B-1

Sex-specific Transcriptional Differences and Loss of Gene Imprinting in Pancreatic Neuroendocrine Tumors

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BACKGROUND: Pancreatic neuroendocrine tumors (PNETs) occur more frequently in men and are associated with higher mortality in males; however, the molecular basis for these sexual dimorphisms is unclear. We hypothesized that transcriptional and epigenetic differences may contribute to these observed epidemiologic differences.

METHODS: We generated RNA sequencing data from 21 primary PNETs (9 (F) emale, 12 (M)ale) resected at our institution. Total RNA was extracted from tumor tissues using the RNeasy mini kit (Qiagen) and sequencing was performed on HiSeq 2500/4000 (Illumina) sequencers. Transcript quantification was performed with Salmon (v1.4.0). To validate our results, we downloaded a publicly available PNET dataset (10F, 14M). To explore the role of DNA methylation (DNAm) in sex-specific gene expression differences, we further downloaded matched DNAm - gene expression data for 23 primary PNET samples (9F, 14M) and DNAm data for 64 non-neoplastic pancreatic islet tissue samples (18F, 46M). Analyses were done in R (v4.0.3) using minfi (v1.36.0) and DESeq2 (v1.30.0) packages.

RESULTS: We found that there were significantly more genes differentially expressed by sex in PNETs as compared to control pancreatic islet tissues (p=6.5x10-5). Furthermore, PNETs were found to be associated with the emergence of unique sex-specific gene expression differences that are not observed in non-neoplastic pancreatic islet tissues. Some of the genes we found to be uniquely differentially expressed by sex in PNETs play known roles in tumorigenesis, including RASSF7, IGF2,and SOX15. Sex-specific PNET gene expression differences were not associated with DNA methylation. However, while widespread sex-specific differences were present in the DNAm landscapes of control pancreatic islets at the level of single CpGs (N=38,623), they were

almost completely erased in the cancer state (N=4). This included a loss of gene imprinting in 87 genes.

CONCLUSION: These results depict an emergence of sex-associated genetic and epigenetic dysregulations in PNETs.

ABSTRACT ID: 41

B-2

RNA-sequencing Identifies Unique Molecular Features of Duodenal Neuroendocrine Tumors

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BACKGROUND: Although duodenal neuroendocrine tumors (DNETs) derive embryologically from the foregut, whether they transcriptionally resemble midgut NETs remains unknown. This study compared gene expression of NETs of the duodenum, foregut (pancreatic NETs; PNETs), and midgut (jejunoileal NETs; SBNETs).

METHODS: RNA-sequencing was performed on primary DNETs (n = 16), PNETs (n = 41), SBNETs (n = 37), and respective normal tissue. Biologically significant genes were identified by filtering for differentially expressed genes (DEGs) with an adjusted p-value of <0.01 and log2(fold change) ≤-2 or ≥2. Ingenuity Pathway Analysis (IPA) identified enriched pathways. Gene expression changes were plotted by principal component analysis (PCA), and median pairwise distance (MPD) compared differences between tumor type.

RESULTS: DNETs had 681 DEGs compared to normal tissue, with upregulation of PNET transcription factors ISL1 and PAX6. DNETs, PNETs, and SBNETs had 355 common differentially-expressed-versus-normal genes, including CGHA, CHGB, SYP, NEUROD1, TPH1, and WNT4. Enriched pathways included those involved in synaptogenesis, CREB signaling in neurons, and insulin secretion. 170 genes were specific to DNETs, with upregulation of glycoprotein VI and cAMP-mediated signaling pathways.Overall DNET gene expression was not more similar to PNETs or SBNETs (MPD 98.5 vs 91.7, p = 0.3). DNET expression was more similar to PNET expression in genes related to GABA receptor signaling (MPD 5.3 vs. 3.6, P = 0.001), but more similar to SBNETs in pathways associated with melatonin degradation, FXR/RXR activation, and SPINK1-associated pancreatic cancer.

CONCLUSION: Compared to normal tissue, DNETs have upregulation of PNET transcription factors ISL1 and PAX6. Although NETs from several sites share common differentially expressed genes, DNETs have distinct gene expression and are not more similar to either PNETs or SBNETs.

ABSTRACT ID: 65

Median pairwise distances between NETs from the duodenum, pancreas, and small bowel

Genes/Pathway	DNET vs PNET	DNET vs SBNET	P
Overall gene expression	98.51	91.7	0.262
PNET vs. SBNET top 1000 differentially expressed genes	25.89	27.12	0.474
CREB Signaling in Neurons (PNET vs. normal canonical pathway)	6.92	7.47	0.181
GABA Receptor Signaling (PNET vs. normal canonical pathway)	3.61	5.25	**0.001**
Synaptogenesis Signaling Pathway (PNET vs. normal canonical pathway)	4.87	4.45	0.277
Superpathway of Melatonin Degradation (SBNET vs. normal canonical pathway)	4.09	3.05	**0.001**
Melatonin Degradation I (SBNET vs. normal canonical pathway)	3.37	2.53	**0.002**
FXR/RXR Activation (PNET vs SBNET canonical pathway)	5.02	4.09	**0.042**
SPINK1 Pancreatic Cancer Pathway(PNET vs SBNET canonical pathway)	5.53	3.45	**0.001**

B-3

Cd36 Mediated Metabolic Reprogramming in Cancer Stem Cells Contributes to Drug Resistance to mTOR Inhibition in Pancreatic Neuroendocrine Tumors

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BACKGROUND: Pancreatic neuroendocrine tumors (PNETs) represent a rare group of neoplasms with robust angiogenesis and heterogeneity. Current therapeutic efficacy is limited, accompanied by resistance to targeted chemotherapies, such as everolimus (a derivative molecule from rapamycin, an mTOR inhibitor), in which cancer stem cells (CSCs) play a critical role. CD36 as a fatty acid receptor that drives cancer cell stemness and promotes drug resistance by importing long chain free fatty acid into the cells to generate energy ATP and fuel CSCs. We hypothesize that CD36 in CSCs reprograms metabolic pathways in PNETs to enhance CSC features via regulation of fatty acid metabolism and thus contributes to mTOR inhibition resistance.

METHODS: A drug-resistance model was established in PNET cells with long-term treatment of rapamycin. Tumorsphere formation efficiency was assayed after knocking down CD36 in the drug-resistant cells, along with characterization of stemness features by performing RT-qPCR, Western blot, and immunofluorescence microscopy. Furthermore, tumor invasion and migration assays were performed in the control and drug-resistant cells with treatment of palmitic acids (long-chain fatty acids) and etomoxir (inhibitor of fatty acids oxidation). CSC-related gene signatures were analyzed by RT-qPCR.

RESULTS: The drug-resistant PNET cells showed increased stemness-associated gene expression and demonstrated CSC features, which were attenuated by knocking down CD36. CD36 knockdown also decreased tumor cell migration and invasion in response to fatty acid exposure, along with decreased CSC marker expression. Moreover, the changes in aggressiveness and CSC gene transcription in drug resistant cells may be associated with CD36-mediated fatty

acid oxidation.

CONCLUSION: CD36-mediated fatty acid metabolism is essential for maintaining stemness features, which may contribute to therapeutic resistance and metastatic relapse in PNETs.

ABSTRACT ID: 128

B-4

Loss of MEN1 Function Inhibits DNA Repair Capability of Pancreatic Neuroendocrine Tumors after Radiation Exposure

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BACKGROUND: Somatic MEN1 mutations occur in up to 50% of pancreatic neuroendocrine tumors (PanNETs). Radiation therapy (IR) is effective in a subset of PanNETs. Herein, we study whether MEN1 loss of function increases radiosensitivity and determine its effect on DNA double strand break (DSB) repair.

METHODS: A MEN1 knockout cell line (MEN1-KO-QGP1) was generated using CRISPR-Cas9. Clonogenic assays were performed and athymic nude mice xenograft models were created using wild type and MEN1-KO-QGP1 clones. Neutral Comet assays and immunofluorescence (IF) co-staining were used to assess DNA damage response. Cytotoxicity of combining IR with poly (ADP-ribose) polymerase 1 (PARP1) inhibitors was evaluated with clonogenic assays.

RESULTS: Both in vitro clonogenic assays and in vivo mice xenograft models showed significantly increased radiosenstivity of the MEN1-KO-QGP1 clone when compared to wild type QGP1 cells ($p<0.01$ and $p<0.0001$). Transient downregulation of MEN1 using siRNA confirmed these findings in 3 PanNET cell lines (QGP1, BON-1 and INS-1). Comet assays showed an increase in DNA double strand breaks (DSB) at baseline, 4 and 24 hours after IR. IF yielded significant variations in _H2AX, Rad51 and 53BP1 levels in MEN1-KO-QGP1 cells at different time points following IR, suggesting a decrease in DNA DSB repair and the homologous recombination (HR) pathway. MEN1 loss of function led to a decrease in BRCA2 mRNA/protein expression levels in MEN1-KO-QGP1 and in MEN1 siRNA-treated QGP1 cells. Lastly, PARP1 inhibition (10nM Talazoparib) significantly increased radiotoxicity in MEN1-KO-QGP1 cells when compared to

wild type QGP1 cells, particularly at lower IR doses ($p<0.01$ to <0.001).

CONCLUSION: MEN1 loss of function sensitizes PanNET cells to IR and influences DNA repair pathway choice by lowering BRCA2 expression and inhibiting HR. Combining IR with PARP inhibition may be beneficial in PanNET patients with somatic MEN1 mutations.

ABSTRACT ID: 132

B-5

RABL6A-Myc Signaling Promotes Pancreatic Neuroendocrine Tumor Cell Proliferation and Survival

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BACKGROUND: New targeted therapies are needed for treating advanced pancreatic NETs (pNETs). RABL6A is required for pNET cell proliferation and survival, but how it functions is incompletely understood. We recently found RABL6A is required for Myc expression in islets and pNET cells, but the importance of Myc in mediating RABL6A oncogenic activity is unknown.

METHODS: The metastatic gene signature of patient pNETs and small bowel (sb) NETs was examined by RNAseq and Ingenuity Pathway Analysis. Molecular and biological effects of altered RABL6A expression was determined in cultured pNET cells. Exogenous Myc-ER was expressed to test Myc's ability to rescue the RABL6A loss phenotype. Tumor suppressive effects of inhibitors targeting Myc (JQ1, CPI203) and CDK4/6 (palbociclib), individually or combined, were measured in pNET cells and xenograft tumors.

RESULTS: Myc pathway activation was found to be the primary, unifying feature of increased RABL6A signaling in pNET and sbNET patient metastases. We explored the RABL6A dependency of Myc transcriptional activity and observed marked reduction of Myc target gene expression in RABL6A-deficient pNET cells. Expression of an estrogen receptor Myc fusion protein (Myc-ER) partially rescued the RABL6A knockdown phenotype by pushing G1 arrested cells into S phase, but it was not enough to enable mitosis and sustained proliferation in the absence of RABL6A. Notably, drugs targeting Myc (Bromodomain inhibitors, JQ1 and CPI203), suppressed pNET cell viability in a RABL6A dependent manner. The bromodomain inhibitors synergized with CDK4/6 inhibitors to effectively kill pNET cells, diminish migration in vitro and reduce pNET xenograft growth in vivo.

CONCLUSION: Our findings demonstrate RABL6A is a new essential regulator of Myc signaling in pNETs whose expression is required for responsiveness to bromodomain inhibitors. Combined targeting of Myc and CDK4/6 kinases enhances RB1 tumor suppressor activity and may be a useful approach for treating pNETs that harbor activated Myc and CDK4/6.

ABSTRACT ID: 147

B-6

Inhibition of Serotonin Biosynthesis Suppresses Tumor Growth

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BACKGROUND: Small bowel neuroendocrine tumors (SBNETs) are a subgroup of NETs originating from enterochromaffin cells in the intestine. SBNETs express high level of Tryptophan Hydroxylase 1 (TPH1), a key enzyme involved in serotonin biosynthesis. High levels of serotonin cause carcinoid syndrome which can be treated with somatostatin analogs and the TPH1 inhibitor telotristat ethyl (TE). Although somatostatin analogs have been demonstrated to have anti-tumor properties, the effects of TE on tumor growth remains inconclusive. Several groups have found that TE has no growth inhibitory activity on NET cells in vitro but one recent study showed inhibition of tumor growth in patients. To investigate this discrepancy, we studied the effect of TPH1 inhibition both in vitro and in vivo using genetic and pharmacologic approaches, and whether serotonin biosynthesis can be further suppressed using inhibitors targeting the nicotinamide dinucleotide (NAD) pathway.

METHODS: We generated stable TPH1 knockdown BON-1 cells using specific shRNAs, assessed their growth rate and angiogenesis potential in vitro and in vivo by measuring cell division, serotonin level, endothelial cell tube formation, tumor weight, and tumor vascularity staining. We treated mice harboring BON-1 tumors with a vehicle control, TE, NAD inhibitor, and both drugs.

RESULTS: TPH1 knockdown cells and TE treated cells showed similar growth rate as control cells in vitro. However, TPH1 knockdown cells formed smaller tumors in vivoand tumors were less vascularized. The combination of TE and NAD inhibitor reduces serotonin biosynthesis and resulted in improved anti-tumor effect.

CONCLUSION: Although TPH1 inhibition showed no effect on tumor cell growth in vitro, TPH1 inhibition reduced tumor formation in vivo. Pairing TE with

NAD inhibitor represents an efficient strategy to metabolically target NETs.

ABSTRACT ID: 152

Effect of telotristat ethyl and NAD inhibitor on neuroendocrine tumors.

Biological Effects	Telotristat Ethyl (TE)	NAD inhibitor	Combo TE & NAD inhibitor
Anti-tumor cell growth *in vitro*	none	++	++
Anti-tumor growth *in vivo*	+	++	+++
Anti-angiogenic properties	+	++	+++
Serotonin biosynthesis inhibition	++	+	+++

B-7

Succinate Accumulation Is Not Sufficient for Tumorigenesis in Mouse Chromaffin Cells But Dual Loss of SDHB and NF1 Yields SDHx-like Pheochromocytomas

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BACKGROUND: Inherited pathogenic Succinate Dehydrogenase (SDHx) gene mutations cause the hereditary pheochromocytoma and paraganglioma tumor syndrome. Syndromic tumors exhibit elevated succinate, an oncometabolite proposed to drive tumorigenesis via DNA and histone hypermethylation, mitochondrial expansion and pseudohypoxia-related gene expression. It remains unproven whether oncometabolites are sufficient to drive tumorigenesis or whether it is feasible to generate an SDHx pheochromocytoma mouse model.

METHODS: To interrogate the prevailing hPPGL tumorigenesis model we disrupted mouse adrenal medulla Sdhb and Nf1 expression (independently and in conjunction) and evaluated pheochromocytoma formation and molecular phenotype. We conditionally knocked out Sdhb in catecholaminergic cells (TH-Cre) and rigorously tracked the SDHB-/- population using a GFP-based Cre-reporter system. Additionally, we utilized a sophisticated mass spectrometry technique (DESI-MS) to measure the spatial distribution of succinate in intact adrenal glands.

RESULTS: Aged SDHB-deficient mice do not develop tumors despite the succinate accumulation, histone methylation and mitochondrial pathology showing that these conditions are insufficient for tumorigenesis. These data suggested that a “second-hit” is required to initiate tumorigenesis in SDHB-/- chromaffin cells. Towards this end, we developed a double knockout mouse with co-deletion of the NF1 tumor suppressor. The SDHB/NF1 mice

develop pheochromocytomas with high levels of succinate as well as many other aspects of human SDHx tumors such as histone methylation, loss of 5-hydroxymethylcytosine and large clusters of swollen mitochondria. Unexpectedly, in vivo depletion of the 2-oxoglutarate (2-OG) dioxygenase cofactor ascorbate reduced SDHB-deficient cell survival, indicating that the lineage-restricted pattern of SDHx tumors may be determined by cellular ascorbate levels.

CONCLUSION: Contrary to the prevailing oncometabolite model, succinate accumulation and 2-OG-dependent dioxygenase inhibition are insufficient for mouse pheochromocytoma tumorigenesis, which requires additional growth-regulatory pathway dysregulation. This work describes the first mouse model for SDHx pheochromocytoma which recapitulates most essential aspects of the human disease.

ABSTRACT ID: 167

B-8

Development of a Real-time Luminescent Sensor for Detecting Serotonin Levels in Neuroendocrine Tumors

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BACKGROUND: Small bowel neuroendocrine tumors (SBNETs) are one of the most commonly occurring neuroendocrine tumors (NETs) that originate from transformed enterochromaffin cells. SBNETs are considered as rare cancers but the incidence is rapidly rising. Current standard of care drugs have limited efficacy at controlling tumor progression. Patients with SBNET metastases experience poor quality of life due to excess production of serotonin secreted by SBNET cells causing them to experience frequent diarrhea, flushing, and cause carcinoid heart valve fibrosis. There are critical needs to identify new medical therapies for treating SBNET progression and symptoms. Yet, research in serotonin regulation has been challenging because serotonin is very difficult to measure and highly sophisticated methodology based on mass spectrometry is required.

