the average number of new referrals rose from 180 to 258 per year (+43%), and follow-up visits from 1,330 to 1,936 per year (+46%). Direct year-to-year comparison shows new referrals increased from 158 in 2019 to 279 in 2024—a 77% increase. Follow-up visits more than doubled from 1,143 to 2,355 (+106%) over the same period. Virtual visits rose from 0 in 2019 to 573 in 2024, helping address geographic barriers. The proportion of patients traveling over 200 miles more than doubled for both new referrals and total visits. Access for Hispanic/Latino patients improved as well, rising from 1.0% of patients in 2019 to 4.6% in 2024.

CONCLUSIONS

The NET Destination Care Program at the University of Utah has substantially expanded access to expert care, increasing patient volumes, enabling virtual care delivery, and extending reach across a large geographic area. Enhanced access for Hispanic/Latino patients and those traveling long distances underscores the program's role in reducing healthcare disparities. This model offers a scalable framework for rare cancer centers aiming to improve regional equity and connectivity.

ABSTRACT ID 33484

O-11

Preventing Early Bioprosthetic Valve Deterioration in Carcinoid Heart Disease: A Case Series and Perioperative Management Strategy

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BACKGROUND

Carcinoid heart disease (CHD), a fibrotic deterioration of primarily right-sided heart valves due to prolonged exposure to serotonin and other vasoactive substances, is a common complication in the presence of carcinoid syndrome (CS). While valve replacement improves symptoms and survival, early bioprosthetic valve deterioration has been observed in patients with persistently elevated serotonin levels. Strategies to reduce serotonin burden may prevent postoperative early complications.

METHODS

This case series examines all patients with CHD who underwent surgical replacement of the tricuspid and pulmonic valves, treated with somatostatin analogs (lanreotide or octreotide). After one patient has experienced rapid deterioration of a newly implanted bioprosthetic pulmonic valve within first 4 weeks postoperatively, with significant thickening of the leaflets likely due to uncontrolled serotonin levels, we have implemented a more aggressive perioperative control of serotonin in patients with suboptimal control of the carcinoid syndrome (predominantly diarrhea). These strategies included the initiation of telotristat ethyl, hepatic tumor embolization or cytoreductive surgeries prior to cardiac surgery. Biomarkers including urinary 5-hydroxyindoleacetic acid (5-HIAA) and NT-proBNP were monitored pre- and post-operatively.

RESULTS

Of 25 patients with CHD that underwent right-sided valve replacement, 6 patients underwent a serotonin reducing strategy before the cardiac surgery. One patient underwent hepatectomy, one patient underwent hepatic tumor embolization in addition to telotristat ethyl and four received telotristat ethyl (250 mg TID). Valve function remained intact on follow-up echocardiographic studies at 3, 6, 9 and 12 months.

CONCLUSIONS

Increased serotonin level can contribute to early bioprosthetic valve failure in patients with CHD. This case series highlights the importance of aggressive perioperative serotonin reduction in patients undergoing valve surgery. The addition personalized serotonin reduction strategies can result in stable valve function and prevent further deterioration. These findings support an individualized multidisciplinary approach to optimize surgical outcomes in CHD.

ABSTRACT ID 33497

O-12

Molecular and Clinical Profiling of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): An Analysis of the Oncology Research Information Exchange Network Database

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BACKGROUND

The incidence of neuroendocrine tumors (NETs) is approximately 7 per 100,000 persons and rising. By location, tumors located in the gastroenteropancreatic (GEP) region, particularly midgut NETs, are most common. The Oncology Research Information Exchange Network (ORIEN) database contains complementary clinical, genomic, and transcriptomic profiling, providing opportunities to identify novel associations between molecular features and clinical outcomes.

METHODS

Survival analyses were performed using the Log-rank testing, and clinical features were evaluated using Wilcoxon and chi-squared tests. Mutational analyses utilized sample-level enrichments from whole exome sequencing data, and statistical tests were performed using the one-sided Fisher Exact test. Transcriptomic analyses utilized a student's t-test. We reviewed well-differentiated GEP-NET samples of these primary sites: pancreatic (n=121), small bowel (n=89), gastric (n=15), and colorectal (n=9). A p-value <0.05 was considered significant.

RESULTS

Across all GEP-NETs, the most common somatic mutations were *TTN* (29%), *MUC16* (25%), *TGIF2LX* (23%), *CCDC168* (21%), *MUC17* (18%), and *MEN1* (18%). The most common copy number amplifications were *MUC3A* (61%), *PRSS2* (32%), *ROCK1P1* (30%), and *MUC19* (30%).

NETs of small bowel origin had significantly higher rates of M1 stage than pancreatic NETs (p=0.02). Quantitative MSI by WES was significantly higher in pNETs compared to sbNETs (p<0.001). *MEN1* was the most common mutation in pNETs (35.6%). Mutations in *ARGAP* (23%), *CEP126* (22%), *MMP20* (17%), *CASP5* (17%), *DDI1* (15%), and *TRPC6* (15%) were the most common in sbNETs and none of these were

frequent in pNETs.

pNETs with a mutation in *ATRX* and/or *DAXX* had significantly higher rates of M1 disease than *ATRX/DAXXwt* pNETs ($p=0.029$). Specifically, the liver was a more common site of metastatic disease in *ATRX/DAXXmut* pNETs compared to *ATRX/DAXXwt*. More than 200 distinct mRNA expression levels by WES were significantly different between *ATRX/DAXXmut* and wt, potentially providing additional information on the prognostic role of *ATRX/DAXX* mutations in pNETs.