METHODS: Our goal is to develop an alternative strategy for measuring serotonin level in NETs in real-time. We developed various Serotonin-Luciferase Sensors (iSero-Luc) using the Renilla Luciferase and Firefly Luciferase as reporter proteins. The activity of the iSero-Luc sensors was characterized in the presence or absence of exogenous serotonin addition and with telotristat treatment.

RESULTS: We have engineered and characterized the activity of various serotonin sensors based on the Renilla Luciferase and Firefly Luciferase as reporter proteins in cell-based assays. Current effort is to evaluate the activity of this sensor in a xenograft model and use it for identification of new drugs targeting serotonin pathway in real-time or use as a diagnostic tool for detecting SBNETs.

CONCLUSION: SBNETs specifically express high levels of serotonin which is responsible for causing carcinoid syndrome in patients. Here, we report on

the development of novel serotonin sensors that allow the measurement of serotonin in live cells in real-time. This novel tool can potentially be used as a biomarker for tumor progression and serve as an imaging platform for assessing serotonin levels in vivo.

ABSTRACT ID: 179

B-9

Natural Compound Verrucarin A Potentiates the Anticancer Effect of Etoposide in NET Cell Lines

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BACKGROUND: First line chemotherapy treatment options for advanced neuroendocrine tumors (NETs) are limited and etoposide remains the standard NET regimen for over 40 years. Etoposide acts by stabilizing a normally transient DNA-topoisomerase II complex, thus increasing the concentration of double-stranded DNA breaks and triggering mutagenic and cell death pathways. Drug resistance, low bioavailability, and systemic toxicity of etoposide are the major obsta_cles in NET treatment. To improve responsiveness to etoposide we propose to combine this drug with a highly potent natural compound - verrucarin A (VC-A), which inhibits NET prosurvival pathway Akt/NF-_B/mTOR.

METHODS: NET cell lines (BON, pancreatic NET and H727, pulmonary NET) were treated with VC-A or etoposide for 72 hours and an MTT assay was used to determine IC50 values. Flow cytometric analysis of bromodeoxyuridine and 7-AAD staining were used to determine the effects on cell cycle of VC-A, etoposide, and combination treatments. Western blot analysis was performed to determine the effects on phospho-AKT and phospho-mTOR signaling.

RESULTS: BON and H727 cell lines demonstrated high sensitivity to VC-A. Pulmonary fibroblasts (WI-38) and normal thyroid cells (NThyori) with doubling times shorter or comparable to BON and H727 cells demonstrated a decreased sensitivity to VC-A. Etoposide reduced the number of cells in S-phase and increased the percentage of cells in the G2/M phase of the cell cycle. Co-treatment with VC-A decreased the number of cells in active cell cycle in a dose-dependent manner compared to etoposide alone. Moreover, a synergistic effect was observed between etoposide and VC-A. Western blot analysis showed a decrease in AKT/mTOR phosphorylation.

CONCLUSION: Verrucarin A and etoposide synergistically inhibit the growth of NET cell lines. Moreover, the combined therapies could avoid the possible drug resistance developed by a single agent. Specifically targeting NETs with VC-A and etoposide within exosomes could improve patient outcomes while limiting toxicities.

ABSTRACT ID: 181

B-10

Novel Fusion Gene UBTF-MAML3 Drives Tumorigenesis in Neuroendocrine Tumor Cells

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BACKGROUND: Pheochromocytomas and paragangliomas (PCC/PGL) are rare neuroendocrine tumors (NET) derived from chromaffin cells. Of those individuals with PCC/PGL, 15-25% have metastatic disease, which can occur even many years after initial diagnosis. The drivers for metastatic disease are not well understood. The Cancer Genome Atlas (TCGA) first identified that 5% of PCC/PGL had a novel fusion gene involving MAML3, and this was associated with metastatic disease. We recently confirmed in a separate cohort that 7% of PCC/PGL had the UBTF-MAML3fusion gene. The aim of this study was to investigate the tumorigenic properties of the UBTF-MAML3fusion.

METHODS: Because there are no human PCC/PGL cell lines, three NET cell lines were used for in vitro studies, SK-N-SH, QGP1, and BON1. Functional assays were conducted after cells were transiently transfected with either UBTF-MAML3 fusion (Fus) or full length MAML3 (FL). Transcriptome analysis also was performed. All assays were done in triplicate and statistical significance was determined by ANOVA.

RESULTS: Both UBTF-MAML3 Fus and MAML3 FL overexpression showed increased invasion compared with empty vector control. In SK-N-SH, invasion across Matrigel increased by 40% ($p=0.0005$) and 31% ($p=0.0029$) for Fus and FL, respectively; and in QGP1, Fus had a 73% ($p=0.0036$) increase and FL had a 27% ($p=0.307$) increase, the latter did not reach statistical significance. Overexpression of UBTF-MAML3 Fus and MAML3 FL in QGP1 showed an increase in colony formation, 37% ($p=0.0036$) and 60% ($p<0.0001$), respectively. Investigation is ongoing into the mechanism of UBTF-MAML3 function. Transcriptome analysis of all three cells lines overexpressing MAML3 FL showed upregulation of the Wnt pathway targets, in addition to canonical Notch targets, consistent with human

PCC/PGL data in TCGA.

CONCLUSION: Overexpressed UBTF-MAML3 fusion gene increased invasion and colony formation, suggesting it is a driver of tumorigenesis and metastatic disease. The mechanism of action is still unknown.

ABSTRACT ID: 184

B-11

Variability of Somatostatin Receptor Type 2 Immunohistochemical Staining Patterns Among Gastroenteropancreatic Neuroendocrine Tumors

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BACKGROUND: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) can be difficult to diagnose with current imaging standards. Somatostatin receptor 2 (SSTR2) can be overexpressed on cellular surfaces, making some patients eligible for SSTR2-based imaging and therapy. However, density of SSTR2 overexpression varies among patients. Determination of which tumors express SSTR2 is critical for deciphering the underlying mechanisms causing some patients to lack SSTR2.

METHODS: We investigated SSTR2 expression among 75 GEP-NET patients at our institution. Tissue microarrays (TMAs) were immunohistochemically stained for SSTR2. Staining was assessed based on published recommendations and scored: 0 = absent, 1 = cytoplasmic only, 2 = membrane reactivity in <50% of tumor cells, 3 = membrane reactivity in > 50% of tumor cells. TMAs were quantified for positive percentage and intensity of SSTR2 staining (membrane versus cytoplasmic) with an automated custom MATLAB code. Chi-square test was used when assumptions were met, otherwise likelihood ratio (LR) was used.

RESULTS: Overall, 71.8% were of pancreatic origin, compared to 28.2% of non-pancreatic origin, including small intestine, ampulla, duodenum, ileum, and stomach. 80.8% of patients were SSTR2 positive and 19.2% were SSTR2 negative. In SSTR2 positive GEP-NETs, staining was scored as 1 for 15.4%, 2 for 7.7%, and 3 for 62.8%. Tissues with high SSTR2 expression were more likely to be of pancreatic origin, where 83.7% of SSTR2 score 3 were of pancreatic origin (df = 1, LR = 9.410,p = 0.024). There was a significant difference between SSTR2 staining

of primary versus metastatic tumors (df = 1, LR = 18.039, $p < 0.001$). 58.3% of patients with SSTR2 score 1 were metastatic, compared to only 22.4% of those with score 3.

CONCLUSION: Our study found an association between high SSTR2 expression and GEP-NETs of pancreatic origin. Tumors with a lower SSTR2 expression were likely to be metastatic than primary tumors.

ABSTRACT ID: 188

B-12

Sunitinib-loaded Chondroitin Sulfate Hydrogels as a Novel Drug-delivery Mechanism for the Treatment of Pancreatic Neuroendocrine Tumors

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BACKGROUND: Pancreatic neuroendocrine tumors (PanNETs) are increasingly common, and experts debate whether small tumors should be resected. Tumor destruction via injection of cytotoxic agents could offer a minimal invasive approach to this controversy. We hypothesize that a new drug delivery system comprising chondroitin sulfate (CS) hydrogels loaded with sunitinib (SUN) suppresses tumor growth in PanNET cells.

METHODS: Injectable hydrogels composed of CS modified with methacrylate groups (MA) were fabricated and loaded with SUN. Loading target was either 200 µg (SUN200-G) or 500 µg (SUN500-G) as well as sham hydrogel with no drug loading (SUN0-G). SUN release from hydrogels was monitored in vitro over time and cytotoxicity induced by the released SUN was evaluated using QGP-1 and BON1 PanNET cell lines. QGP-1 xenografts were developed in 35 mice and directly injected with 25 µL of either SUN200-G, SUN500-G, SUN0-G, 100 µL Sunitinib Malate (SUN-inj) or given 40mg/kg/day oral sunitinib (SUN-oral).

RESULTS: SUN-loaded CSMA hydrogel retained complete in vitro cytotoxicity towards the QGP-1 PanNET and BON-1 PanNET cell lines for 21 days. Mouse xenograft models with QGP-1 PanNETs showed a significant delay in tumor growth in the SUN200/500-G, SUN-inj and SUN-oral groups when compared to SUN0-G (p=0.0014). SUN500-G hydrogels induced significantly more tumor necrosis than SUN0-G (p=0.04, Table1). There was no difference in tumor growth delay between SUN200/500G, SUN-inj and SUN-oral.

CONCLUSION: Herein we demonstrate that CSMA hydrogels loaded with SUN suppress PanNETs growth. This drug delivery approach represents a novel way to treat PanNETs and other neoplasms via intra-tumoral injection.

ABSTRACT ID: 40

B-13

The MAP Kinase-activated Protein Kinase 2 Promotes the Development and Progression of Pancreatic Neuroendocrine Tumors Involving Action Mediated by Macrophages

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BACKGROUND: Accumulating evidence highlights the significance of immune response in the development and progression of pancreatic neuroendocrine tumors (PNETs). The MAP kinase-activated protein kinase 2 (MK2) is a crucial regulator of numerous processes including cell division and differentiation and is an important mediator of inflammation. The aim of our study was to determinate the contribution of signaling mediated by MK2 in the development and progression of PNETs.

METHODS: MK2 inhibitors were administrated for five weeks to the rat insulin promoter 1 driven viral SV40 large T antigen (RipTag2) transgenic mice. PNETs from RipTag2 mice were obtained, weighted and dissected into 8 mg pieces, incubated in complete RPMI medium for 18 h and supernatants were analyzed for cytokines and chemokines by multiplex array. Tumor killing assays were performed using PNET cells derived from untreated RipTag2 mice and activated wild type or MK2-/- bone marrow-derived macrophages. Cells were incubated for 24 h and stained with F4/80 and annexin V, and analyzed by flow cytometry.

RESULTS: In the RipTag2 transgenic mice model of PNETs, inhibition of MK2 led to significant reduction of tumor weight and was related to improvement of survival time. Ex vivo analysis of PNETs obtained from RipTag2 mice revealed that MK2 inhibition prevented secretion of cytokines and chemokines related to macrophage function. Finally, MK2-/- macrophages showed increased tumor cell killing by annexin V analysis.

CONCLUSION: The results indicated that MK2 inhibition suppresses the

development and progression of PNETs and these phenomena seems to be associated with anti-tumorigenic macrophage response.

ABSTRACT ID: 112

B-14

Establishment of Two Patient-derived Neuroendocrine Carcinoma Spheroid and Xenograft Models for Drug Testing

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BACKGROUND: Gastroenteropancreatic neuroendocrine carcinomas (GEP NECs) are rare neoplasms with poor prognosis. Few reliable pre-clinical models exist to study GEP NECs, limiting investigation of novel imaging and treatment modalities. Here, we describe the establishment and characterization of two patient-derived GEP NEC spheroid and xenograft (PDS and PDX) models and their application for drug testing.

METHODS: The NEC913 and NEC1452 cell lines were derived from surgically resected human GEP NEC tumors, originated from nodes from ampullary and small bowel primaries, respectively. Expression of neuroendocrine markers was confirmed by immunohistochemistry, immunofluorescence, and quantitative PCR in vitro,and drug screening experiments were performed and cell viability was measured. Mice were subcutaneously injected with these GEP NEC cells to create PDXs and used in drug treatment experiments.

RESULTS: The NEC913 PDS and PDX models expressed neuroendocrine differentiation markers chromogranin A (CgA), synaptophysin (SYP), and somatostatin receptor-2 (SSTR2), as well as NEC markers ASCL1 and CXCR4. They expressed a truncated form of p53 and showed no expression of pRb. The NEC1452 PDS and PDX models only stained positive for CgA and SYP. Both NEC models have a high Ki-67 expression (>90%) and can be maintained in suspension culture as PDSs and used to screen 147 FDA approved anti-cancer drugs and over 300 structurally diverse compounds to identify new inhibitors for NECs. Both PDS lines injected into immunocompromised mice developed into tumors with >90% uptake rate. Subcutaneous injection of 1x106 cells grew into

tumors about 1500 mm3 in size after 4 weeks.

CONCLUSION: The NEC913 and NEC1452 PDS lines are useful pre-clinical models for the study of neuroendocrine carcinoma. NEC913 expresses many NEC markers and maintains the histologic morphology of the original patient tumor. NEC1452 expresses few NEC markers. These two NEC models represent a valuable resource for identification of novel treatment modalities for NECs.

ABSTRACT ID: 175

B-15

Comparison of Drug Sensitivity Profiles of Various NEN Spheroids

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BACKGROUND: Neuroendocrine neoplasms (NENs) are rare cancers that arise from neuroendocrine cells. NENs are classified as well-differentiated neuroendocrine tumors (NETs) and poorly-differentiated neuroendocrine carcinomas (NECs). Small bowel NETs (SBNETs) and pancreatic NETs (PNETs) are generally slow-growing but commonly metastasize to the liver and can become aggressive cancers. Little is known about the drug sensitivity profile of SBNETs, PNETs and NECs due to the lack of cellular and animal models of these malignancies. Recently, we have developed a general protocol to culture NET and NEC cells from patient tumors as patient-derived spheroids (PDS) for drug screens and showed that they express NEN markers. In this study, we compare the drug sensitivity profile of SBNET, PNET, and NEC spheroids in order to identify specific classes of inhibitors for each of these categories of NENs.

METHODS: We used 11 SBNET, 3 PNET, and 2 NEC PDS cultures in a systematic drug screen where each PDS line was tested against a panel of 175 compounds consisting of 147 FDA-approved anti-cancer drugs and 28 other compounds. We identified common and unique sets of inhibitors targeting specific NEN spheroid subgroups.

RESULTS: Our systematic drug screens identified 21, 35, and 67 drugs that can inhibit SBNET, PNET, and NEC spheroid growth, respectively. All 3 categories of spheroids are highly sensitive to proteasome, histone deacetylase, and tyrosine kinase inhibitors. Additionally, SBNET spheroids were sensitive to a larger number of topoisomerase inhibitors, while PNET spheroids were predominantly sensitive to PI3K and mTOR inhibitors. NEC spheroids were more sensitive to

antineoplastic compounds.

CONCLUSION: Our NEN patient-derived spheroid drug testing approach allows us to compare the drug sensitivity profiles of different NEN spheroids and better understand molecular pathways for therapeutic applications. These PDS cultures are a valuable model for NEN and can facilitate the process of drug discovery.

ABSTRACT ID: 177

B-16

Prevalence of TP-53/Rb-1 Co-Mutation in Large Cell Neuroendocrine Carcinoma

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BACKGROUND: High grade poorly differentiated neuroendocrine carcinoma (HG-NEC) is a rare and highly aggressive neoplasm, which can arise from anywhere in the body. In 2016, Rekhtman et. al. differentiated genomic profiles of large cell NEC into: small cell lung cancer (SCLC)-like, characterized by TP53 + RB1 co-mutation/loss, and non-small cell lung cancer (NSCLC)-like, characterized by the lack of co-altered TP53 + RB1. TP53 and RB1 co-mutation was only found in 40% of their cohort. The objective of this study was to prospectively evaluate prevalence of TP53 + RB1 co-mutation in HG-NEC.

METHODS: HG-NEC patients were prospectively enrolled after IRB approval for tissues based somatic tumor mutation testing with help of Human Longevity Initiative's next generation sequencing platform.

RESULTS: 32 patients were consented. Only 15 patients had research quality tissue available for final analysis. Average age of cohort was 62 years with 46% females. Primary sites included Lung 4, Colo-Rectal 2, Pancreas 1, Esophagus 1, Parotid 1, Cervix 1, Ovary 1, Skin 1, Bladder 1, Trachea 1, Unknown Primary 1. 40% (6/15) patients were positive for TP 53 mutation and loss of Rb-1. As expected, the only two small cell lung cancer patients were positive for TP-53/Rb-1 co-mutation which is a universal biomarker of SCLC. However this was not found to be consistent for extrathoracic small cell as well as large cell neuroendocrine carcinoma. Median tumor mutation burden of cohort was 3.9. Parotid small cell carcinoma had highest TMB of 46.7 in our cohort.

CONCLUSION: Extra-thoracic high grade NEC are potentially molecularly distinct entities as compared to SCLC. Extrapolation of therapeutic strategies from SCLC to extra-thoracic HG-NEC might not be optimal. Large prospective studies are needed to refine our understanding of molecular differences between small cell vs large cell NEC and thoracic vs extra-thoracic HG-NEC.

ABSTRACT ID: 201

B-17

Pre-clinical Evaluation of Alpha-particle Radiotherapy Targeting CXCR4 in Small Cell Lung Cancer

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BACKGROUND: Small cell lung cancer (SCLC) is currently incurable, accounting for 15% of lung carcinoma. There is thus critical needs for new diagnostic and therapeutic strategies. Chemokine receptor 4 (CXCR4), is known to drive proliferation and metastases in multiple types of cancer. We have demonstrated high CXCR4 expression in SCLC cell lines, as well as specific receptor-mediated tumor targeting by 68Ga-Pentixafor PET imaging in mice. Alpha-particles, with high linear energy transfer have potential for effective cell-killing and low off-target radiation exposure. Therefore, targeted _-therapy is estimated to be 100-500 fold more potent than _-particle therapy. We hypothesize that 212Pb-Pentixather would be an effective radiopharmaceutical in controlling SCLC expressing CXCR4. We evaluated the efficacy and toxicity of 212Pb-Pentixather in vitro and in animal model.

METHODS: 212Pb-Pentixather was successfully labeled and tested for stability by RTLC and HPLC. In vitro cytotoxicity of 212Pb-Pentixather was evaluated by alamar blue assay. 212Pb-Pentixather therapy efficacy, renal, hematological and bone marrow toxicity was evaluated in nu/nu mice bearing DMS273 tumor xenografts.

RESULTS: 212Pb-Pentixather was stable for 40 hours in mouse serum at 37°C and was 98% radiochemical pure by HPLC chromatogram at 48 hours in solution without serum. 212Pb-Pentixather demonstrated dose-, time-dependent cytotoxicity to typical lung carcinoid and SCLC cell lines. Moreover, single iv administration of 212Pb-Pentixather (1 µCi/g BW) effectively inhibited DMS273 progression and significantly extended the overall survival (P= 0.01), without body weight loss. There was no significant kidney injury by Q-PCR of NGAL and KIM1 expression. And there were no significant bone marrow toxicity by flow

cytometry assay.

CONCLUSION: 212Pb-Pentixather has demonstrated significant radiotherapeutic effect with little renal or bone marrow toxicity in mice bearing SCLC xenografts. Future experiments will explore dose optimization with and without thioredoxin reductase inhibitors to improve therapeutic efficacy and to further reduce renal and bone marrow toxicity.

ABSTRACT ID: 34

C-1

Efficacy of Checkpoint Inhibitors in Combination with Chemotherapy in Patients with High-grade Extrapulmonary Neuroendocrine Carcinoma

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BACKGROUND: Most extrapulmonary neuroendocrine carcinomas (EP NECs) are metastatic at presentation and survival is poor. Platinum and etoposide (CTX) is the standard first-line therapy. Data on CTX and checkpoint inhibitors (CPIs) for patients with EP NECs are largely extrapolated from lung cancer data. The DART SWOG 1609 trial suggested a benefit of dual CPI therapy in patients with high-grade NENs but did not evaluate the combination of CTX and CPI. A randomized trial of CTX with and without CPI is in development but unlikely to yield results for several years.

METHODS: The study was approved by the Mayo Clinic IRB. The retrospective cohort included patients with a diagnosis of EP NEC at Mayo Clinic between 2000 and 2021. We matched patients according to age, sex, and primary site of tumor. Chi-squared (_2) and Fisher's exact tests were used to assess clinical and demographic factors.

RESULTS: We identified 57 patients with EP NECs treated with either CTX monotherapy or CTX + CPI as first line treatment. Thirty-eight were treated with CTX monotherapy and 19 with CTX + CPI. For patients treated with CTX monotherapy the median overall survival (OS) and progression free survival (PFS) of 11 months (95% CI: 9-22) and 6 months (95% CI: 5-11), respectively. Patients treated with CTX + CPI had a median OS and PFS of 9 months (95% CI: 6-not reached [NR]) and 4 months (2-NR) respectively. The overall response rate (ORR) and disease control rate (DCR) in patients treated with CTX monotherapy was

63.2% and 73.7%, respectively. The ORR and DCR in patients treated with CTX + CPI was 42.1% and 63.2%, respectively.

CONCLUSION: CTX + CPI therapy did not show benefit over CTX alone as first line therapy in patients with EP NECs. Further development of novel treatment is necessary to improve the prognosis.

ABSTRACT ID: 52

C-2

The Role of Microbiome in Gastroentero-pancreatic Neuroendocrine Neoplasms (GEP-NENs)

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BACKGROUND: Gut microbiome balance has a key role in human health and is linked to a variety of diseases, including cancer. In this study, we analyzed the role of gut microbiome (both fungal and bacterial species) alterations in patients with metastatic gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs).

METHODS: Fecal samples were collected and matched with healthy control samples using linear regression models. Differences in microbiome profiles between GEP-NENs and control samples were performed. Next, the association of microbiome profiles with different behavioral and dietary habits, clinicopathological features (differentiation, grade, primary tumor site) and therapeutic responses was examined. All tests are two-sided and P-values ≤ 0.05 were considered statistically significant.

RESULTS: Gut samples of 36 patients (14 males, 22 females, median age 65 years) with metastatic GEP-NENs (24 small bowel, 10 pancreatic, 1 gall bladder, and 1 unknown primary) were analyzed. 31 patients were diagnosed with well differentiated GEP-neuroendocrine tumors (GEP-NETs), (G1= 20, G2=13, G3=3) versus 5 patients with GEP-poorly differentiated neuroendocrine carcinomas (GEP-NECs). Our data showed that GEP-NENs had significant decrease in relative abundance of bacterial species and an increase in relative abundance of fungi (notably Candida species) compared to controls (Figure 1). GEP-

NECs had significantly enriched bacteria and fungi (such as Enterobacter hormaechei, Bacteroides fragilis and Trichosporon asahii) compared to those with GEP-NETs (p=0.048, 0.0022 & 0.034 respectively), (Figure 2A). In addition, higher grade GEP-NETs were associated with significant higher Bacteroides fragilis(p=0.022), Eubacterium dolichum(p=0.049), and Eggerthella lenta (p=0.00018) species compared to lower grade tumors (Figure 2B). There were substantial differences associated with dietary habits and therapeutic responses (Table.1).

CONCLUSION: This is the first study to analyze the role of the microbiome environment in patients with GEP-NENs. There were significant differences between GEP-NETs and GEP-NECs, supporting the role of the gut microbiome in the pathogenesis of these two distinct entities.

ABSTRACT ID: 60

C-3

Patient-reported Clinical and Productivity Outcomes From the Longitudinal Telotristat Ethyl Treatment Registry

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BACKGROUND: Neuroendocrine tumor patients report substantial burden from inadequate control of carcinoid syndrome diarrhea (CSD) with somatostatin analog (SSA) monotherapy. We report outcomes from patients receiving telotristat ethyl (TE) in the RELAX study.

METHODS: Patients can opt-in to online surveys before starting TE (baseline) and every 6 months for up to 3 years. Descriptive statistics summarized patient characteristics, rescue medications, clinical symptoms, weight, work productivity and activity impairment (WPAI), and satisfaction with TE treatment. Changes were evaluable for patients with pre- and post-TE responses.

RESULTS: A total of 215 patients completed pre-TE surveys (mean age, 61 years; 60% female). One-third (36%) were satisfied with control of their CSD before starting TE; 206 (96%) were taking long-acting SSAs and 47 (22%) were taking short-acting SSA rescue medication at baseline. Reduced or stable rescue medication use was reported at Months 6 (19% and 75%, respectively), 12 (16% and 76%) and 18 (17% and 83%). Among patients with pre- and post-TE responses (n=107), 84% reported reduced number of daily bowel movements and 80% reported improvement in CS symptoms after 6 months of TE treatment. Stable or increased weight was reported at Months 6 (76%, 81/107), 12 (80%, 53/66), and 18 (74%, 31/42). Of 22 employed patients, mean decrease in WPAI productivity loss was 13.2 (SD=18.31) points. Of 106 responders, mean decrease in WPAI overall activity impairment was 9.4 (SD=26.76) points. Patients were satisfied with 6-month TE control of CSD (78%), CS symptoms (76%) and CS-related flushing (57%). Patient-reported changes in daily bowel movements

and satisfaction with TE control of CS symptoms have been consistent from 2018-2021.

CONCLUSION: Patients receiving TE reported improved CSD, satisfaction with control of CS symptoms, weight gain or maintenance, and reduced WPAI impairments after 6 months of TE treatment in the context of stable or reduced rescue medication use.

ABSTRACT ID: 98

C-4

An Open-Label, Phase II Investigation of Trifluridine/Tipiracil in Patients With High-Grade, Extrapulmonary Neuroendocrine Carcinoma

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BACKGROUND: High-grade neuroendocrine carcinomas (NECs) of gastroenteropancreatic origin are rare but are associated with rapid disease progression, widespread metastatic disease, and poor overall survival. Treatment with platinum and etoposide is the generally accepted first-line therapy for advanced disease, but there is a paucity of data regarding management for relapsed or refractory disease. FTD/TPI, an oral combination of trifluridine and tipiracil, is currently approved for the treatment of metastatic colorectal cancer and metastatic gastric cancer in late-line settings. Based on remarkable activity of single agent FTD/TPI in a phase I study, an exploratory phase II trial was designed to further evaluate this therapy in a disease with historically dismal outcomes and minimal prospective data.

METHODS: This was an open-label study of high-grade, extrapulmonary neuroendocrine carcinoma patients who had failed first-line treatment with a platinum-containing regimen. A sample size of 14 patients was targeted with a primary endpoint of objective response rate (ORR). All patients received FTD/TPI in a 28-day treatment cycle at a dose of 35 mg/m2/dose twice daily on days 1-5 and days 8-12. Radiologic assessments were performed every 8 weeks. If no responses were noted within the first 7 patients, the study would be discontinued for inactivity.

RESULTS: A total of 7 patients were enrolled in the study. 1 patient withdrew and was considered not-evaluable. Of the remaining patients, no objective responses

were observed. Median TTP was 3.2 months, and median OS was 6.2 months. One patient experienced prolonged stable disease of 11.3 months, however, 3 of 6 patients experienced immediate disease progression at the first radiographic evaluation.

CONCLUSION: While one patient did experience prolonged stable disease, the study was halted due to pre-specified metrics of inactivity. FTD/TPI was not found to be effective in the second-line setting for high-grade, extrapulmonary neuroendocrine carcinoma.

ABSTRACT ID: 103

C-5

Interim analysis results of surufatinib in US patients with neuroendocrine tumors (NETs)

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BACKGROUND: Surufatinib is a targeted inhibitor of tyrosine kinases VEGFR1, 2, & 3, FGFR1, and CSF-1R. A manageable safety profile, and statistically significant efficacy have previously been demonstrated in patients with advanced NETs of extrapancreatic (epNET) and pancreatic (pNET) origin in 2 phase 3 randomized trials conducted in China (SANET-ep & SANET-p [Xu, 2020]).

METHODS: This Phase 1b, dose escalation/expansion study was conducted to evaluate and confirm the efficacy and safety of surufatinib in US patients. The recommended phase 2 dose determined and used for dose expansion was 300mg QD. The primary endpoint of dose escalation was investigator-assessed PFS rate at 11 mo.

RESULTS: 32 patients with heavily pre-treated progressive NETs (16 epNET and pNET, respectively) were enrolled. 65.6% of patients had received ≥ 3 prior lines of treatment; all patients previously received everolimus and/or sunitinib. PFS rate at 11 mo was 51.1% (95% CI: 12.8, 80.3) for patients with epNETs; and 57.4% (95% CI: 28.7, 78.2) for patients with pNETs. mPFS was 11.50 mo (95% CI: 6.47, 11.50), and 15.18 mo, (95% CI: 5.19, NR), for patients with epNETs and pNETs, respectively. An ORR of 6.3% was observed for epNET patients, and 18.8% for pNET patients. A disease control rate of 90.6% (95% CI: 75.0, 98.0) was observed for all NET patients. All patients reported at least one adverse event, and 24 patients (75%) reported AEs ≥ grade 3. The most common AEs of any grade reported were: fatigue (46.9%), hypertension (43.8%), proteinuria (37.5%), diarrhea (34.4%), vomiting (28.1%), and nausea (25.0%). The most commonly reported AEs ≥ grade 3 (>5%) were hypertension (37.5%), diarrhea (9.4%),

proteinuria, dysphagia, and anemia (6.3%).

CONCLUSION: Surufatinib has demonstrated antitumor activity in heavily pretreated US patients with progressive NETs with a manageable safety profile that is consistent with 2 completed phase 3 studies.

ABSTRACT ID: 105

C-6

Impact of Capecitabine and Temozolomide on the Primary Tumor in Pancreatic Neuroendocrine Tumors

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BACKGROUND: Capecitabine/Temozolomide (CAPTEM) is an established regimen for metastatic pancreatic neuroendocrine tumors and is often considered for preoperative tumor volume reduction. However, data regarding the impact of CAPTEM on radiographic features of resectability are lacking. We sought to understand radiographic response in patients treated with CAPTEM particularly with respect to primary tumor behavior and the tumor vessel interface (TVI).

METHODS: This is a retrospective, single institution study of patients with locally advanced or metastatic pancreatic neuroendocrine tumors (PNET) treated with CAPTEM between 2010-2020. Tumor measurements and TVI assessments were performed on pre- and post-therapy images by experienced radiologists, with post-hoc surgical review of all cases.

RESULTS: 47 patients with locally advanced (n=3) or metastatic (n=44) PNET patients who received CAPTEM were included. The most common site of metastatic disease was the liver (n=40). An objective radiographic response in the primary tumor was observed in 11 of 47 patients (23%; 95%CI 12-38), and TVI was modified from > 180° to < 180° in 4 patients (9%; 95% CI 2-20), although this did not alter the decision for surgery.

CONCLUSION: CAPTEM is associated with an objective response rate of 23% in the primary tumors of patients with locally advanced or metastatic PNET. However, CAPTEM-associated changes of TVI did not impact surgical management.

ABSTRACT ID: 119

C-7

The Safety and Efficacy of PEN-221 Somatostatin Analog (SSA)-DM1 Conjugate in Patients (Pts) with Advanced GI Mid-gut Neuroendocrine Tumor (NET): Phase 2 Results

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BACKGROUND: PEN-221 is a small molecule drug conjugate composed of a SSTR2 binding somatostatin analog linked to the toxin DM1. PEN-221-001 was a study which assessed the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of PEN-221 in well differentiated neuroendocrine tumors (NETs) and small cell lung cancer.

METHODS: Pts with advanced, SSTR2+ GI mid-gut NETs were enrolled in this cohort of study PEN-221-001. The primary objective was to determine the safety and efficacy of PEN-221 given intravenously, every (q) 3 weeks. Preliminary

efficacy was assessed using RECIST 1.1. A clinically meaningful efficacy result was defined as a Clinical Benefit Rate (CBR) > 75% and a median progression-free survival (mPFS) > 8 months.

RESULTS: 32 patients were enrolled between January 2018 to June 2020 and the data cut-off for this report is July 31, 2020. The mean number of cycles received was 7 (range 1-18), with 5 pts still on treatment at time of data lock. PEN-221 was well tolerated in all pts at the dose of 8.8 mg/m2. The most frequent (≥20% pts) PEN-221 related adverse events were nausea (50%), fatigue (47%), diarrhea (47%), decreased appetite (47%), peripheral neuropathy (34%), infusion reaction (31%), AST/ Alk Phos/ALT increase (28/25/22%), and anemia (25%). Only 11 (34%) of these events were ≥grade 3. Of the 26 pts who were evaluable for response, 23 (88.5%) had stable disease (SD) reported as their best response with a CBR of 88.5%. Target lesion shrinkage was observed in 10 (38%) patients. The mPFS for this cohort was 9 months (CI 5 - 16.5 months). Tumor marker data will also be presented.

CONCLUSION: PEN-221 appears well tolerated at 8.8 mg/m2 q 3 weeks and has demonstrated efficacy exceeding its clinical efficacy goals with a CBR of 88.5% and a mPFS of 9 months.

ABSTRACT ID: 120

C-8

Lanreotide Autogel/Depot (LAN) in Patients with Advanced Bronchopulmonary (BP) Neuroendocrine Tumors (NETs): Results From the Phase 3 SPINET Study

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BACKGROUND: Well-differentiated BP-NETs (typical [TC] and atypical carcinoids [AC]) account for ~25% of NETs. SPINET evaluated LAN in advanced somatostatin receptor (SSTR)-positive TCs and ACs.

METHODS: SPINET (NCT02683941) was a phase 3, randomized (2 LAN:1 PBO, stratified by TC vs AC), double_blind (DB) study of LAN (120 mg/28 days), with optional open_label LAN treatment (OL_LAN). Enrollment was stopped due to slow accrual; ongoing patients without centrally assessed progression in the DB phase could transition to open-label LAN. The primary endpoint was adapted: centrally assessed (RECIST 1.1) PFS during the DB/OL-LAN phases in patients

randomized to LAN. Secondary endpoints included PFS, objective response rate (ORR) [central], and time to treatment failure (TTF) in each treatment arm during DB phase, and safety.