CONCLUSIONS

We report the first clinical, genomic, and transcriptomic analysis of ORIEN GEP-NET cases. These findings create multiple avenues for further investigation and reinforce the value of multi-institutional consortia such as ORIEN in deepening our knowledge of well-differentiated NETs.

ABSTRACT ID 33678



O-13

Peculiar Prostate Peculiarity: Exploring Ectopic Cushing's Disease in Prostate Neuroendocrine Carcinoma

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BACKGROUND

Neuroendocrine tumors (NETs) of the prostate are rare malignancies, accounting for less than 1% of all prostate cancers. These tumors can occasionally produce adrenocorticotrophic hormone (ACTH), leading to ectopic Cushing's syndrome. Diagnosing a neuroendocrine tumor of the prostate that produces ACTH is challenging due to its rarity and atypical presentation. Here we discuss a case of a patient with metastatic prostate cancer who exhibited signs and symptoms of Cushing's syndrome and was subsequently found to have paraneoplastic ACTH production. The patient was subsequently treated with oral Ketoconazole and experienced improvement in symptoms.

METHODS

A 78 year old male presented with complaint of severe generalized weakness, exertional dyspnea and worsening lower body edema. Comprehensive history and physical were obtained. Past medical history included OSA, HTN, HLD, and known prostate neuroendocrine cancer. The patient additionally reported lower limb swelling, abdominal distension and weight gain of approximately 20 lbs over the course of one year. Septic workup, echocardiogram, and chest x-ray were all functionally negative. Clinical examination of cardiovascular and respiratory systems were also negative. Patient disclosed that he had been diagnosed with prostate adenocarcinoma in 2019 via MRI showing extensive abdominal metastases as well as PIRADS 5 lesions throughout the prostate itself. The patient accordingly underwent castration and ADT. Transperineal biopsy was consistent with high grade neuroendocrine carcinoma- small cell type, Ki67 > 90%.

RESULTS

When the patient was noted to have 24-hour urine cortisol of 2300, elevated random serum cortisol and ACTH, ectopic Cushing's Syndrome was confirmed and suspected to be ACTH dependent. Options for possible ACTH suppression included metyrapone and ketoconazole. The patient was started on Ketoconazole 600 mg BID via tablet and noted significant improvement in symptoms within 48 hours. Repeat urine cortisol was shown to be 1100. Given the patient's improvement, he was discharged to SAR with the goal of returning to chemotherapy afterward.

CONCLUSION

The diagnosis requires a high index of suspicion, especially in patients with Cushing's syndrome without obvious adrenal or pituitary causes. Treatment typically involves managing the hormonal effects and addressing the underlying tumor through surgical resection, radiation, or systemic

therapies such as chemotherapy or peptide receptor radionuclide therapy (PRRT). In this instance, the patient's paraneoplastic condition was suppressible. However, the standard of care mandates a multidisciplinary approach for accurate diagnosis and effective management.

ABSTRACT ID 33679

T-1

NETTER-3: [¹⁷⁷Lu]Lu-DOTA-TATE in patients with newly diagnosed, Grade 1/2 (Ki-67 <10%) advanced gastroenteropancreatic neuroendocrine tumors and high disease burden

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BACKGROUND

Patients with newly diagnosed, Grade 1 (G1) and 2 (G2), somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are typically treated with somatostatin analogs (SSAs); however, the optimal treatment for patients with high disease burden who are at elevated risk of rapid deterioration and disease progression is unknown, and prospective clinical data are lacking. NETTER-3 will evaluate the efficacy and safety of the radioligand therapy [¹⁷⁷Lu]Lu-DOTA-TATE (¹⁷⁷Lu-DOTATATE) in patients with high disease burden who were newly diagnosed with G1 and G2 (Ki-67 < 10%) advanced GEP-NETs.

METHODS

NETTER-3 (NCT06784752) is a Phase III, open-label, randomized study of ¹⁷⁷Lu-DOTATATE + octreotide long-acting release (LAR) vs octreotide LAR in patients aged ≥12 years with newly diagnosed (≤6 months), well-differentiated, G1 and G2 (Ki-67 <10%) advanced GEP-NETs and high disease burden (investigator's opinion; guided by tumor bulk, liver involvement, disease spread, and symptoms due to tumor burden or hormone excess). Prior systemic therapy is not permitted (except ≤4 prior cycles of SSAs without disease progression). Radioligand imaging using locally approved SSTR imaging agents ensures SSTR uptake on all target lesions. An estimated 240 patients will be randomized 1:1 to receive either ¹⁷⁷Lu-DOTATATE (7.4 GBq × 4 Q8W) + octreotide LAR (30 mg Q8W during treatment with ¹⁷⁷Lu-DOTATATE then Q4W thereafter) or octreotide LAR (30 mg Q4W) until disease progression. Randomization will be stratified by NET grade (G1 vs G2) and origin (pancreas vs other). The primary endpoint is progression-free survival based on blinded central review according to RECIST v1.1. A key secondary endpoint is time to deterioration in selected quality-of-life domains; other secondary endpoints include objective response rate, disease control rate, duration of response, overall survival,

and safety. Dosimetry and pharmacokinetics of ^{177}Lu -DOTATATE will be assessed in a subset of patients.

RESULTS

NETTER-3 is being conducted in North America, Europe, and Asia.