RESULTS: Seventy-seven patients were randomized and treated (LAN, n=51; PBO, n=26; [OL_LAN, n=40]). Mean (SD) age was 66.2 (12.5) years; 42 patients (54.5%) were male, 45 (58.4%) and 32 (41.6%) had TC and AC respectively, all (Octreoscan) patients had a Krenning score ≥2, 6 (7.8%) had received prior chemotherapy, and 71 (92.2%) had hepatic tumor load ≤25%. Median (95% CI) PFS in the LAN randomized group was 16.6 (12.8-21.9) months (TC 21.9 [12.8-not calculable (NC)]; AC 14.1 [5.6-16.6]). Key secondary endpoints are shown in the Table. In the DB phase, PFS for LAN and PBO, respectively, was 21.9 (13.8-NC) vs 13.9 (13.4-NC) months in TC and 13.8 (5.6-16.6) vs 11.0 (2.8-16.9) in AC.

Secondary endpoints.

	DB LAN (n=51)	DB PBO (n=26)	LAN vs PBO: HR [95% CI]
PFS (TC and AC), median (95% CI), months	16.6 (11.3-21.9)	13.6 (8.3-NC)	0.90 [0.46-1.88] (p = 0.769)
ORR, % (95% CI)	14.0 (5.8-26.7)	0 (0.0-13.7)	-
TTF, median (95% CI), months	13.3 (5.6-14.1)	9.8 (5.4-13.6)	0.86 [0.50-1.50]
Treatment-emergent adverse events, n (%)[a]	DB LAN (n=51)	DB PBO (n=26)	OL-LAN (n=40)
Any	49 (96.1)	25 (96.2)	26 (65.0)
Treatment-related	38 (74.5)	14 (53.8)	13 (32.5)
Grade 3/4/5	13 (25.5)/1 (2.0)/1 (2.0)	8 (30.8)/0/0	3 (7.5)/0/0
Serious treatment-related adverse events	2 (3.9)	1 (3.8)	0

[a]Excludes death/progression (part of PFS assessment)

CONCLUSION: SPINET, the largest prospective study to date with a somatostatin analog in SSTR-positive BP_NETs, suggests LAN 120 mg could be an appropriate treatment option, especially for TC. This study is funded by Ipsen.

ABSTRACT ID: 126

C-9

Real World Use of Lanreotide in Management of Neuroendocrine Tumours

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BACKGROUND: Majority of neuroendocrine tumors (NETs) arise from the gastrointestinal tract and present with metastases. Treatment is often with somatostatin analogues (SSA) such as lanreotide in the first line setting. We studied real world use of lanreotide in management of NETs.

METHODS: We performed a single-site retrospective chart review of all patients (n=69) on lanreotide for NETs at The Ottawa Hospital Cancer Center. We studied patient characteristics and provider practices surrounding lanreotide use.

RESULTS: 68% of patients were male and mean age was 63 years (range 35-93 years). The most common primary sites were the ileum (n=24, 35%) and pancreas (n=22, 32%). Most common sites of spread were to the liver (n= 49, 33%) and lymph nodes (n=46, 31%). Lanreotide was the first line of systemic treatment in 60 (87%) patients. Starting dose of 120 mg q4weeks was used in 66 (96%) patients. Dose escalation to 120 mg q3weeks occurred in 4 (6%) patients.The primary intention for treatment was tumour control (n= 32, 46%) or symptom and tumour control (n=34, 49%). Patients were on lanreotide for a median time duration of 22 months (range: 0-35). Radiographic disease stability was seen in 30 patients (43%) and progression in 29 patients (42%). Lanreotide discontinuation occurred in 32 (46%) patients mainly due to disease progression (n=17, 25%) or adverse events (n=7, 10%). Lanreotide was continued post progression in 19 (28%) patients.

CONCLUSION: Overall, the use of lanreotide at our center was in first line setting which is in keeping with current guidelines. Lanreotide was used for its antiproliferative properties in majority of cases. Dose escalation was seldom seen and it will be interesting to see how this practice changes given results of the CLARINET FORTE study which showed improvement in disease progression with q2weeks administration of lanreotide while maintaining known safety profile.

ABSTRACT ID: 129

C-10

Genomic Profiling of Responders and Non-responders to Checkpoint Inhibition in Neuroendocrine Carcinoma

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BACKGROUND: The role of immune checkpoint inhibitors (ICI) in the treatment of neuroendocrine carcinoma (NEC) has yet to be established. While objective responses have been observed, it is still unknown which patients are likely to derive benefit. We investigated the genomic profiles of patients who did and did not respond to ICI.

METHODS: This is a retrospective series of patients with extrapulmonary NEC. RECIST 1.1 criteria were used to categorize patients as responders (CR, PR, or SD) vs non-responders (PD). The electronic medical record was reviewed to identify patients who had genomic panels performed, and results were extracted for analysis.

RESULTS: Of 31 patients eligible for RECIST assessment, 19 had genomic panels available (9 responders - 4 SD, 5 PR and 10 non-responders - PD). Of those with a NEC histology specified, 9 were small cell, 1 combined large and small cell, 3 were large cell. All tumors were microsatellite-stable. All but one (with TMB = 25) of 16 tumors with TMB status available were < 10 m/MB. Of the responders, 67% had both TP53 and RB1alterations, compared with only 10% in the non-responders; this was statistically significant (p = 0.0198, Fisher exact). Of 7 total tumors with TP53+RB1alteration, 4 were specified as small cell carcinoma. Half of non-responders showed alterations in CTNNA1or CTNNB1, compared to only one of the responders, but this did not reach significance (p= 0.1409, Fisher exact).

CONCLUSION: In this small series, the small cell lung cancer-like genomic signature of TP53and RB1mutations was significantly more frequent in responders to ICI compared to non-responders. Further study is warranted to determine whether the presence of having simultaneous TP53and RB1mutations predicts response to ICI in NEC.

ABSTRACT ID: 131

C-11

Lurbinectedin in Extrapulmonary Metastatic Neuroendocrine Carcinomas

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BACKGROUND: Patients with metastatic neuroendocrine carcinomas (NECs) have limited therapeutic options after progressing through platinum-based regimens. Off-label use of lurbinectedin for metastatic NECs is a potential treatment option for progression after standard frontline therapies. Here, we describe our institutional experience for using lurbinectedin for extrapulmonary metastatic NECs.

METHODS: We identified patients with extrapulmonary NECs who received lurbinectedin through advanced text explorer (ATE) using search terms "neuroendocrine" and "lurbinectedin". Of the 29 unique patients identified using our search strategy, we excluded patients who did not receive lurbinectedin as planned, and those with small cell lung cancer or non-small cell lung cancer with neuroendocrine differentiation. Four patients met our criteria and data on the following variables were extracted for each: age at diagnosis, sex, biology, Ki-67, the primary site, number of prior lines of therapy, prior platinum, and atezolizumab therapy, number of cycles, date of lurbinectedin initiation, and date of progression.

RESULTS: Within the cohort, the median age at diagnosis was 62.5 years, with 50% females. Of these, 2 small cell, 1 large cell, and 1 poorly differentiated NEC, NOS were identified (Ki-67:80% in 2 patients). The primary sites included: pancreas (2), esophagus (1) and ureteropelvic junction (1). All patients received a prior platinum/etoposide and atezolizumab with median number of 1.5 prior lines of therapy. The median number of cycles of lurbinectedin was 3.5. The median time to treatment failure was 2.6 months. No drug discontinuations, interruptions, or dose reductions due to toxicities were observed.

CONCLUSION: Lurbinectedin is a potential option for metastatic NECs relapsed after platinum agents and immunotherapy, with the median time to treatment

failure of 2.6 months in our small retrospective cohort.

ABSTRACT ID: 135

Patient Characteristics for Lurbinectedin in Extrapulmonary Neuroendocrine Carcinomas

Age/Sex	Biology	No. of prior lines of therapy	No. of cycles of Lurbinectedin	Time to Treatment Failure (TTF) (months)
72 M	Small Cell	1	5	3.5
66 F	Poorly differentiated	2	4	3.6
59 M	Large Cell	1	2	1.1
35 F	Small Cell	3	3	1.8

C-12

Urinary Neuroendocrine Neoplasms (NENs) Treated in the "Modern Era": A Multicenter Retrospective Review

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BACKGROUND: Treatment of gastroenteropancreatic (GEP) and lung NENs has evolved substantially since 2010, with several new NCCN-recommended treatments available. Urinary NENs (UNENs) are very rare, thus treatment often extrapolated from NENs arising in other sites. We present an updated multicenter analysis of care patterns and overall survival (OS) in UNENs treated in the "modern era".

METHODS: Multicenter retrospective review of patients diagnosed after 2005 and alive after 2010. Modern-era therapies (METs) were those FDA approved and recommended by NCCN after 2010 for any NEN primary, off-label immunotherapies, and therapy received in a clinical trial from 2010 onward. Duration of treatment efficacy measured using time to next treatment (TTNT). Log-rank and Cox proportional hazards used to test differences in OS.

RESULTS: 134 UNENs patients: 94 (70.1%) bladder, 32 (23.9%) kidney, 2 (1.5%) ureter, 2 (1.5%) urethra, 4 (3.0%) other urinary primary. 53 (39.6%) alive, 65 (48.5%) deceased, 16 (11.9%) lost follow up. Well differentiated NETs (WDNETs) in 20.2% of cases (78.1% kidney origin), 37.5% stage IV, median OS (mOS) (9.28 yrs); poorly differentiated NECs (PDNECs) in 70.9% (92.2% bladder origin), mOS (4.65 yrs), 26.6% stage IV. Patients received a median of two therapies (range 0-10); 47 (35%) received METs, mOS 7.89 yrs. DOTA-avidity, primary resection, and primary

site were significantly associated with OS. Bladder NENs demonstrated worse OS than other sites when adjusted for differentiation, smoking, DOTA-avidity, but not for those received METs.

CONCLUSION: This is the largest series of UNENs receiving METs. The results suggest that treatment patterns overlap with GEP and Lung NENs, with preliminary evidence suggesting comparable benefits in selected treatments for WD-UNENs. That said, WDNETs and PDNECs are two distinct entities, arising in different parts of the urinary tract with very different clinical pathologic features. Prospective studies need to validate application of GEP/lung treatment guidelines to U-NENs.

ABSTRACT ID: 145

C-13

Health-related Quality-of-life Analysis of Surufatinib Versus Placebo for Advanced Neuroendocrine Tumors: Pooled Results From Two Phase 3 Studies (SANET-p and SANET-ep)

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BACKGROUND: Two previous phase 3 studies (NCT02589821, NCT02588170) have demonstrated surufatinib significantly improved progression-free survival

compared with placebo in patients with advanced pancreatic neuroendocrine tumors (NETs) and extrapancreatic NETs. We performed a pooled analysis of the two studies to assess the overall health-related quality of life (HRQoL) among these patients.

METHODS: Patient-reported HRQoL was measured at baseline, Day 15 of cycle 1, Day 1 of each subsequent cycle and at the time of discontinuation using EORTC QLQ-C30 and QLQ-G.I.NET-21. Time until definitive deterioration (TuDD) was defined as the time from randomization to deterioration of 10 points in domain score compared with baseline score (without subsequent observations of deterioration of <10 point or any improvement compared to baseline score), or death due to any cause. Change of scores from baseline were evaluated using longitudinal method. TuDD was assessed with Kaplan-Meier estimators and unstratified Cox models. P-values were derived from unstratified log rank test.

RESULTS: Patients were randomized (2:1) to surufatinib (N=242) and placebo (N=128). The compliance rate of EORTC QLQ-C30/GI.NET21 was >99% in both groups at baseline. For TuDD, surufatinib significantly decreased risk of deterioration in dyspnea (HR 0.58, p=0.0058), but significantly increased risk of deterioration in diarrhea (HR 2.91, p=0.0001), compared to placebo using QLQ-C30 Scales. No significant difference was observed in TuDD between two treatment groups in the remaining QLQ-C30 and QLQ-G.I.NET-21 scales. Least-squares mean differences from baseline to week 40 showed a favored trend of surufatinib at most visits for most QLQ-C30 and QLQ-G.I.NET-21 scales, except diarrhea QLQ-C30 scale (increase of 14.9 points vs 1.1 points, p<0.0001) and muscle/bone pain symptoms QLQ-GI.NET21 scale (increase of 9.3 vs 3.9, p=0.0303).

CONCLUSION: Surufatinib showed a comparable effect on HRQoL to placebo for patients with advanced NETs.

ABSTRACT ID: 150

C-14

Exploring Real World Outcomes of Ipilimumab and Nivolumab in Patients with Metastatic Gastroenteropancreatic Neuroendocrine Carcinoma (GEP-NEC)

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BACKGROUND: Dual blockade of immune checkpoints (ICPIs) using ipilimumab and nivolumab has improved outcomes in patients with refractory high-grade neuroendocrine neoplasms (NENs) in phase II clinical trials (DART SWOG 1609 and CA209). There was no adequate description of the tumor differentiation (high-grade well-differentiated neuroendocrine tumor vs poorly differentiated NEC). Our study aims to report the effectiveness and toxicity profile of dual ICPIs in a real world GEP-NEC patient population.

METHODS: Data on metastatic GEP-NEC patients treated with either ICPIs (single and dual ICPIs) or chemotherapy in the second line setting were retrieved from three cancer centers (Seidman , Vanderbilt-Ingram, and Fox Chase Cancer Centers). Associations between treatment characteristics and outcomes, including progression free survival (PFS) and overall survival (OS), were evaluated.

RESULTS: 70 patients (2007-2020) with metastatic GEP-NEC, of whom 41 patients (22 males, 19 females, median age 62 years old) were eligible for the final analysis. All patients were refractory to platinum etoposide in the first line setting. The median PFS for patients who received dual ICPIs (11 patients), single agent ICPI (8 patients), and cytotoxic chemotherapy (19 patients) were 258 days, 56.5 days, and 47 days, respectively (p=0.0001). Median overall survival (OS) for those groups were not reached (NR), 18.7 months, and 10.5 months, respectively

(p=0.004). There were no significant differences in treatment outcomes in patients according to tumor mismatch repair (MMR) or tumor mutational burden (TMB) status. Grade 3-4 adverse events (AEs) were reported in 11.1% of the patients who received dual ICPIs, however none of these AEs led to permanent treatment discontinuation.

CONCLUSION: In the second line setting, patients with GEP-NECs treated with dual ICPIs (ipilimumab and nivolumab) experienced improved PFS and OS compared to patients treated with single agent ICPI or cytotoxic chemotherapy. These results need to be validated in future prospective studies.

ABSTRACT ID: 157

C-15

Efficacy of Capecitabine and Temozolomide in Small Bowel (Midgut) Neuroendocrine Tumors

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BACKGROUND: The capecitabine/temozolomide regimen has proven significant activity in pancreatic NETs, however data are limited in NETs of the small bowel (midgut).

METHODS: Retrospective study of all patients with metastatic midgut NETs seen at Moffitt Cancer Center between 1/2008 and 6/2019 treated with CAPTEM.

RESULTS: 32 patients with proven or suspected primary small bowel NETs (excluding duodenum) were identified. 6 patients were found to have a radiographic response (19%), 5 of whom had high-grade (well-differentiated) disease. Only 1 patient among 23 with low/intermediate grade disease responded (4%), whereas the response rate for patients with high-grade disease was 56%. Among patients with low/intermediate-grade disease, 44% discontinued for poor tolerability.

CONCLUSION: The CAPTEM regimen appears to have activity in patients with WD high-grade small bowel NETs, and is largely inactive in patients with low/intermediate grade tumors. In this cohort of patients, tolerability was relatively poor among patients with low/intermediate grade tumors. CAPTEM use should largely be reserved for midgut NET patients with high-grade disease.

ABSTRACT ID: 158

C-16

Efficacy of Ipilimumab and Nivolumab in Patients with High-grade Neuroendocrine Neoplasms

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[1]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [2]Mayo Clinic, Rochester, MN

BACKGROUND: Dual checkpoint inhibitor therapy with anti-PD-1 and anti-CTLA-4 therapy has shown promising results in patients with high-grade neuroendocrine neoplasms, demonstrating varying response rates of 9 - 44%. More data are needed to evaluate the true response in a real-world cohort of patients.

METHODS: Retrospective study of all patients with high-grade NENs treated at the Moffitt Cancer Center and Mayo Clinic between 9/2017 and 7/2020 who received combination therapy with ipilimumab and nivolumab.

RESULTS: 34 patients met eligibility criteria. Patients had received an average of 2 prior lines of therapy, including at least one cytotoxic chemotherapy regimen. 27 (79.4%) of patients had poorly differentiated NECs, and 7 (20.6%) had well-differentiated high-grade NETs. The most common primary site (10, 29.4%) was pancreas; other primary sites of disease included colon (n=5), endometrium (n=3), anorectum (n=2), esophagus (n=2), cervix (n=1), stomach (n=1), small intestine (n=1), and unknown primary (n=9). 5 patients (14.7%) exhibited a best response of PR per RECIST 1.1 criteria, 9 (26.5%) SD, and 17 (50%) PD:
3 patients did not have a follow-up scan as they discontinued treatment shortly after initiation due to clinical progression. ORR was 14.7%, and DCR was 41.2%. Median PFS was 1 month (95% CI, 0.54 - 1.46); median OS from time of treatment initiation was 5.0 months (95% CI, 4.07 - 5.93), and median OS from diagnosis was 14.0 months (95% CI, 11.79 - 16.21). The median duration of treatment was 1 month (range 0 - 10 months). 28 patients discontinued treatment for progression, 4 patients for toxicity, and 2 remain on treatment at the time of data cut off.
12 patients (35%) experienced grade 3 and 4 treatment-emergent toxicities.

CONCLUSION: The ipilimumab and nivolumab regimen has modest activity in aggressive and heavily pretreated high-grade NENs who have progressed on prior cytotoxic chemotherapy.

ABSTRACT ID: 159

C-17

Treatment Response and Clinical Outcomes of Neuroendocrine Neoplasms (NENs) Treated with Immune Checkpoint Inhibitors (ICIs): a Single Institution Experience

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BACKGROUND: ICIs have antitumor activity in some solid tumors, however a role for ICI's in NEN treatment is uncertain. We analyzed response and outcomes of NENs, well differentiated neuroendocrine tumors (WDNET) and poorly differentiated neuroendocrine carcinomas (PDNEC), treated with ICIs at MSK during the past decade.

METHODS: Patients with NENs who received ICIs between 2010-2021 were identified. Demographics, clinical and pathology characteristics were recorded. PFS/OS were estimated using Kaplan-Meier methods. Analysis of next-generation sequencing (NGS) results from archival tumor tissue was performed.

RESULTS: 57 patients were identified (WDNET-16; PDNEC-41). All patients had heavily-treated metastatic disease (median number of prior systemic treatments, WDNET-4, PDNEC-2). Median time from diagnosis to ICI treatment was 41.5 months in WDNET, 8 months in PDNEC. WDNET response: 1 (6%) partial response (PR), 4 (25%) stable disease (SD), 10 (63%) progressive disease (PD). PDNEC response: 6 (15%) PR (5 microsatellite stable, 1 unknown), 3 (7%) SD, 32 (78%) PD. Median duration of ICI treatment: 2 months (range 0-27) in WDNET, 1 month (range 0-16) in PDNEC; median duration of treatment for the 7 responders was 11 months (range 2-27). While receiving ICIs, 3 PDNEC responders developed PD in an escape lesion (2 brain, 1 nodal) after response in all other disease sites and successfully continued ICI treatment post-RT of escape lesion. Six-month PFS was 20%[95%CI: 7%-55%] and 9.8%[95%CI: 4%-25%], OS 60%[95%CI: 40%-91%] and 37%[95%CI: 25%-56%], respectively in WDNETs and PDNECs. NGS results

were available in archival tumor tissue of 35 patients (61%); most common alterations were TP53 (20/26, 77%) and RB1 (14/26, 54%) in PDNEC versus ATM, SMAD4, CREBBP, and IRS2 (all 1/9, 11%) in WDNET.

CONCLUSION: We observed limited activity for ICI's in NEN treatment, primarily restricted to a subset of PDNEC. PFS/OS findings were consistent with historical data, reflecting the pathogenesis of distinct NEN subtypes.

ABSTRACT ID: 161

C-18

A Phase 2 Study of Surufatinib in Combination with Toripalimab in Patients with Advanced Neuroendocrine Carcinoma

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BACKGROUND: Surufatinib is a multi-kinase inhibitor of VEGFR1-3, FGFR1 and CSF-1R. Toripalimab is a PD-1 inhibitor. Combination therapy of the agents has showed promising antitumor activity for the 2L treatment of advanced neuroendocrine carcinoma (NEC). This study reports an updated analysis to further investigate the efficacy of the combination.

METHODS: In this multicenter, open-label, single-arm phase 2 study (NCT04169672), eligible patients with advanced NEC who failed 1L chemotherapy received 3-week cycles of 250mg surufatinib (orally, QD) plus 240mg toripalimab (IV, Q3W), until disease progression, death, or unacceptable toxicity, but for up to 24 months with toripalimab. The primary endpoint was objective response rate (ORR) per RECIST 1.1.

RESULTS: Twenty-one eligible patients (81.0% primary lesion in extra-pulmonary NECs, 76.2% PD-L1 CPS<10, 85.7% Ki-67 >55%) were enrolled. Median treatment

duration of both surufatinib and toripalimab was 4 months. At this updated data cutoff (June 15, 2021), 5 patients had confirmed partial response and 10 patients had stable disease among evaluable patients (n=21). The confirmed ORR was 23.8% (95%CI: 8.22%-47.17%) and the DCR was 71.4% (95%CI: 47.82%-88.72%). The median DoR of the responders was 4.11 months (95%CI: 2.99-NR). Median PFS was 4.14 months (95%CI: 1.45-5.45), and median OS was 10.18 months (95%CI: 9.03-NR). Nine (42.9%) patients had grade ≥3 treatment-related adverse events (TRAEs), with hyperglycemia (3 [14.3%]), hypertension (2 [9.5%]) and hypertriglyceridemia (2 [9.5%]) the most common (>2 patients). Nine (42.9%) or 3 (14.3%) patients had surufatinib or toripalimab interruption, due to TRAEs, respectively, however no TRAEs leading to treatment discontinuation or treatment-related deaths were reported.

CONCLUSION: Surufatinib plus toripalimab demonstrated clinically meaningful anti-tumor activity, and is a potential treatment option for 2L treatment of NEC that should be further investigated. A randomized phase 3 study is initiated to further confirm the efficacy of this combination therapy in 2L NEC.

ABSTRACT ID: 168

C-19

Phase 2 Trial of Pembrolizumab-based Therapy in Previously Treated Extrapulmonary Poorly-differentiated Neuroendocrine Carcinomas: Results of Part B (Pembrolizumab Plus Chemotherapy)

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BACKGROUND: The efficacy of immune checkpoint inhibitor therapy has not been established in extrapulmonary poorly-differentiated neuroendocrine carcinomas (EP-PDNECs). We investigated the efficacy and safety of pembrolizumab (PEM)-based therapy in biomarker-unselected patients with EP-PDNECs. In Part A, PEM alone was inactive (ASCO GI 2019). We now report the results of Part B (PEM plus chemotherapy).

METHODS: We conducted an open label, multicenter, phase 2 study of PEM-based therapy in patients with EP-PDNECs with disease progression on first-line systemic therapy. Patients were treated with PEM 200 mg IV every 3-week cycle plus dealers' choice chemotherapy: weekly irinotecan (IRI, 125 mg/m2 day 1,8 of every 21-day cycle) or weekly paclitaxel (PAC, 80 mg/m2). After a PEM/IRI safety lead-in (N=6), 16 additional patients were enrolled. Primary endpoint was objective response rate (ORR) by RECIST 1.1. Secondary endpoints included safety, overall survival (OS), and progression-free survival (PFS).

RESULTS: Of 22 patients enrolled: male/female 15/7; median age 57 years (range

34-75); ECOG PS 0/1: 10/12; histology: 6 large cell, 8 small cell, 3 mixed, 5 NOS. Primary site: GI 50%, pancreas/biliary 23%, GYN 5%, unknown 23%. Chemo choice: 17 IRI and 5 PAC. Median cycles of therapy administered was 3 (range 0-13). Treatment-related Gr 3-4 AE occurred in 8 patients. Gr 3 AE attributed to PEM included fatigue, pain, ALT increase, nausea, fever. Grade 3-4 AE attributed to chemo included fatigue, neutropenia, diarrhea, pain, ALT increase, nausea. ORR was 5%: PR in 1 patient (5%), SD 4 (18%), PD 13 (59%); 4 (18%) unevaluable. Median PFS 2 mo. Median OS 4 mo. Reasons for treatment discontinuation in 21 patients included PD (76%), AE (10%), withdrawal of consent/other therapy (14%).

CONCLUSION: PEM + chemotherapy was not effective in this pretreated, biomarker-unselected population of EP-PDNECs arising in different organs. Biomarker studies are planned. Clinical trial information: NCT03136055.

ABSTRACT ID: 172

C-20

Randomized Blinded Study Comparing Injection Site Pain From Octreotide Long-acting-release (LAR) Versus Lanreotide During the Treatment of Well-differentiated Neuroendocrine Tumors (WDNETs)

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BACKGROUND: The somatostatin analogs (SSAs) octreotide LAR (OCT) and lanreotide (LAN) are equally acceptable per NCCN to treat WDNETs. Average Sales Price for 1 year of LAN (120mg) is $106,802 versus $53,471 for 1 year of OCT (20mg) and $80,206 for 1 year of 30mg. LAN is given "deep subq" while OCT is given intramuscularly. We conducted a randomized, blinded trial evaluating patient (pt) experience, measured by injection site pain, with OCT and LAN, during nonfunctional WDNET treatment.

METHODS: Pts received q4w injections for 6 months; Arm 1: OCT (3 injections) then LAN (3 injections); Arm 2: LAN (3 injections) then OCT (3 injections). Self-reported injection site pain scores were obtained after first 3 injections (0-10 scale). Primary endpoint was mean pain score comparison over first 3 injections. Secondary endpoints included pt-reported SSA preference, willingness to pay for preferred therapy, assessed by questionnaire.

RESULTS: 51 pts were enrolled (Arm 1: N=26, Arm 2: N=25), all evaluable for primary endpoint. All pts received LAN 120mg monthly; among those (N=49) receiving OCT, 30 (61%) 20mg, 18 (37%) 30mg, 1 (2%) 10mg. No significant difference was identified in mean pain scores; Arm 1: mean 2.4, standard deviation (SD) 1.9; Arm 2: mean 1.9, SD 1.5 (p=0.5). 34/51 pts (15 Arm 1; 19 Arm 2) completed questionnaires. 7 (47%) Arm 1 and 8 (42%) Arm 2 indicated no drug

preference. There was a trend towards OCT preference in both arms, with more pts indicating mild or strong preference. In Arms 1 and 2, 7 (50%) and 10 (56%) pts, respectively, were unwilling to pay more for preferred SSA; the other pts were willing to experience increased financial toxicity for preferred SSA.

CONCLUSION: This randomized, blinded study evaluating pt comfort found minimal pain with OCT and LAN and no significant differences in pain scores.

ABSTRACT ID: 173

C-21

Validation of a Clinical Score (CS) for Patients With Well-Differentiated Neuroendocrine Tumors (WD NETs) Under Consideration for Peptide Receptor Radionuclide Therapy (PRRT) With ^{177}Lu-Dotatate

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BACKGROUND: We originally developed a CS prospectively at Vanderbilt Ingram Cancer Center (VICC) for patients being considered for PRRT and demonstrated the score to be associated with progression-free survival (PFS) in patients receiving PRRT. Herein, we present the performance of the CS in a validation cohort (VC) and combined cohort (CC).

METHODS: Our original cohort (OC) included patients under consideration for PRRT(N=122) between 3/1/2016-3/17/2020 at VICC while our VC included patients under consideration for PRRT(N=126) between 1/25/2017-3/6/2020 at Ochsner, Markey and Rush Cancer Centers. All patients in the OC were prospectively scored while patients in the VC were scored retrospectively, with the CS-assigning investigator blinded to patient outcomes. The primary outcome PFS, was estimated by the Kaplan_Meier method; a Cox proportional hazards model adjusting for primary tumor site, tumor grade and number of PRRT doses administered(0, 1-2 or 3-4) was used to analyze effect of CS.

RESULTS: In our VC, on multivariable (MV) analysis, for each 2-point increase in

CS, the hazard ratio (HR) for PFS was 2.58 (95% CI 1.62-4.11). We combined the OC and VC for this analysis to increase the predictive power of our originally developed Cox proportional-hazards model. In our CC(N=248), median patient age, CS and number of prior treatments were 63.3 years, 4 and 1, respectively. A total of 140, 82 and 26 patients received 3-4, 0 or 1-2 doses of PRRT, respectively. On MV analysis, for each 2-point increase in CS, the HR for PFS was 2.52 (95% CI 1.90-3.35). No interaction between PRRT doses administered and CS was observed.

CONCLUSION: Increases in CS were strongly associated with worsening PFS in our VC, validating findings from our OC. The CS is at minimum prognostic and represents the first clinical metric which can estimate the anticipated benefit from PRRT for individual patients with WD NETs.

ABSTRACT ID: 31

C-22

Defining MRI Superiority Over CT for Neuroendocrine Liver Metastases

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BACKGROUND: Across the US and world, CT tends to be the easiest and most readily available modality to detect neuroendocrine liver metastases (NLM). A thorough understanding of their size, location, and proximity to vessels is critical in determining resectability and surgical approach. The potential advantages of MRI over CT in preoperatively staging NLM have not been well established.

METHODS: Patients with NLM with both a contrast-enhanced CT and MRI within three months of each other were extracted from our prospectively maintained institutional database. The studies were anonymized, and two radiologists (RADS1 & RADS2) independently evaluated the studies for the number of liver lesions and their smallest and largest sizes. The CTs and MRIs were evaluated separately and in different orders to minimize recall bias.

RESULTS: We identified 45 patients with NLM for whom we had contemporary CT and MRI imaging of the liver. Males (n=23; 51%) and females (n=22; 49%) were equally represented; the median age was 61 [interquartile range (IQR) 55-69]. The median number of days between the studies was 51 (IQR 36-78). Data reliability was excellent with low inter-rater variability (intraclass correlation coefficient 0.932 for CT and 0.954 for MRI). The mean number of lesions seen by both radiologists on MRI was significantly higher than CT (14 vs. 12 lesions; P=0.001). In a subgroup analysis, Eovist®-enhanced MRI detected significantly smaller lesions than CT (RADS1: 4mm vs. 6mm, P=0.001; RADS2: 3mm vs. 5mm; P=0.003) when the studies contained two or more lesions.

CONCLUSION: Our data suggest that more NLM, especially small lesions when Eovist® is used, are detected on MRI than on CT. Preoperative image modality

selection may therefore alter the observed tumor burden landscape and, consequently, surgical planning.

ABSTRACT ID: 42

C-23

Long-term Outcomes Following ^{90}YRadioembolization of Neuroendocrine Liver Metastases

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BACKGROUND: ^{90}Y radioembolization has been studied as an effective therapy for neuroendocrine liver metastases (NELM). We aim to further characterize treatment outcomes as it relates to the primary lesion location.

METHODS: 170 patients with NELM were enrolled in the Radiation-Emitting SIR-Spheres in Non-Resectable liver tumor (RESiN) registry (NCT 02685631). Before 90Y, 23 (14%) patients had hepatic resection, 118 (83%) were on octreotide, and 47 (33%), and 57 (40%) received biologic or cytotoxic therapy. 62 patients (36%) had previous arterial embolization. 76 patients had extrahepatic disease. 86 were ECOG 1 or more. Tumor grade was known in 81 (48%): 57 well-, 12 moderate- and 12 poorly differentiated. Kaplan-Meier analysis and log rank tests compared overall survival (OS) by tumor location: foregut (FG, n=39), midgut (MG, n=54), hindgut (HG, n=10), pancreas (P, n=36) and unknown (U, n=13). Toxicities were reported using Common Terminology Criteria for Adverse Events v.5.

RESULTS: 80 patients (47%) underwent bilobar treatment and 90 (53%) had unilobar. Median tumor burden was 26% (IQR: 11.8-49.7). 1, 2, and 3-year OS was 75%, 61% and 44%. Median OS was 30 months. Longest OS was pancreas and hindgut tumors (42 and 41 months, respectively) while the shortest OS was

in foregut primaries (25 months). This difference was not statistically significant (X2=6.1, p=0.2). Well-differentiated tumors had a median OS of 35 months, compared to 13 and 25 months for moderate and poorly differentiated tumors. There were no grade 4 or 5 toxicities. Most common grade 3 toxicities were bilirubin increase (n=10, 5.9%) and new ascites (n=3, 1.8%).

CONCLUSION: In a heavily pre-treated population with a high incidence of extrahepatic disease and limited performance status, ^{90}Y was effective and safe in treatment of NELM, with median OS of 35 months for well differentiated tumors. Grade 3+ hepatic toxicity was identified in <6% of patients.

ABSTRACT ID: 53

C-24

Peptide Receptor Radionuclide Therapy (Lu-177 DOTATATE) in Progressive Neuroendocrine Tumors (NETs): Potential Predictors of Progression Free Survival (PFS)

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BACKGROUND: Lu-177 DOTATATE is widely used for well-differentiated NETs following progression on somatostatin analogs. We sought to evaluate the impact of peritoneal metastases, intrahepatic biliary ductal dilatation, ascites, number of Lu-177 DOTATATE cycles and intestinal obstruction on PFS in patients receiving Lu-177 DOTATATE

METHODS: Patients who received Lu-177 DOTATATE between September 2018 and October 2019 at Mayo Clinic, Rochester were included. CT or MRI was done 3 months and 6 months after their last treatment cycle and repeated every 6 months for follow-up. We reviewed the medical records for documentation of peritoneal metastases, intrahepatic biliary ductal dilatation, ascites, number of Lu-177 DOTATATE cycles and intestinal obstruction. Kaplan-Meier test, univariate and multivariate analyses were used as appropriate.