CONCLUSIONS

N/A

ABSTRACT ID 33272



T-2

STELLAR-311: A randomized phase 2/3 study of zanzalintinib versus everolimus in patients with previously treated advanced neuroendocrine tumors

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BACKGROUND

Targeted therapy options for patients with previously treated neuroendocrine tumors (NETs) include the mammalian target of rapamycin (mTOR) inhibitor everolimus and the vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) sunitinib and cabozantinib. Zanzalintinib, a novel, oral, multi-targeted inhibitor of VEGFR, MET, and the TAM (TYRO3, AXL, and MER) kinases, has a similar kinase inhibition profile to cabozantinib but has a shorter half-life and has shown preferential in vivo tumor distribution. In early-stage clinical studies, zanzalintinib has demonstrated promising antitumor activity and a consistent safety profile across multiple solid tumors. Based on these attributes, STELLAR-311 was designed to evaluate the efficacy and safety of zanzalintinib versus everolimus in patients with locally advanced or metastatic NETs.

METHODS

STELLAR-311 (NCT06943755) is a multicenter, randomized, open-label, phase 2/3 study. Key eligibility criteria include age ≥ 18 years; locally advanced/unresectable or metastatic, well-differentiated, grade 1–3 NET originating from the gastrointestinal tract, lung, pancreas, thymus, or other primary sites; measurable disease per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1); and documented radiographic disease progression per RECIST v1.1 within 12 months before randomization. Patients must have received prior systemic treatment based on the site of the NET and functional status (pancreatic NET and nonfunctional extra-pancreatic NET, up to one prior line; functional extra-pancreatic NET, one prior line). Somatostatin analogs do not count toward the requirement of a prior line of systemic therapy. Previous treatment with an mTOR inhibitor or VEGFR-TKI is not permitted.

Patients will be randomized to either once-daily oral zanzalintinib or everolimus. Planned enrollment is 440 patients. The primary endpoint is progression-free survival (PFS) by blinded independent central review (BICR). Secondary endpoints include investigator-assessed PFS; overall survival; BICR- and investigator-assessed objective response rate, duration of response, and disease control rate; quality of life; and safety.

RESULTS

STELLAR-311 is open and enrolling patients.

CONCLUSIONS

N/A

ABSTRACT ID 33270



T-3

Obixtamig (BI 764532) in relapsed/refractory delta-like ligand 3 (DLL3)-high extrapulmonary neuroendocrine carcinoma: Phase II DAREON®-5 dose-expansion trial in progress

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BACKGROUND

Patients with relapsed/refractory extrapulmonary neuroendocrine carcinoma (epNEC) have poor outcomes with currently available therapies. DLL3 is expressed on the surface of many epNEC cells, offering a promising therapeutic target. Obixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager that binds simultaneously to CD3 on T-cells and to DLL3 on tumor cells, resulting in immune-mediated tumor cell lysis. In an ongoing first-in-human Phase I trial (NCT04429087), obixtamig monotherapy had promising efficacy in patients with DLL3+ small-cell lung cancer (SCLC), epNEC or large-cell NEC of the lung (LCNEC-L) and a manageable toxicity profile, justifying further clinical investigation. The Phase II DAREON®-5 trial (NCT05882058) is a dose selection and expansion trial of obixtamig monotherapy in patients with histologically confirmed relapsed/refractory SCLC, epNEC or LCNEC-L after prior standard of care. The completed dose selection part evaluated the safety and efficacy of two obixtamig doses in patients with relapsed/refractory SCLC, epNEC or LCNEC-L. We describe the expansion part of the study that is currently enrolling.

METHODS

The expansion part of DAREON®-5 is assessing obixtamig antitumor activity at the selected dose for expansion in patients with centrally assessed DLL3-high expressing epNEC. DLL3-high is defined as ≥50% of evaluable tumor cells with moderate to strong membrane and/or cytoplasmic DLL3 staining using the VENTANA DLL3 (SP347) assay. Eligible patients have relapsed/refractory, advanced/metastatic, histologically confirmed DLL3-high epNEC after prior platinum-based chemotherapy (≥1 lines of therapy). Patients will receive intravenous obixtamig infusions as step-up doses followed by the target dose, which was defined in the dose selection part of the trial. The primary endpoint is objective response per RECIST v1.1, assessed by blinded independent central review. Secondary endpoints include duration of objective response, progression-free survival, disease control rate,

overall survival, treatment-emergent adverse events, and patient-reported outcomes. The planned enrollment for the expansion cohort is ~50 patients recruited from the following countries: Belgium, China, Germany, Japan, South Korea, Spain, UK, and USA.

RESULTS

N/A

CONCLUSIONS

N/A

ABSTRACT ID 33389



T-4

CAREFNDR: Phase 3, Randomized, Placebo-Controlled Study of Paltusotine in Adults With Carcinoid Syndrome Due to Well-Differentiated Neuroendocrine Tumors

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BACKGROUND

Paltusotine is a once-daily, oral, nonpeptide, selective SST2 receptor agonist in development for the treatment of acromegaly and carcinoid syndrome (CS). In a phase 2, open-label, dose-ranging study, paltusotine reduced the frequency and severity of CS symptoms and was well tolerated (NCT05361668).