RESULTS: 94 patients were included (mean age 63±10 years, 55% male). The most common site of NETs primaries was the small intestine (52%). 40% of patients had prior targeted therapy (e.g. everolimus), 37% had prior chemotherapy and 16 % of patients received both chemotherapy and targeted therapy. In 3-year-follow-up after PRRT (median 17 months), median PFS was 19 months. In a Cox regression model, an increase in PFS was associated with completing 4 cycles of Lu-177 DOTATATE (HR= 0.04, P= <0.001) and no prior chemotherapy (HR= 0.4, P=0.027), whereas shorter PFS was associated with the history of intestinal obstruction after receiving Lu-177 DOTATATE (HR= 4.3,

P=0.023). Other factors were not statistically significant factors impacting PFS.

CONCLUSION: Lu-177 DOTATATE is an effective treatment modality in pretreated NET. Intestinal obstruction before receiving PRRT, intrahepatic biliary ductal dilatation, ascites, and peritoneal metastases were not associated with deteriorated PFS in patients treated with Lu-177 DOTATATE. History of intestinal obstruction after Lu-177 DOTATATE was an independent predictor of shorter PFS, while completing 4 cycles of Lu-177 DOTATATE and no prior chemotherapy showed improved PFS.

ABSTRACT ID: 54

C-25

Comparing Periprocedural Hemodynamic Instability in Y-90 Radioembolization and Bland Embolization for Neuroendocrine Tumor Liver Metastases

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BACKGROUND: Transarterial bland embolization (TAE) and transarterial radioembolization (TARE) are two common treatments for neuroendocrine tumor liver metastases (NETLMs). The difference in likelihood of periprocedural hemodynamic instability (PPHDI) between TAE and TARE secondary to hormonal release has not been explored. The purpose of our study was to compare the occurrence of PPHDI in TAE vs. TARE.

METHODS: From January 2009 to December 2019, 409 (217 male, 191 female, median age 64) NETLM patients were treated with TAE and/or TARE. Retrospective review of medical records was performed. Acute PPHDI was defined as systolic blood pressure above 160 mmHg or below 100 mmHg, diastolic blood pressure above 110 mmHg or below 60 mmHg, or a pulse below 60 beats per minute (bpm) and required IV administration octreotide and/or antihypertensive medication. For patients with baseline values outside these parameters, a 30-point systolic and/or 20-point diastolic deviation from baseline or a drop in heart rate by 10 bpm was considered abnormal. Delayed PPHDI was considered to have occurred if the patient required new antihypertensive medication for blood pressure control within 24 hours after the procedure. Chi-squared analysis was used to compare the TAE and TARE data.

RESULTS: 639 total TAEs and 186 total TAREs were performed on 409 patients. 26/409 patients received both TAE and TARE during the given time period. 426 (67%) TAEs and 42 (23%) TAREs were associated with PPHDI (P = .0001). Acute PPHDI occurred during 317 (50%) TAEs and 33 (18%) of TAREs (P = .0001).

Delayed PPHDI occurred following 305 (48%) TAEs and 16 (9%) TAREs (P = .0001).

CONCLUSION: This retrospective analysis suggests that PPHDI is more likely to occur during or following TAE than TARE. Further prospective studies are required to better elucidate the relative occurrence of hemodynamic instability in patients with NETLMs receiving TAE and TARE.

ABSTRACT ID: 56

C-26

Peptide Receptor Radionuclide Therapy (PRRT) in Advanced Pheochromocytoma and Paraganglioma From a Single Institution Experience

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BACKGROUND: Pheochromocytoma and paraganglioma (PPGL) are rare tumors with heterogenous prognosis and hence lack of treatment guidelines and limited therapy options. We present our experience with peptide receptor radionuclide therapy (PRRT) in advanced PPGL.

METHODS: Six patients (1 woman and 5 men, mean±SD: 59.7±11.7-year-old) with progressive, somatostatin receptor (SSR)-expressing PPGL (4 paraganglioma, 2 pheochromocytoma) were treated with 177Lu-DOTATATE. 68Ga-DOTATATE PET was obtained at baseline, after 2 cycles, and post-treatment. Follow-up imaging occurred every 3 months. Laboratory tests were performed before each cycle and every 2 months at follow-up. Toxicity was determined using NCI CTCAE V5.0.

RESULTS: All patients received 4 cycles of each 7400 MBq 177Lu-DOTATATE. 1/6 (16.7%) patient had a one-time reduced dose of 3700 MBq 177Lu-DOTATATE at third cycle due to grade 3 thrombocytopenia which resolved before the fourth cycle. After the first cycle, neutropenia and lymphopenia grade 3 was seen in 1/6 (16.7%) and 1/6 (16.7%) patients, respectively, and resolved in both cases after 1 month. 2/6 (33.3%) patients showed lymphopenia grade 3: one patient 1 month after the last PRRT cycle which persisted 5 months later while the other patient developed lymphopenia 5 months after last cycle, which might be related to newly initiated radiation therapy, and resolved 12 months later. No other grade 3 toxicity was seen, especially no liver or renal toxicity. Progression-free survival (PFS) was 83%, 58%, and 39% at 11-month, 15-month, and 18-month follow-up, respectively. The objective response rate (ORR) (complete and partial response)

was 40% at post-treatment evaluation. Disease control (DC) (complete, partial response, and stable disease) was 80% at 11-month follow-up.

CONCLUSION: Our preliminary data show overall good results for patients with progressive PPGL treated with PRRT: high DC of 80%, ORR of 33% and PFS of 83% at 11-month follow-up. Hematotoxicity included grade 3 transient neutropenia and lymphopenia (33.3%).

ABSTRACT ID: 62

C-27

Subgroup Analysis by Ki-67 and Primary Tumor Origins of the Randomized, Placebo-controlled Phase 3 Study of Surufatinib in Advanced Well-differentiated Extrapancreatic Neuroendocrine Tumors (SANET-ep)

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BACKGROUND: Surufatinib showed significant prolonged progression-

free survival (PFS) benefit with a tolerable safety profile in patients with extrapancreatic neuroendocrine tumors (NETs) in a phase 3 study (SANET-ep). Here we present the post-hoc subgroup efficacy analysis according to Ki-67 and primary tumor origins from SANET-ep study.

METHODS: Totally, 198 patients were randomized (2:1) to surufatinib or placebo. The post-hoc subgroup analyses were performed based on Ki-67 subcategories: < 3% (n = 21 vs 11), 3-10% (n = 78 vs 44), > 10% (n = 30 vs 14); and primary tumor origin subcategories: foregut (n = 49 vs 29), midgut (n = 12 vs 6), hindgut (n = 40 vs 17), others (n = 8 vs 5) and unknown (n = 20 vs 12). The primary endpoint was investigator-assessed PFS, and the secondary endpoints mainly included objective response rate (ORR) per RECIST 1.1.

RESULTS: Median PFS was significantly prolonged in subgroups of Ki-67 3_10% (HR 0.47, 95% CI 0.29-0.74) and Ki-67 >10% (HR 0.14, 95% CI 0.05-0.40) with surufatinib versus placebo. ORR in the subgroups of Ki-67 <3%, 3-10%, >10% were 4.8% (95% CI 0.1-23.8), 7.7% (95% CI 2.9-16.0) and 20.0% (95% CI 7.7-38.6) respectively with surufatinib, versus none with placebo. Median PFS was significantly longer in the subgroups of foregut (HR 0.29, 95% CI 0.15-0.54) and hindgut (HR 0.35, 95% CI 0.18-0.67) with surufatinib versus placebo. ORR in the subgroups of foregut, midgut and unknown origin were 18.4% (95% CI 8.8-32.0), 16.7% (95% CI 2.1-48.4) and 10.0% (95% CI 1.2-31.7) respectively with surufatinib, versus none with placebo.

CONCLUSION: Results of this post-hoc analysis were consistent with the primary reports on surufatinib in the SANET-ep primary analysis, and improved outcomes were observed across major subgroups in patients with advanced well-differentiated extrapancreatic NETs.

ABSTRACT ID: 107

C-28

Subgroup Analysis by Ki-67 and Baseline CgA of the Randomized, Placebo-controlled Phase 3 Study of Surufatinib in Advanced Well-differentiated Pancreatic Neuroendocrine Tumors (SANET-p)

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BACKGROUND: In the phase 3 SANET-p trial (NCT02589821), surufatinib significantly increased progression-free survival (PFS) versus placebo in patients with progressive, well-differentiated, advanced pancreatic neuroendocrine tumors (NETs). Here we report the relationship of Ki-67 and baseline Chromogranin A (CgA) on efficacy outcomes.

METHODS: Overall, 172 eligible patients were randomized (2:1) to surufatinib or placebo. Investigator-assessed PFS and objective response rate (ORR) per RECIST 1.1 were used for the analysis. The post-hoc subgroup analyses were performed on Ki-67 subcategory: <5% (n = 40 vs 21), 5-10% (n = 57 vs 31), >10% (n = 16 vs 7), and baseline CgA subcategory: ≤2 times of upper limit of normal (ULN) (n = 59 vs 31), >2 _ ULN (n = 44 vs 24).

RESULTS: In the intent-to-treat population, surufatinib was superior to placebo, median PFS (mPFS) of 10.9 vs 3.7 months (mo) (p = 0.0011), with a stratified HR of 0.491 (95% CI: 0.319, 0.755). mPFS was significantly longer with surufatinib than that with placebo in subgroups of Ki-67 5-10% (11.0 vs 3.7 mo, HR = 0.33, p= 0.0002), Ki-67 >10% (11.1 vs 2.8 mo, HR = 0.04, p = 0.0003) and CgA >2 _ ULN (11.0 vs 3.7 mo, HR = 0.36, p = 0.0036). ORRs in the subgroups of Ki-67 <5%, 5-10%, and >10% with surufatinib were 15.8%, 24.0% and 12.5% respectively. There was only one partial response in the placebo arm (with Ki-67 <5%). ORRs in the subgroups of CgA ≤2 _ ULN and >2 _ ULN with surufatinib were 18.9% and 21.4% (with only one partial response in the CgA ≤2 _ ULN subgroup).

CONCLUSION: Surufatinib showed substantial improvement in PFS compared to placebo in patients with advanced, progressive, well-differentiated pancreatic NETs, irrespective of Ki-67 expression levels or baseline CgA.

ABSTRACT ID: 108

C-29

Efficacy and Safety of [^{177}Lu]Lu-DOTA-TATE in Patients With Advanced Pancreatic Neuroendocrine Tumours (panNETs): Data From the NETTER-R International, Retrospective Registry

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BACKGROUND: Peptide receptor radionuclide therapy with [^{177}Lu]Lu-DOTA-TATE (177Lu-DOTATATE) is used for the treatment of adults with somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine tumours. Additional efficacy and safety of 177Lu-DOTATATE in patients with pancreatic neuroendocrine tumours (panNETs) are presented here.

METHODS: NETTER-R is a retrospective registry of patients with unresectable/metastatic, well-differentiated, SSTR-positive, progressive panNETs treated with ≥1 administration of 177Lu-DOTATATE. The primary endpoint was progression-free survival (PFS) by RECIST v1.1. Secondary endpoints included overall survival (OS), safety and tumour response.

RESULTS: A total of 110 patients were identified. 70.0% of patients received all four cycles of 177Lu-DOTATATE. Cumulative activity was 29.6 GBq ±10% (26.6-32.6 GBq) in 65.5% of patients. Twelve patients received 1-4 additional cycles of 177Lu-DOTATATE after the initial treatment. By RECIST v1.1, evaluable in

62 patients, median PFS was 24.8 months (95% confidence interval [CI] 17.5-34.5) and objective response rate was 40.3% (95% CI 28.1-53.6); all responses were partial. With a median follow up of 24.5 months (range 2.0-123.4), median OS in 110 patients was 41.4 months (95% CI 28.6-50.2). PFS (hazard ratio [HR] 3.672; p=0.0009) and OS (HR 3.360; p<0.0001) were improved in patients who had not previously received chemotherapy compared with those that had. 71.8% of patients (n=79/110) had ≥1 treatment-emergent adverse event (TEAE). The most frequent TEAEs were nausea (28.2%) and fatigue (22.7%), predominantly grade 1/2. No TEAEs led to treatment discontinuation. Grade 3 anaemia, lymphopenia and thrombocytopenia occurred in 0.9%, 5.4% and 0.9% of patients, respectively. Renal TEAEs occurred in six patients (5.5%; grade 1: n=1, grade 2: n=2, grade 3: n=3). All renal grade ≥3 events were transient and did not lead to treatment modification. No acute leukaemia or myelodysplastic syndrome was reported.

CONCLUSION: These results reinforce 177Lu-DOTATATE as a treatment option in patients with advanced, SSTR-positive panNETs.

ABSTRACT ID: 110

C-30

Compose: Pivotal Phase III Trial of ^{177}Lu-Edotreotide Versus Best Standard of Care in Well-differentiated Aggressive Grade 2 and Grade 3 Gastroenteropancreatic Neuroendocrine Tumors

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BACKGROUND: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), which represent approximately 70% of NETs, frequently develop metastatic disease with limited treatment options. Current standard therapies for the subset of well-differentiated high grade 2 and grade 3 GEP-NETs include cytoreductive procedures, somatostatin analogues, molecular targeted therapies (everolimus or sunitinib), chemotherapy and peptide receptor radionuclide therapy (PRRT), with no specified sequence of use. PRRT may stabilize disease and induce objective tumor responses. This treatment uses radiolabeled somatostatin analogues to selectively target tumor cells expressing somatostatin receptor 2. PRRT in the form of ^{177}Lu-edotreotide is an innovative radiolabeled somatostatin analogue with a favorable safety profile and promising efficacy. The currently recruiting Phase III trial COMPETE in grade 1 and grade 2 GEP-NETs is comparing the efficacy and safety of ^{177}Lu-edotreotide, versus everolimus. Retrospective

data in metastatic GEP-NETs treated with two or more ^{177}Lu-edotreotide cycles demonstrated a PFS of at least 30 months.

METHODS: COMPOSE (NCT04919226) is a prospective, randomized, controlled, open-label, multi-center Phase III study to evaluate efficacy, safety and patient-reported outcomes of first- or later-line treatment with ^{177}Lu-edotreotide PRRT compared to best standard of care in patients with well-differentiated high grade 2 and 3 (Ki-67 index 15_55), SSTR+, GEP-NETs. It aims to randomize 202 patients 1:1 to a defined number of cycles of 177Lu-Edotreotide or an active comparator - either chemotherapy (CAPTEM or FOLFOX) or everolimus - according to investigator´s choice. The primary endpoint is progression free survival, assessed every 12 weeks until disease progression (RECIST v1.1), or death, whichever occurs earlier. Secondary outcomes include overall survival, assessed up to 2 years after disease progression.

RESULTS: Study recruitment for COMPOSE commenced in September 2021.

CONCLUSION: It is expected that COMPOSE will increase treatment options for patients with well-differentiated high grade 2 and grade 3 GEP-NETs, including for first-line therapy.

ABSTRACT ID: 136

C-31

Safety and Effectiveness of ^{177}Lu-Satoreotide Tetraxetan in Patients with Progressive Neuroendocrine Tumors (NETs): Interim Analysis of a Phase I/II Study

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BACKGROUND: ^{177}Lu-satoreotide tetraxetan is a novel SSTR antagonist, associated with higher tumor uptake compared to SSTR agonists. We report safety and effectiveness data of an ongoing phase I/II study (NCT02592707) investigating ^{177}Lu-satoreotide tetraxetan in progressive NETs, in which kidney (maximum 23 Gy) and bone marrow (maximum 1.5 Gy) dosimetry is used to guide administered activity.

METHODS: The study started on 6 Mar 2017 and enrolled 40 patients with unresectable/metastatic NETs; it is conducted in two parts. Part A comprises 15 patients who completed 3 cycles of ^{177}Lu-satoreotide tetraxetan at a fixed administered activity of 4.5 GBq/cycle and a peptide mass of 300 µg/cycle. Part B enrolled 25 patients who completed 1-5 cycles at different administered activities (4.5 or 6.0 GBq/cycle) and peptide masses (300, 700, or 1,300 _g/cycle).

RESULTS: As of 1 Apr 2021, median cumulative activity of ^{177}Lu-satoreotide tetraxetan was 13.0 GBq over 3 cycles. Most common grade 3/4 treatment-related adverse events (TRAEs) were lymphopenia, thrombocytopenia, and neutropenia

(Table). No grade 3/4 nephrotoxicity was observed. Serious hematological TRAEs were myelodysplastic syndrome (n=1) (part A), grade 4 thrombocytopenia (n=1), and acute myeloid leukemia (n=1) (part B). Disease control rate (DCR) was 94.7% (95% CI, 82.3-99.4), and objective response rate 21.1% (95% CI, 9.6-37.3). Median PFS has not been reached. No association between peptide mass of ^{177}Lu-satoreotide tetraxetan/cycle (300 to 1,300 µg) and increased toxicity was observed.

CONCLUSION: These preliminary data, reporting an acceptable safety profile and a high DCR, are promising and support a potential role for ^{177}Lu-satoreotide tetraxetan in treating advanced NETs.