METHODS

CAREFNDR is a phase 3, multicenter, randomized, parallel-group, placebo-controlled trial to evaluate the symptom control and safety of paltusotine in patients with CS due to well-differentiated neuroendocrine tumors (NETs). The study will enroll patients with documented, grade 1-2 NETs with CS who exhibit symptoms of flushing with or without frequent bowel movements (BMs). Patients naïve to somatostatin receptor ligands (SRLs) or untreated for ≥ 4 months must have >1 flushing episode/day (14-day average) and plasma 5HIAA or serotonin $\geq 2 \times$ ULN. Patients who had symptom control on SRLs (average ≤ 2 flushing episodes/day and ≤ 3 BMs/day in first 2-week injection cycle) must demonstrate symptom worsening after SRL washout (increase in average flushing episodes/day and >1 flushing episode/day [14-day average]). More than 50% of enrolled patients must meet eligibility criteria for flushing and >3 BMs/day. Patients with significant disease progression within the previous 6 months will be excluded. Approximately 141 patients will be randomized 2:1 to receive paltusotine 80 mg or placebo. The 16-week randomized controlled period will be followed by an open-label extension (OLE) of paltusotine treatment for up to 104 weeks. Antidiarrheal medications and short-acting octreotide are permitted, based on protocol-standardized criteria. A CS Symptom Diary of 7 of the most impactful CS symptoms will be completed daily during screening and the randomized controlled period, and periodically throughout the OLE. The primary endpoint will be the change from baseline to Week 12 in the number of flushing episodes/day (14-day average) for paltusotine versus placebo. The key secondary endpoint will be change from baseline in the number of BMs/day. Other secondary

endpoints will include flushing severity, BM urgency episodes, and percentage of days with short-acting octreotide use. Safety and tolerability assessments will include the incidence of treatment-emergent adverse events and changes in safety parameters. The antitumor effect of paltusotine will also be explored. Global enrollment in CAREFNDR is ongoing.

RESULTS

N/A

CONCLUSIONS

N/A

ABSTRACT ID 33408



T-5

Trial in progress: A Phase Ib/II, Open-label, Multi-center Study of ZL-1310 in Participants with DLL3 positive Neuroendocrine Carcinomas (NECs) and other Selected Solid Tumors

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BACKGROUND

Neuroendocrine carcinomas (NECs) are highly aggressive cancers characterized by poor prognosis and rapid disease progression. Platinum-based chemotherapy, using either cisplatin or carboplatin plus etoposide, is recommended as the first-line therapy for advanced and metastatic disease. No standard regimen after first-line therapy has been established, underscoring the need for additional treatment options. ZL-1310 is an antibody–drug conjugate (ADC) against delta-like ligand 3 (DLL3), an inhibitory Notch pathway ligand, that is highly expressed in neuroendocrine carcinomas (NECs), including small cell lung cancer (SCLC). Recent clinical data from an ongoing Phase 1 study evaluating ZL-1310 in participants with relapsed SCLC shows encouraging results indicated that ZL-1310 is a promising agent for SCLC, and it is valuable to explore its preliminary efficacy and safety in NEC and other solid tumors with DLL3 expression. Based on these promising results, this Phase Ib/II study will evaluate safety, tolerability and the anti-tumor efficacy of ZL-1310 as a single agent in patients with locally advanced or metastatic NEC, and other solid tumors with DLL3 expression.

METHODS

This is an ongoing Phase Ib/II study, currently enrolling in the US and China, to investigate the safety and anti-tumor effect of ZL-1310 in NECs and DLL3-expressing solid tumors. This Phase Ib study enrolls participants in two cohorts. Cohort 1 enrolls participants with previously treated Gastroenteropancreatic (GEP)-NEC, and Cohort 2 enrolls participants with de novo or treatment-emergent neuroendocrine prostate cancer (NEPC), large cell neuroendocrine cancer (LCNEC), SCLC transformed from epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC), other NECs or DLL3-expressing solid tumors. The primary objective in Phase Ib is to evaluate safety and tolerability of ZL-1310 as a single agent, and secondary objective is to evaluate objective response rate (ORR) and disease control rate (DCR) as measured by RECIST v1.1. Other end points are to evaluate progression-free survival (PFS), overall survival (OS), duration of response, pharmacokinetics (PK) and immunogenicity detected by incidence of anti-drug antibodies (ADAs) to

ZL-1310. Tumor response will be assessed every 6 weeks relative to the first dose of ZL-1310 for the first 30 weeks and every 9 weeks thereafter until disease progression by RECIST v1.1.

RESULTS

N/A

CONCLUSIONS

N/A

ABSTRACT ID 33422

T-6

Multicenter Phase 2 Trial of Yttrium-90 Radioembolization with Capecitabine-Temozolomide for Grade 2 Liver-Dominant Metastatic Neuroendocrine Tumors: interim report

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BACKGROUND

Capecitabine and temozolomide (CapTem) are classic radiosensitizers used in combination with radiation therapy for many cancers. A feasibility study of integrated CapTem and Y90 transarterial radioembolization (TARE) for Grade 2 neuroendocrine tumors (NETs) demonstrated tolerance and suggested synergy with PFS of 36 months. This multicenter phase 2 study was initiated to estimate the efficacy of this regimen.

METHODS

Patients with hepatic dominant well-differentiated Grade 2 NET were treated with capecitabine 600 mg/m² twice daily for 14 days and temozolomide 150-200 mg/m² in 2 divided doses on day 10-14 (CapTem regimen), with 14 days between cycles. Simulation angiography with Tc99m-MAA SPECT was performed in the first cycle of CapTem. The dominant lobe was treated on day 7 of the second cycle. Resin Y90 microspheres (SIR-Spheres; Sirtex Medical) were administered using the body surface area method. For bilobar disease, the other lobe was treated in the third or fourth cycle. CapTem is continued until progression or intolerance. Clinical and laboratory assessment are done monthly while on chemotherapy. Imaging is performed every 3 months for 2 years.