ABSTRACT ID: 141

Grade ≥3 TRAEs

Number of patients (%)	Part A (N=15)	Part B (N=25)	Total (N=40)
Total	*5 (33.3)*	*10 (40.0)*	*15 (37.5)*
Lymphopenia	2 (13.3)	5 (20.0)	7 (17.5)
Thrombocytopenia	2 (13.3)	3 (12.0)	5 (12.5)
Neutropenia	0	3 (12.0)	3 (7.5)
Anemia	1 (6.7)	0	1 (2.5)
Acute myeloid leukemia	0	1 (4.0)	1 (2.5)
Myelodysplastic syndrome	1 (6.7)	0	1 (2.5)
Presyncope	1 (6.7)	0	1 (2.5)
Musculoskeletal pain	0	1 (4.0)	1 (2.5)

C-32

The Phase 3 NETTER-1 Study of ^{177}Lu-DOTATATE in Patients with Midgut Neuroendocrine Tumors: Updated Progression-free Survival Analyses

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BACKGROUND: In NETTER-1, primary analysis of centrally-assessed progression-free survival (PFS; primary endpoint: HR, 0.18 [95% CI, 0.11, 0.29]; p<0.0001, data cut-off [DCO] 24-July-2015), median PFS (mPFS) was not reached in the ^{177}Lu-DOTATATE arm.

METHODS: 231 patients were randomized to four cycles of ^{177}Lu-DOTATATE 7.4 GBq (200 mCi) Q8W plus long-acting octreotide 30 mg or long-acting octreotide 60 mg Q4W. After required PFS events for primary analysis, central assessment continued until disease progression (PD) or 18 months after randomization. Exploratory analyses of updated PFS (post hoc) and time from randomization to second investigator-assessed progression or death (PFS2; pre-specified) were performed.

RESULTS: At 31-August-2017 DCO, updated, centrally-assessed mPFS was 28.4 months (95% CI: 28.4, NE) and 8.5 months (95% CI: 5.8, 11.0) in the ^{177}Lu-

DOTATATE and control arms (HR, 0.21 [95% CI: 0.14, 0.33]); investigator-assessed mPFS was 26.0 months (95% CI: 19.4, 31.0) versus 8.5 months (95% CI: 6.0, 11.2; HR, 0.31 [95% CI: 0.21, 0.45]). At final analysis (18-January-2021 DCO), there were 54/117 (46.2%; PD: 41/117) and 73/114 (64.0%; PD: 63/114) investigator-assessed PFS events in ^{177}Lu-DOTATATE and control arms; mPFS was 25.0 months (95% CI: 17.8, 28.4) and 8.5 months (95% CI: 6.0, 11.2; HR, 0.30 [95% CI: 0.21, 0.44]). Similar numbers in each arm received everolimus and more patients in the control arm received PRRT as first subsequent treatment (Table). Median PFS2 was 45.0 months (95% CI: 39.6, 50.4) and 23.2 months (95% CI: 18.5, 28.4) in the 1^{177}Lu-DOTATATE and control arms (HR, 0.42 [95% CI: 0.29, 0.60]).

CONCLUSION: Updated PFS results by central and investigator assessment were consistent and clinically remarkable. The benefit with ^{177}Lu-DOTATATE was sustained into the subsequent line of therapy. First subsequent systemic anti-cancer treatment during long-term follow-up.

ABSTRACT ID: 142

C-33

Utility of Midpoint Imaging in Patients Receiving Peptide Receptor Radionuclide Therapy (PRRT) for Advance Progressive Gastroenteropancreatic-Neuroendocrine Tumors (GEP-NETs)

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BACKGROUND: The NETTER-1 trial formed the basis for standard practice of PRRT, consisting of 4 cycles with follow-up imaging during midtreatment and after completion to evaluate disease response. However, in clinical practice the timing of midpoint imaging varies if performed at all, and it is unclear how often it influences subsequent management. We aimed to determine the frequency at which midpoint imaging is performed during PRRT in patients with primary GEP-NET, the imaging modality most used, and if imaging results changed subsequent clinical management

METHODS: We reviewed patients at Mayo Clinic who started treatment with PRRT (Lu-177 DOTATATE) as of November 2020. Baseline patient demographics including oncology history were collected.

RESULTS: Out of 157 patients (median age 64, 0.5 male:female), 113 received midpoint imaging. Clinicians did not obtain midpoint imaging for 30. Prior to the midpoint of PRRT, 6 developed pancytopenia precluding further PRRT, and 8 passed. Midpoint imaging was obtained for 1, 91, and 21 patients before cycle 2, 3, and 4 respectively. The imaging modalities used were: 68Ga-DOTATATE PET MR (3), FDG PET MR (3), MR (41), CT (77). Some patients received 2 imaging types at midpoint.Of the 43 patients who did not complete PRRT, 12 passed prior to the next anticipated PRRT cycle. 27 had early PRRT termination based on clinical decision; of these, 21 received midpoint imaging which changed management for only 6. In the remainder, PRRT was stopped due to cytopenias (9), functional

status decline (4), or patient intolerance (2). At the time of analysis, 2 patients were lost to follow-up and 2 were still receiving PRRT.

CONCLUSION: In our clinical cohort, PRRT midpoint imaging rarely changed subsequent clinical management (6 of 113 cases).

ABSTRACT ID: 154

C-34

Secondary Hematological Malignancies Following High-specific Activity Iodine-131 Metaiodobenzylguanidine Treatment of Advanced Pheochromocytoma and Paraganglioma: a Case Series

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BACKGROUND: High-specific activity iodine-131 metaiodobenzylguanidine (HSA I-131 MIBG; AZEDRA®) is the only FDA approved systemic treatment for locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL). Systemic cytotoxic therapies are known risk factors for developing secondary hematological malignancies (myelodysplastic syndrome or acute leukemia). These events were reported in 6 (6.8%) of the 88 patients with PPGL who received a therapeutic dose of HSA I-131 MIBG. To better understand the risk, we undertook a detailed examination of the case reports of patients enrolled in these clinical trials.

METHODS: Two clinical trials (NCT00458952, NCT00874614) were performed to assess the efficacy and safety of HSA I-131 MIBG in patients with advanced PPGL. Adverse events (AEs) were graded according to CTCAE (v3.0) and were coded according to MedDRA (v19.0). Case reports were prepared by compiling and reviewing relevant MedWatch forms for FDA safety reporting (form 3500A) completed by study site investigators.

RESULTS: All six patients who developed a secondary hematological malignancy

(4 MDS, 1 ALL, 1 AML) had been exposed to at least one prior cytotoxic therapy prior to receiving two therapeutic doses of HSA I-131 MIBG (total range: 897.1-1032.54 mCi). These prior treatments included: low specific activity (LSA) I-131 MIBG, chemotherapy and external beam radiation therapy (EBRT) (n=1); chemotherapy and EBRT (n=2), LSA I-131 MIBG and EBRT (n=1); LSA I-131 MIBG only (n=1); and chemotherapy only (n=1). Alternatively, of 23 patients who received HSA I-131 MIBG as first line systemic cytotoxic therapy, none have developed a secondary hematological malignancy as of June 2021.

CONCLUSION: Secondary hematological malignancies following HSA I-131 MIBG treatment for PPGL must be considered in context of the number and intensity of prior cancer treatments. Earlier use of HSA I-131 MIBG in the treatment sequence prior to other cytotoxic agents may reduce the incidence of secondary malignancies.

ABSTRACT ID: 155

C-35

^{177}Lu Dotatate Peptide Receptor Radionuclide Therapy in Chronic Kidney Disease Patients: a Single Center Experience

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BACKGROUND: Chronic Kidney Disease (CKD) is common in metastatic neuroendocrine tumors. Unfortunately, therapy with ^{177}Lu-dotatate PRRT has not been well studied in this group. Our objective was to evaluate the incidence of acute kidney injury (AKI) and the risk of hematological toxicity among the CKD patients.

METHODS: A retrospective review of all consecutive adult patients that received ^{177}Lu-dotatate at our center between April 1, 2018 to April 30, 2019. We defined CKD as eGFR <60 ml/min or eGFR >60 ml/min with proteinuria and AKI as an increase in creatinine > 0.3 mg/dl within 48 hours or > 50% within 7 days.

RESULTS: 86 patients were included. Of these, 39 (45%) had pre-existing CKD. Average dose received was 632.1 mCi in CKD and 696 mCi in non-CKD patients (p 0.1675). AKI was reported in 4 (4.6%) patients with predominant cause being hypotension and were not attributed to ^{177}Lu-dotatate. In CKD group, the mean eGFR improved after Cycle 1 cycle from baseline of 49 (13) to 53.5 (17) ml/min (p 0.01). No statistically significant decline of kidney function was found at 3- and 6-month follow up. Higher rates of thrombocytopenia and leukopenia were noted in the CKD group but reached statistically significance only for platelets with median change in platelet count between baseline labs and pre-cycle 4 of -78 (-45 to -130) vs -37 (-10.25 to -96.75) cells/ml, p 0.0371. No significant correlation to cumulative drug dose or prior chemotherapeutic regimen received was found.

CONCLUSION: CKD patients are at an increased risk of acute hematological

toxicity with possibly a cumulative effect. Drug dosing and monitoring may need to be individualized based on unique patient bone marrow health profile by factoring in their age, comorbidities, and prior marrow toxic drug use. Long term impact of ^{177}Lu-dotatate in the CKD patients is still unclear.

ABSTRACT ID: 160

C-36

Cap-Tem-Y90 for Grade 2 Liver-dominant Net Metastases

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BACKGROUND: Grade 2 NET liver metastases have less durable PFS than low-grade tumors following embolotherapy (12 mo vs. 18 mo, Chen 2017). Capecitabine-Temozolomide (CapTem) is an effective regimen in NETs and both drugs are radiosensitizers. A feasibility study of integrated CapTem and Y90 transarterial radioembolization (TARE) demonstrated tolerability with expected additive toxicities and encouraging ORR and PFS. This study expands that report to a larger cohort with oncologic follow-up.

METHODS: Initial therapy consisted of capecitabine 600 mg/m2 twice daily for 14 days and temozolomide 150-200 mg/m2 in two divided doses on day 10-14, with 14 days between cycles. During the initial cycle of chemotherapy, the patient underwent simulation angiography with Tc99m-MAA SPECT. Once deemed to be eligible for radioembolization, the dominant lobe was treated on day 7 of the second cycle of CapTem. Resin Y90 microspheres (SIR-Spheres; Sirtex Medical) were administered according to the body surface area method. Patients with bilobar disease had the other lobe was treated on day 7 of the third or fourth cycle. CapTem was continued until progression or intolerance. Imaging was performed every 3 months.

RESULTS: 35/37 patients completed the prescribed regimen. Two patients did not receive a planned second lobar TARE due to post-embolization toxicities. Primary sites of disease were pancreas (16), lung (10), gut (7) and unknown (4). Mean duration of CapTem was 11 months (range, 4-32 mo). >G2 toxicities included cytopenias (8), pain (2), hepatic (2), fatigue (1), vomiting (1). ORR was 62%. Median hepatic-PFS was 26 mo. Differences in PFS among primary sites were not significant. 19 patients have died, with median OS from diagnosis not reached and 38 mo from treatment.

CONCLUSION: Radiosensitization with CapTem during TARE is tolerable and

provided durable control of liver metastases substantially longer than historical expectations for embolotherapy alone in this single-institution cohort.

ABSTRACT ID: 174

C-37

Treatment Response and Clinical Outcomes of Well-differentiated (WD) High-grade (HG) Neuroendocrine Tumors (NETs) to ^{177}Lu-DOTATATE

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BACKGROUND: ^{177}Lu-DOTATATE is an approved therapy for SSTR-positive gastroenteropancreatic NETs. Little data are available on response and outcomes for WD HG NETs treated with ^{177}Lu-DOTATATE.

METHODS: Patients with progressive WD HG NETs treated with ^{177}Lu-DOTATATE at MSK from 2018-2020 were identified. Demographics, treatment response, PFS (estimated using Kaplan-Meier methods) were determined. Next-generation sequencing (NGS) was performed in tumor samples through an institutional platform (MSK-IMPACT).

RESULTS: 19 patients were identified (mean age 54, 63% female, 14/19 (74%) pancreatic NET). Median Ki-67 32% (range 22-56). All tumors were SSTR-avid on pre-treatment Ga68-DOTATATE. Median number of prior systemic/liver-directed treatments 4 (range 2-7). Thirteen patients (68%) completed all four treatment cycles; treatment incomplete in 6 patients (treatment-related toxicities (N=3), clinical progression (N=3)). Best response by radiographic report (17 evaluable pts): 12/17 (71%) partial response, 5/17 (29%) disease progression. Three patients with response received additional cycles of ^{177}Lu-DOTATATE at progression. Median PFS (from date of first ^{177}Lu-DOTATATE treatment until progression/death) was 11.8 months (95% CI 10.6 to 18.6). Five patients (26%) experienced dose modifying toxicity. Most common treatment-related toxicities were thrombocytopenia (9 patients, 47%; G3/4 in 1 patient, 5%), anemia (7 patients, 37%; G3/4 in 2 patients, 11%), leukopenia (6 patients, 32%; G3/4 in 0 patients), AST/ALT elevation (4 patients, 21%; G3/4 in 0 patients). NGS results were available

in the tumor of 13 patients (68%). Most observed alterations were in MEN1 (6/13, 46%), DAXX (4/13, 31%). No RB1 alterations identified.

CONCLUSION: We observed a meaningful disease response of 71% during WD HG NET treatment with ^{177}Lu-DOTATATE. In this heavily pre-treated population, more than half of patients received all four treatment cycles. Treatment-related toxicities were largely bone-marrow related. As would be expected in SSTR-avid tumors, most had alterations in chromatin remodeling genes (MEN1, DAXX) consistent with WDNETs, with no RB1 alterations identified.

ABSTRACT ID: 178

C-38

Clinical Utility of Qualitative Post-treatment SPECT After Peptide Receptor Radionuclide Therapy

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BACKGROUND: Peptide receptor radionuclide therapy (PRRT) is an established treatment modality for NETs, usually using ^{177}Lu-DOTATATE. Although ^{177}Lu primarily emits beta particles, ^{177}Lu also emits gamma photons which can be imaged with SPECT. Most US centers do not currently perform post-PRRT scintigraphy. However, qualitative information on post-PRRT scintigraphy has the potential to impact clinical management.

METHODS: 24 hours after each administration of ^{177}Lu-DOTATATE, patients with metastatic well-differentiated NET underwent planar and SPECT/CT imaging from vertex to thighs. Images were evaluated by a board-certified nuclear medicine physician and compared to prior imaging (CT, MRI, SSTR PET, and prior post-PRRT scintigraphy). Cases in which post-PRRT scintigraphy findings contributed to a change in management were retrospectively recorded, including the nature of the findings (improvement, new lesions, etc.) and associated changes in management. Common themes in imaging findings and management changes were identified.

RESULTS: 13 cases were found in which post-PRRT imaging impacted management (patient characteristics in Table 1). Findings fell into the following 4 categories: new/growing lesion (n=4); marked response (n=4); mild to moderate response in the setting of toxicities and/or prior radionuclide therapy (n=3); and pseudoprogression (n=2). Management changes based on these findings fell into the following 4 categories: targeted treatment of new/growing lesion before resuming PRRT (n=4); deferring further PRRT for later progression (n=6); delaying next PRRT cycle (n=1); and continuing treatment in the setting of confirmed pseudoprogression (n=2). Case examples of each type of imaging finding with corresponding management change will be shown.

CONCLUSION: Qualitative findings on post-PRRT imaging can have a meaningful impact on the clinical management of NET patients. Routine next-day imaging of PRRT patients should be considered to help guide management.

ABSTRACT ID: 180

Table 1. Patient characteristics.

Characteristic	Parameter	Data
Sex	Female / Male	8 (61.5%) / 5 (38.5%)
Median age at first PRRT(years) (range)		67.5 (34-78)
Primary location	Small bowel / Pancreas / Bronchial / Rectal	5 (38.5%) / 5 (38.5%) / 2 (15.3%) / 1 (7.7%)
Tumor grade	G1 / G2 / G3	3 (23.1%) / 9 (69.2%) / 1 (7.7%)
Previous treatments	SSA / Liver-directed therapy / Surgery	12 (84.6%) / 9 (69.2%) / 5 (38.5%)
	Chemotherapy / Everolimus / External beam radiation	5 (38.5%) / 2 (15.4%) / 1 (7.7%)
	PRRT: Intravenous (4 cycles) / Intra-arterial to liver (1 cycle)	1 (7.7%) / 1 (7.3%)
Median dose of PRRT(mCi/Gbq) (range)		202.0 (187.4-205.3)/7.5 (6.9-7.6)
Median cycles of PRRT(range)		3 (2-4)

C-39

Blood-based Genomic Assessment of Clinical Efficacy and Toxicity of ^{177}Lu-DOTATATE of Neuroendocrine Tumors

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BACKGROUND: ^{177}Lu-DOTATATE is effective in NETs. Accurate monitoring of tumor response is constrained by radiation response. There are no effective predictors for response or toxicity. We utilized three independent blood-based gene expression assays: a 51-marker gene NETest to monitor therapeutic efficacy, PRRT Predictor Quotient (PPQ) - a molecular marker used to predict PRRT-responsiveness and a 16 gene radiation-toxicity (RAD-TOX assay) to assess hematological toxicity.