RESULTS

Planned accrual of 50 patients at 4 centers was completed between 2022-2025. All patients completed their planned cycle of radioembolization while on CapTem. Median duration on CapTem was 12 months (range 4-16 mo) with 17 patients still on treatment. There have been four grade 4 cytopenias, leading to CapTem hold and dose reduction. Grade 3 toxicities include hematologic (13), GI (6), mucositis (1) and PPE (1).

CONCLUSIONS

Integrated CapTem chemotherapy and radioembolization showed acceptable toxicity, not greater than expected in this cohort of Grade 2 NET patients. Assessment of response and PFS is ongoing.

ABSTRACT ID 33445

T-7

Trial-in-Progress: A Phase 2 Study of ONC206 in Patients with Advanced Pheochromocytoma and Paraganglioma

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BACKGROUND

Treatment options for patients with metastatic pheochromocytoma and paraganglioma (PCPG) are limited following surgical resection and radiotherapy. ONC206 is an inhibitor of dopamine receptor D2 (DRD2) and an agonist of caseinolytic protease proteolytic subunit (ClpP). This small molecule is a potent derivative of dordaviprone that was previously reported to induce responses in patients with PCPG. In vitro models have demonstrated ONC206 efficacy across multiple tumor types, including PCPG. Downstream effects of ONC206 in tumors cells induce disruption of mitochondrial function, degradation of mitochondrial enzymes commonly altered in PCPG such as succinate dehydrogenase, and induction of apoptosis. Phase 1 clinical trials have evaluated the safety and tolerability of multiple doses and schedules of ONC206 in patients with advanced CNS tumors.

METHODS

This open-label, multicenter, two-stage Phase 2 clinical study will evaluate efficacy and safety of ONC206 in adult patients with advanced PCPG who have locally advanced or metastatic disease and have exhausted or declined available therapy. Eligible patients have histologically confirmed PCPG, are ineligible for curative surgery, and have failed prior PCPG therapy or declined further standard systemic therapies. The primary objective is to determine the antitumor activity of ONC206 as assessed by overall response rate by RECIST v1.1 criteria. Imaging will be collected pre-baseline, baseline, and every 12 weeks (± 7 days) thereafter until disease progression. Key secondary objectives include evaluating the effect of ONC206 on PCPG growth trajectory, antihypertensive medication use and dosing, biochemical disease markers (plasma metanephrines), safety, pharmacokinetic parameters, and quality of life assessments. Total anticipated enrollment is 90 patients.

RESULTS

N/A

CONCLUSIONS

N/A

ABSTRACT ID 33447

T-8

NCI 10479: A Phase I Dose Escalation-Expansion Trial of Sunitinib Malate plus Lu 177 Dotatate in SSTR+ Pancreatic Neuroendocrine Tumors

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BACKGROUND

Patients with metastatic or unresectable pancreatic neuroendocrine tumors (PanNETs) have a poor prognosis, even with currently available treatments, with a 5-year overall survival (OS) of less than 20%. Lutetium Dotatate (Lu-177) was approved by the FDA in 2018 for treatment of somatostatin receptor (SSTR)-positive gastroenterohepatic NETs, but it is limited in its efficacy to achieve cytoreduction and provide durable responses. Sunitinib malate, an oral small-molecule tyrosine kinase inhibitor targeting VEGFRs, PDGFRs, and KIT and is also FDA approved as a monotherapy for the treatment of metastatic unresectable PanNETs. There is preclinical, as well as clinical evidence of sunitinib being used as a radiosensitizer with classic radiation, but it has never been combined with a radiolabeled analogue in patients with PanNETs.

METHODS

This is a Phase I dose escalation/expansion study aiming to enroll up to 24 patients across several sites. Eligible patients will be offered fixed dose Lu-177 at 200 mCi for 4 fractions with concurrent oral sunitinib administration initiating on C1D1 and concluding 28 days after the last Lu-177 infusion. Dose escalation applies to sunitinib and will be guided by a 3+3 design to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Once the RP2D has been established, up to 12 more patients will be offered participation in the expansion phase in an attempt to further record antitumor activity and correlation with imaging, tumor markers, as well as Lu-177 dosimetry. Treatment will continue until disease recurrence/progression, unacceptable toxicity, or completion of planned protocol. Key eligibility criteria include age ≥ 18 years, ECOG performance status ≤ 2 , histologic diagnosis of metastatic, unresectable well- or moderately-differentiated SSTR-positive PanNETs of any grade, up to 1 prior treatment except for somatostatin analogues and appropriate baseline hematological parameters. Key exclusion criteria are prior use of sunitinib, Lu-177 or other radiopharmaceuticals, myocardial or cerebrovascular accident within the prior 12 months and left ventricular ejection fraction of $\leq 50\%$. The study uses an 8-week safety window to determine its primary endpoint, which is DLTs during administration of the combination. Secondary endpoints are objective response (ORR), duration of response (DOR), progression-free survival (PFS) and overall

survival (OS), intensity of tumor uptake on pre-treatment SSTR PET and post Lu-177, chromogranin A level response as well as optional dosimetry imaging.

RESULTS

Enrollment is ongoing.

CONCLUSIONS

Clinical trial information: NCT05687123.

ABSTRACT ID 33450



T-9

Alliance A021901: Randomized Phase II Trial of Lutetium Lu 177 Dotatate Versus Everolimus in Somatostatin Receptor-Positive Bronchial Neuroendocrine Tumors

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BACKGROUND

There is an unmet need for treatment of patients with bronchial neuroendocrine tumors (NETs). Everolimus is FDA approved for the treatment of bronchial NETs based on the RADIANT-4 trial. 177Lu-dotatate is approved for the treatment of gastroenteropancreatic NETs based on the NETTER-1 and NETTER-2 trials. However, there has been no previous clinical trial examining 177Lu-dotatate for bronchial NETs.

METHODS

A021901 (NCT04665739) is an Alliance for Clinical Trials in Oncology / ECOG-ACRIN NCTN cooperative group trial that randomizes patients with metastatic bronchial NETs to receive either everolimus (10 mg oral per day until disease progression or unacceptable toxicity) or 177Lu-dotatate (200 mCi intravenous every eight weeks for four cycles). Randomization is 1:1 between the treatment arms within the stratification factor of prior/concurrent somatostatin analog use. Patients must have well- or moderately-differentiated NETs of bronchial origin (i.e. carcinoid) as assessed by local pathology (including one of the following: well- or moderately-differentiated NET, low- or intermediate-grade NET, or carcinoid tumor including typical or atypical carcinoid tumors). Recurrent or locally advanced/unresectable or metastatic disease that is RECIST 1.1 measurable is required. Patients who are treatment naïve (if disease progression in the last 12 months) and those previously treated (if disease progression on prior line of therapy) are eligible. Baseline somatostatin receptor PET images are centrally reviewed prior to randomization to determine that patients have uptake in all measurable lesions above background liver. Patients are followed every 12 weeks until disease progression, and then every 6 months for survival until 5 years following registration. Patients randomized to everolimus have the option to cross over to receive 177Lu-dotatate at time of progression. The study is designed to accrue a minimum of 70 patients.

RESULTS

The primary objective of A021901 is to compare the radiographic progression-free survival of 177Lu-dotatate to that of everolimus. Secondary objectives include comparing overall survival, overall

response rate, and toxicity profiles between the 177Lu-dotatate and everolimus arms. Exploratory endpoints include evaluation of late toxicities (renal dysfunction and marrow toxicity), impact of baseline tumor volume on treatment response and response rate stratified between typical and atypical bronchial NETs. SPECT/CT images after cycle 1 are acquired as part of exploratory analysis.

CONCLUSIONS

A021901 is currently enrolling in 26 sites in the NCTN cooperative group network with ongoing opportunity for additional sites to activate and accrue. Support: U10CA180821, U10CA180882 (Alliance), U10CA180820 (ECOG-ACRIN), <https://acknowledgments.alliancefound.org>.

ABSTRACT ID 33456



T-10

NET RETREAT: a CCTG-SWOG Phase II Study of 177Lu-Dotatate Retreatment vs. Standard of Care in Metastatic GEPNET Patients.

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BACKGROUND

177Lu-DOTATATE is an FDA and Health Canada-approved treatment option for metastatic, progressive GEPNET patients. 177Lu-DOTATATE is now often considered an effective treatment for gastroenteropancreatic neuroendocrine tumor (GEPNET) patients who have progressed on somatostatin analogs (SSA). Despite 177Lu-DOTATATE's effectiveness, many patients will eventually progress. Progression after prior use of PRRT does not necessarily render these tumors resistant to future PRRT treatments. PRRT retreatment strategies have been tested in various European centers where PRRT has been available for the past two decades. Several studies report single institute, non-randomized, retrospective data on PRRT retreatment with varying degrees of efficacy and relatively safe toxicity profiles. Despite a growing body of evidence favoring limited dose PRRT retreatment, as well as real world experience, prospective randomized data is lacking in support of a PRRT retreatment strategy. Prior studies also suffer from a heterogeneous patient population and inconsistent PRRT regimens. NET-RETREAT fulfills an unmet medical need by exclusively studying limited dose retreatment of 177Lu-DOTATATE PRRT in GEPNET patients who have previously benefitted from PRRT.

METHODS

This multi-center prospective randomized study will evaluate the efficacy of the PRRT retreatment strategy and will also confirm the safety profile of a limited dose PRRT re-challenge. PRRT retreatment strategy builds on the fact that SSTR receptor expression remains intact in most patients post-initial PRRT progression and retreatment may be a safe and effective treatment.

RESULTS

N/A

CONCLUSIONS

N/A

ABSTRACT ID 33462

T-11

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), including poorly differentiated neuroendocrine carcinomas (NECs) and well-differentiated grade 3 neuroendocrine tumors (NETs), are aggressive malignancies with limited effective treatment options. Immune checkpoint inhibitors (ICIs) have demonstrated limited clinical activity in these tumors. Seneca Valley Virus (SVV-001) is a novel oncolytic RNA virus that has shown synergistic activity with ICIs in preclinical models. Additionally, SVV-001 has been observed to reverse CPI resistance in vivo, supporting its evaluation in combination with nivolumab and ipilimumab.

METHODS

This is an investigator-initiated, phase 1, dose-escalation and cohort-expansion study evaluating intratumoral SVV-001 in combination with nivolumab and ipilimumab in patients with histologically confirmed poorly differentiated NEC or well-differentiated grade 3 NET. The trial was activated in March 2025, with patient enrollment currently ongoing and a target of up to 36 patients. A standard 3+3 dose-escalation design is being employed to determine the recommended phase 2 dose (RP2D). Following dose escalation, an expansion cohort will further evaluate safety and preliminary signals of activity. Tumor endothelial marker 8 (TEM8), a potential biomarker of SVV-001 sensitivity, will be assessed as part of correlative studies. NCT06889493

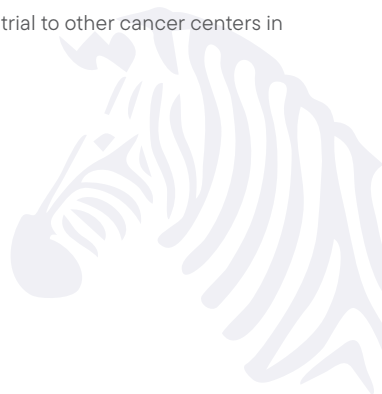
RESULTS

This Phase 1 trial is active at University of Miami and plans to expand the trial to other cancer centers in the US.

CONCLUSIONS

N/A

ABSTRACT ID 33468



T-12

A Prospective Observational Study of GLP-1 and GLP-1/GIP Receptor Agonists in Patients with Well-Differentiated Neuroendocrine Tumors

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BACKGROUND

Neuroendocrine tumors (NETs) are heterogeneous neoplasms with rising incidence and diverse clinical behavior. Although well-differentiated, low- to intermediate-grade NETs typically exhibit indolent growth, their management is complex, especially when addressing metabolic comorbidities such as obesity and diabetes.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists (e.g., tirzepatide) have demonstrated substantial benefits for weight loss, glycemic control, cardiovascular health and are increasingly utilized. Preclinical studies have demonstrated expression of GLP-1 and GIP receptors in NETs and raised concerns for tumor proliferation with receptor activation, while some recent retrospective clinical analyses suggest possible benefits. However, prospective safety data in patients with active NETs are lacking.

METHODS

This is a single-institution, prospective observational study designed to evaluate the safety and metabolic efficacy of GLP-1 and GLP-1/GIP receptor agonists in patients with grade 1 or 2 NETs who are receiving these agents for weight or metabolic indications.

Eligible patients must have histologically confirmed well-differentiated NETs, measurable (RECIST v1.1) stable disease on imaging within 90 days prior to enrollment, and no evidence of progression in the preceding 6 months. Key exclusions include grade 3 NETs, neuroendocrine carcinomas, history of medullary thyroid carcinoma, or MEN2.

Patients will receive semaglutide (up to 2.4 mg weekly) or tirzepatide (up to 15 mg weekly) following standard titration schedules. Radiographic assessments will occur every 12 weeks to monitor tumor progression. Biochemical progression will be assessed in functional NETs on the same schedule via relevant biomarkers (e.g., chromogranin A, 5-HIAA).

The primary endpoints are rate of radiographic progression and biochemical (defined as a change of $\geq 50\%$ from baseline) progression. Key secondary endpoints include changes in quality-of-life scores via EORTC QLQ-GI.NET21, percent weight loss, changes in hemoglobin A1c and lipid profiles. An exploratory analysis will examine correlation of outcomes with GLP-1 and GIP receptor expression in tumor tissue.

RESULTS

Enrollment is ongoing with a planned accrual of 30 patients. Interim analyses will evaluate progression and safety signals.

CONCLUSIONS

This is the first prospective study to assess the safety of GLP-1 and GLP-1/GIP receptor agonists in patients with active NETs. Findings will guide future clinical decision-making and support evidence-based use of these agents in this population.

ABSTRACT ID 33472



T-13

Stratification of Biochemical Response to Somatostatin Analogs in Carcinoid Syndrome: Implications for Risk of Carcinoid Heart Disease

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BACKGROUND

Carcinoid syndrome, driven by the systemic release of serotonin and other vasoactive substances, can lead to carcinoid heart disease (CHD). Somatostatin analogs (lanreotide and octreotide) are standard first-line therapies to suppress hormone secretion. However, biochemical response is variable, and persistent serotonin elevation may increase the risk of CHD. Identifying partial responders to somatostatin analogs may help guide additional therapeutic strategies.

METHODS

We retrospectively analyzed patients with carcinoid syndrome initiated on standard-dose somatostatin analog (SA) therapy (lanreotide 120 mg SQ every 4 weeks or octreotide LAR 30 mg IM every 4 weeks). Patients underwent determination of serum 5-hydroxyindoleacetic acid (5-HIAA) after 3 months of SA therapy. Biochemical response was stratified into two groups: responders (5-HIAA decreased to <123 ng/mL) and partial responders (5-HIAA decreased from baseline but remained \geq 123 ng/mL). Rates of cardiac involvement were assessed using echocardiography and NT-proBNP levels. Patients were included in the TELEHEART study and were randomized to SA + Placebo versus SA + Telotristat Ethyl.

RESULTS

Among 53 patients with carcinoid syndrome treated with somatostatin analogs, 35 (66%) were classified as responders and 18 (34%) as partial responders. All 10 patients randomized to Telotristat have additionally decreased the level of serum 5HIAA, with 80% improving to “responders’ group” at 3 and 6 months follow up, while the eight patients randomized to placebo continued to have serum 5HIAA levels, with a relative linear pattern, above the 123ng/mL threshold, “partial-responders”.

CONCLUSIONS

Biochemical monitoring of serum 5-HIAA allows identification and stratification of patients that may be at increased risk of developing carcinoid heart disease. This approach enables timely consideration of adjunctive serotonin-lowering therapies for partial responders, who fail to suppress 5-HIAA below 123 ng/mL. Long-term studies can establish the survival impact of this approach.

ABSTRACT ID 33499

T-14

First-in-Human Study of a Novel Nonpeptide Drug Conjugate (CRN09682) in Patients With Somatostatin Receptor 2-Expressing Tumors

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BACKGROUND

Somatostatin receptor 2 (SSTR2) is an established target for the treatment of neuroendocrine tumors (NETs) and a possible target for other solid tumors expressing SSTR2, including breast cancer, melanoma, small cell lung cancer, and meningioma. CRN09682 is a novel, nonradioactive, nonpeptide drug-conjugate (NDC) targeting SSTR2-expressing tumors with a monomethyl auristatin E (MMAE) payload. Here, we report the study design and methodology for the first-in-human evaluation of CRN09682.

METHODS

This phase 1/2, multicenter, open-label, nonrandomized study consists of two phases: dose escalation and dose expansion. In the dose escalation phase, the primary objective is to evaluate the safety and tolerability of CRN09682, while secondary objectives include evaluation of CRN09682 pharmacokinetics, identification of the maximum tolerated dose (MTD), and selection of the expansion phase dose. Eligible patients with progressive metastatic/unresectable SSTR2-expressing tumors (confirmed by SSTR imaging) will be enrolled in the dose escalation phase. CRN09682 will be administered every 3 weeks via intravenous infusion, at a starting dose based on ICH S9 guidelines. Dose escalation will utilize a BOIN design to establish the MTD. The recommended dose for expansion

will be based on the totality of data, including available exposure response from the dose escalation phase. The dose expansion phase will enroll cohorts of patients with SSTR2-expressing neoplasms, including: well-differentiated grade 1-3 pancreatic NETs; well-differentiated grade 1-3 extra-pancreatic NETs; poorly differentiated neuroendocrine carcinomas (NECs; including small- and large-cell pulmonary carcinomas, extrapulmonary NECs, and Merkel cell carcinoma); and, if feasible, relapsed or refractory non-neuroendocrine SSTR2-expressing tumors. Patients will continue therapy until disease progression, unacceptable toxicity, or other discontinuation criteria are met. The primary endpoints in the dose expansion phase are safety and tolerability (eg, incidence of adverse events, dose interruptions). Secondary endpoints include assessments of antitumor activity (eg, objective response rate, duration of response, and disease control rate, based on RECIST 1.1 criteria; progression-free survival, overall survival) and pharmacokinetic assessments.

RESULTS

N/A

CONCLUSIONS

Results of this study will be used to inform subsequent clinical trials to investigate the efficacy and safety of CRN09682 for patients with metastatic or locally advanced/unresectable neuroendocrine neoplasms or other SSTR2-expressing tumors.

ABSTRACT ID 33397



T-15

ETCTN 10558: A Phase II Randomized Control Trial of Triapine Plus Lutetium 177 Dotatate Versus Lutetium 177 Dotatate Alone for Well-Differentiated Somatostatin Receptor-Positive Neuroendocrine Tumors.

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¹University of Miami; ²Wexner Medical Center, Ohio State University; ³Markey Cancer Center; ⁴Huntsman Cancer Institute, University of Utah; ⁵City of Hope, CA; ⁶MD Anderson; ⁷Northwestern Medicine; ⁸Weill Cornell College of Medicine; ⁹University of Florida; ¹⁰Rutgers University; ¹¹UW Health; ¹²UC Davis; ¹³UPMC; ¹⁴NCI; ¹⁵National Institutes of Health.

BACKGROUND

Radiolabeled somatostatin analogues provide a means of delivering targeted radiation with a high therapeutic index to NETs that express somatostatin receptors (SSTRs). Radiolabeled somatostatin analogue Lutetium 177 DOTATATE (Lutathera) is a beta-emitting radionuclide, FDA approved for use in SSTR positive gastroenteropancreatic neuroendocrine tumors (GEPNETS) in the US based on the NETTER-1 Phase III trial. Despite favorable PFS and safety profile, the drug has limited cytoreductive capability with a 14% ORR. Peptide receptor radionuclide therapy (PRRT) also doesn't seem to be very effective in treating peritoneal disease. We hypothesize that addition of an effective radiation sensitizer could help improve antitumor activity of Lutathera. Radiation is a potent inducer of DNA double-strand breaks, and ribonucleotide reductase (RNR) is the rate-limiting enzyme in the synthesis and repair of DNA, making RNR-targeted therapy a rationale therapeutic strategy for radiosensitization. ETCTN 10388 (NCT04234568) evaluated safety and efficacy of the combination of lutetium 177 DOTATATE, a beta-emitting radionuclide in combination with triapine, a ribonucleotide reductase (RNR) inhibitor. The combination of triapine and Lu-177 DOTATATE was safe with preliminary efficacy signals.

METHODS

This study is an investigator initiated, NCI sponsored, multicenter randomized phase 2 trial of triapine and lutetium Lu 177 DOTATATE in well-differentiated somatostatin receptor-positive neuroendocrine tumor. A total of 94 patients will be equally randomized to either Lu-177 dotatate or Triapine + Lu-177 dotatate arm. The study will be open through the NCI ETCTN (National Cancer Institute Experimental Therapeutics Clinical Trials Network) program. Triapine will be administered orally from D1-14 with each dose of PRRT [200 mCi]. Primary endpoint is to evaluate overall response rate (ORR). Secondary endpoint is to evaluate median PFS. We are also evaluating triapine PK, plasma deoxyribonucleosides, circulating DNA and plasma hPG80, a novel blood based diagnostic biomarker. NCT05724108

RESULTS

N/A

CONCLUSIONS

N/A

ABSTRACT ID 33464