METHODS: MSKCC ^{177}Lu-DOTATATE-treated SSTR-positive GEP and lung NETs: n=55; median age 62; 47% female; 47% pancreatic; 39 G1/G2, 9 G3. All were metastatic (89% liver) and received 1-5 prior treatments (median 3) including somatostatin analogues (85%), surgery (49%), chemotherapy (53%). Response: OS and PFS. RECIST1.1; Responders: stable & partial response (DCR); Non-responders: progression. Blood collection: before each cycle and at follow-up. Samples de-identified, assay and analyses blinded. Gene expression assays: RNA isolation, real-time qPCR and multi-algorithm analyses. NETest (0-100 score). RAD-TOX score (-20 to +20). PPQ (positive = predict “responder”/negative = predict “non-responder”) at baseline. RADTOX-gene signature derived from genome-wide transcriptomic evaluations of radiation-toxicity/-sensitivity/-response gene expression studies (n=10,000 samples). Statistics: Mann-Whitney U-Test (2-tailed), Kaplan-Meier (PFS/OS), AUC.

RESULTS: 38 patients (70%) were responders. PPQ was accurate in 97% (32/33 responders). In responders, NETest decreased significantly (p=0.05) before cycle 3 (-17±9%); in "non-responders," NETest increased (+64±15%, p=0.0003). Hematological toxicity (>Grade 2) developed in 24 (44%). RAD-TOX significantly

increased (pre-PRRT: -1.94±6.8 vs. 4.7±2.7, p<0.0001) in those who developed toxicity but was unchanged in the non-toxic group (-7.6±3.6 vs. -7.9±3.7, p=0.81). AUC of RAD-TOX for predicting hematological toxicity: 0.75±0.06 (p=0.0004).

CONCLUSION: NETest decreased during ^{177}Lu-DOTATATE in responders, increased in non-responders and can be used as an early monitor of response. PPQ predicted response in 97%. RAD-TOX correlated with hematological toxicity and pre-PRRT scores predicted toxicity with 75% accuracy. Blood-based gene signatures are promising noninvasive tools to enhance management during ^{177}Lu-DOTATATE.

ABSTRACT ID: 183

C-40

Hepatotoxicity From Peptide Receptor Radionuclide Therapy (PRRT) in Neuroendocrine Tumors (NETs) Patients with Very High Liver Tumor Burden

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BACKGROUND: In patients with metastatic NET, high liver tumor burden correlates with poor prognosis. Although there is concern for an increased risk of radiation-induced hepatitis with increasing liver involvement, PRRT with ^{177}Lu-Dotatate has been shown to be both safe and effective in patients with >50% liver involvement. However, it is unclear if PRRT is safe in patients with very high liver involvement. We aim to describe the risk of hepatotoxicity for patients undergoing PRRT with tumor involving > 75% of the liver.

METHODS: After obtaining IRB approval, we conducted a retrospective analysis of 371 patients who received at least one cycle of PRRT. We did a refined search for "innumerable liver metastasis" within the imaging report. Three independent reviewers confirmed 19 patients with > 75% liver involvement on CT/MRI and 68Ga DOTATATE PET-CT.

RESULTS: Of the 19 patients with >75% liver involvement, only 3 experienced hepatotoxicity (defined as grade 2 or higher using the Common Terminology Criteria for Adverse Events v4.0). No patients had grade 4 or 5 hepatotoxicity. In this group, 4/19 patients completed fewer than 4 cycles, but none stopped because of liver failure. No patients died within 100 days of receiving PRRT.

CONCLUSION: When considering risk of liver injury from PRRT due to burden of disease, our data suggests that PRRT may be a safe option, even in patients with >75% liver involvement.

ABSTRACT ID: 190

C-41

Concurrent Everolimus with Hepatic Transarterial Bland Embolotherapy [Evero-Embo] in Patients with Bulky and/or Progressive Metastatic Well Differentiated Neuroendocrine Tumor

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BACKGROUND: Hepatically directed intra-arterial therapies in patients with well differentiated neuroendocrine tumors (NETs) offer improved outcomes with predictable and manageable toxicities. Systemic targeted therapies, such as everolimus and sunitinib, are frequently held 2-4 weeks prior to and after procedures. Embolotherapy results in anoxic injury, while everolimus effects cell growth, proliferation, and survival. Safety and response rates of concurrent use of everolimus with bland hepatic transarterial embolization (TAE) have been previously reported (ASCO 2019). Historically, bland TAE and chemoembolization have median hepatic progression-free survivals (mPFS) of ~9 and 18 months, respectively. We hypothesize that by continuing everolimus during and after bland TAE, hepatic mPFS will be greater than 18 months.

METHODS: A review of clinical and radiographic data was conducted for all sequential patients who underwent evero-embo between September 2016 and September 2020 at the University of Kentucky Markey Cancer Center. An independent radiologist performed response evaluation criteria in solid tumors (RECIST) measurements. To be included in this study, patients were required to have had systemic everolimus for ≥ one month prior to embolization and to be on everolimus immediately post procedure. Patients with at least 20 months post procedure follow-up were included for mPFS analysis.

RESULTS: A total of 96 TAEs with concurrent systemic everolimus were performed in 51 NET patients. Thirty of the 51 patients had 24 or more months of follow-up post-procedure. The median hepatic free progression (hPFS) is 30+

months.

CONCLUSION: Evero-embo results in a median hPFS exceeding that of bland or chemoembolization. A prospective clinical trial is planned to confirm the efficacy and safety of combining everolimus with hepatic bland embolotherapy.

ABSTRACT ID: 193

C-42

A Case of G3-WD Gastric Carcinoid Tumor in a MEN1 Patient with Discrepant Treatment Response to PRRT in Primary and Nodal Disease Sites

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BACKGROUND: Gastric carcinoid tumors occur in 15% to 50% of patients with multiple endocrine neoplasia-1 (MEN-1).

METHODS: We present a 69 year-old man with gastric carcinoid tumor in the setting of MEN1 with widespread metastatic liver disease. Although the ki67 was not available from his gastric biopsy, the liver biopsy showed well-differentiated, G3 metastasis of gastric origin with ki67 40%. The IHC showed positive chromogranin, synaptophysin, CD56. Serum gastrin, serotonin and urine 5-HIAA were negative. Prior to commencement of PRRT the patient has received Cisplatin + Etoposide, Carboplatin + Etoposide, Hepatic Embolization and SAS. Prior to PRRT, patient had a 68Ga-DOTATATE PET/MRI that showed the primary gastric mass (SUV 55) and the liver metastasis which progression in primary and metastatic disease sites. A consensus was obtained for this patient to move ahead with PRRT, in which he has received 4 cycles and achieved 25 mo PFS. During the first 4 cycles, he developed only mild side effects including nausea and fatigue, which both recovered before his next PRRT cycles. A follow up 68Ga-DOTATATE PET/MRI showed complete treatment response of the gastric carcinoid but progression of the metastatic liver lesions (SUV 32) with a single new bone lesion (SUV 71) . Patient was discussed in multidisciplinary setting and was offered the salvage PRRT to be complemented by TACE (Figure 1).

RESULTS: PRRT is becoming more prevalent to the management of GEP-NETs. Although gastric carcinoids are uncommon compared to pancreas and small bowel NETs, we show complete functional and anatomical treatment response at the gastric carcinoid despite progression of liver metastases requiring salvage PRRT.

CONCLUSION: Treatment response pattern in the primary and metastatic carcinoid tumor sites may be difficult to assess but certainly can alter the management. DOTATATE PET/MRI may help in patient selection and combining the treatment agents.

ABSTRACT ID: 198

C-43

MRI Has Improved Detection of Small Neuroendocrine Liver Metastasis Compared with Ga-68 DOTATATE

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BACKGROUND: Ga-68 DOTATATE has gained popularity as an imaging modality for neuroendocrine tumors (NET). It has proven useful in many clinical situations, such as identification of occult primary lesions and distant metastasis. However, for surgical planning, precise localization and understanding of disease burden is essential to determine resectability. MRI is often the preferred imaging modality for evaluation of liver pathology with excellent resolution. Unfortunately, there is a paucity of data comparing Ga-68 DOTATATE and MRI imaging specific to NET liver metastasis.

METHODS: A retrospective analysis was performed on patients with NET liver metastasis that had MRI and DOTATATE completed within 3 months of each other The studies were anonymized, and two radiologists independently evaluated the studies for the number of liver lesions and their smallest and largest sizes.

RESULTS: We identified 41 patients with NET liver metastasis and recent imaging with both Ga-68 DOTATATE and MRI. The median number of days between the imaging modality was 30 days [interquartile range (IQR) 5-20]. Our cohort was well balanced with 51% males (n=21) and 49% females (n=20) and a median age of 62 (IQR 55-68). Independent review of all imaging by two blinded radiologists showed low inter-rater variability with an intraclass correlation coefficient of 0.98 for MRI and 0.90 for DOTATATE. When excluding cases with extensive liver metastasis (>20 hepatic lesions), we found MRI was superior in detection of hepatic lesion, with a mean of 10.9 lesions with MRI vs 7.1 lesions in DOTATATE ($p<0.001$). Furthermore, in those patients with multiple lesions, MRI was able to detect significantly smaller lesions than DOTATATE (MRI mean 3.3mm vs DOTATATE mean 9.0mm, $p<0.001$).

CONCLUSION: Although Ga-68 DOTATATE imaging has significant utility in the diagnosis and surveillance of NET deposits, MRI may be more useful for identification of smaller most subtle lesions for pre-operative planning.

ABSTRACT ID: 200

C-44

Multifocality Is Not Associated with Worse Survival in Sporadic Pancreatic Neuroendocrine Tumors

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BACKGROUND: Sporadic pancreatic neuroendocrine tumors (pNETs) are typically unifocal and the incidence of multifocality and its impact on prognosis in sporadic pNETs is unknown.

METHODS: Patients who underwent resection of pNETs at Mayo Clinic from 2000 to 2019 were identified and clinical data obtained from records. Syndromic disease was defined as pNETs in the setting of MEN1, VHL, or NF1 and charts carefully reviewed to exclude the presence of an undiagnosed hereditary syndrome by clinical or familial criteria. Statistical comparisons were made using Chi-square and Kruskal-Wallis tests and survival assessed using the Kaplan-Meier method.

RESULTS: 661 patients with sporadic and 59 with syndromic pNETs were identified. 4.8% (n=32) of sporadic patients and 84.7% (n=50) of syndromic patients had multifocal disease ($p<0.001$). Of those with multifocal sporadic disease, 22 had two tumors and 10 three or more tumors. 26.4% of patients with unifocal sporadic disease and 25.0% of those with multifocal sporadic disease had functional tumors ($p>0.999$). Patients with one or two sporadic tumors had similar clinicopathologic features, while those with three or more sporadic tumors had slightly more favorable features (though non-significant), such as lower Ki-67 (30.0% <3% compared to 19.2% for unifocal and 18.2% for two tumors, $p=0.841$) and lower stage (90.0% stage 1-2 compared to 63.1% for unifocal and 63.6% for two tumors, $p=0.511$). Kaplan-Meier curves were similar for recurrence-free ($p=0.100$) and overall ($p=0.300$) survival. 5-year overall survival was 82.9% (95% CI 79.2-86.7) for unifocal sporadic and 89.9% (95% CI 77.6-100.0) for multifocal sporadic disease.

CONCLUSION: Multifocal sporadic pNETs are rare and multifocality is not associated with worse survival or increased recurrence risk. Hereditary cancer syndromes should be carefully ruled out in patients with multifocal tumors. Patients with multifocal sporadic pNETs can likely be safely managed with a combination of resection and observation as indicated for each tumor.

ABSTRACT ID: 58

C-45

Management of Duodenal Neuroendocrine Tumors: Surgical Versus Endoscopic Mucosal Resection

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BACKGROUND: Management of duodenal neuroendocrine tumors (DNETs) is not standardized, with lesions <1-2 cm treated by endoscopic mucosal resection (EMR) and larger DNETs by surgical resection (SR). This study analyzed how patients were selected for resection and compared outcomes.

METHODS: Patients with DNETs undergoing resection were identified through institutional databases, and clinicopathologic variables recorded. Chi-squared and Wilcoxon tests compared variables. Survival was determined by Kaplan-Meier analysis, and Cox regression tested association with survival.

RESULTS: In 104 patients, 64 underwent EMR and 40 had SR. Patients selected for SR had larger tumors, higher T-stage, more frequent metastases, and younger age. There was no difference in progression-free (PFS) and overall survival (OS) between EMR and SR patients. Ten patients had local recurrence post-EMR. Of these, 4 underwent repeat EMR and 4 underwent SR. In 1-2 cm DNETs, PFS was not different between SR vs. EMR. However, improved OS was seen in SR vs. EMR patients (median NR vs. 112 months, P = 0.01). In 1-2 cm DNETs, SR patients were more likely to be node-positive and younger. After adjustment for age, resection method did not correlate with survival. Comparison of SR patients with DNETs vs. 278 with jejunoileal NETs revealed significantly longer PFS (median NR vs. 73.4 months, P = 0.001) and OS (median NR vs. 119 months, P = 0.004) in DNET patients.

CONCLUSION: More advanced DNETs are selected for SR. For 1-2 cm DNETs, SR was associated with longer OS, likely due to older age in the EMR group.

Recurrences could be salvaged, suggesting initial EMR is a reasonable strategy. In comparison to jejunoileal NETs, DNETs treated by surgery had improved PFS and OS.

ABSTRACT ID: 64

Duodenal neuroendocrine tumors: endoscopic mucosal vs. surgical resection

Category	Level	EMR (n = 64)	Surgical resection (n = 40)	P value
Age at resection,median (range)		69.4 (28.5-87)	57.9 (36.9-75.6)	**<0.001**
N stage (%)	N0	26 (90%)	14 (40%)	**<0.001**
	N1	3 (10%)	21 (60%)	
M stage (%)	M0	54 (98%)	27 (71%)	**<0.001**
	M1	1 (2%)	11 (29%)	
Tumor size (mm), median (range)		7 (1-36)	15 (5-148)	**<0.001**
PFS, median, months		NR	NR	0.66
OS, median, months		141	NR	0.11
Follow-up, median, months		92	97.8	0.82

C-46

Alternative Lengthening of Telomeres Is Associated with Aggressive Pathologic Features and Increased Recurrence Risk in Large Pancreatic Neuroendocrine Tumors

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BACKGROUND: The behavior of pancreatic neuroendocrine tumors (pNETs) ranges from indolent to aggressive. The decision to observe or resect a pNET is primarily based on size, but size is an imperfect indicator of tumor aggressiveness. Recently, alternative lengthening of telomeres (ALT) has emerged as a promising marker of aggressive behavior in pNETs.

METHODS: Patients with well-differentiated non-functional sporadic pNETs >3 cm in size who underwent resection at Mayo Clinic from 2000 to 2019 were identified and clinical data obtained from medical records. ALT status was assessed by fluorescence in situ hybridization (FISH). Patients were classified as low-risk if they had both Ki-67 <3% and were ALT-negative or high-risk if they had either Ki-67 >3% or were ALT-positive.

RESULTS: Of 82 patients identified, 42 (51.2%) were ALT-positive and 40 (48.8%) ALT-negative. ALT-positivity was associated with larger tumor size (50 vs. 41 mm, p=0.010), higher Ki-67 index (82.6% vs. 40.0% >3%, p=0.018), and lymphovascular invasion (LVI) (56.7% vs. 18.8%, p=0.031). ALT-positive patients had worse recurrence-free survival (RFS) (p=0.002) but not overall survival (p=0.362). In univariate analysis, ALT (HR 3.78, p=0.003), LVI (HR 4.94, p=0.005), and perineural invasion (PNI) (HR 22.99, p=0.003) were associated with recurrence. In multivariate analysis, only Ki-67 index >3% (HR 14.61, p=0.009) and PNI (HR 7.03, p=0.001) remained significant predictors of recurrence. Patients who had both Ki-67 and ALT data available were stratified into low-risk (n=9) or high-risk (n=29) groups. RFS was significantly different between the two groups (p=0.049), with a

5-year RFS of 100.0% in the low-risk group and 43.3% in the high-risk group.

CONCLUSION: ALT is associated with aggressive pathologic features and worse RFS in large resected pNETs. Combined use of Ki-67 and ALT status could improve recurrence risk stratification following resection and potentially improve treatment selection for patients who are candidates for both observation and resection.

ABSTRACT ID: 111

C-47

Pathologic Features of Small Pancreatic Neuroendocrine Tumors with Liver Metastasis

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BACKGROUND: Management of pancreatic neuroendocrine tumors (PanNETs) ≤3cm is controversial as many remain localized, but metastasis can occur. We sought to identify pathologic features associated with metastatic disease in small PanNETs (≤3cm).

METHODS: Institutional approval was obtained for this HIPAA-compliant study. Surgical Pathology archives were searched for PanNET resections (pancreatectomy/enucleation) between 01/01/2005 to 12/30/2019. Ninety-three cases with tumor size ≤3.0 cm, slides available to review and follow-up data were included in the study. Hematoxylin and Eosin (H&E) slides were reviewed for various pathologic features. Pathology reports and electronic medical records were also reviewed.

RESULTS: Liver metastasis was discovered at initial presentation in 3 and developed during follow-up in 5 of 93 patients. No liver metastases were identified in the 17 cases with a tumor size up to 1 cm, whereas 4 of 48 (8%) patients with a tumor size >1 cm to 2 cm and 4 of 28 (12%) with a tumor size >2 cm to 3 cm presented with synchronous or metachronous liver metastasis. None of 8 insulinoma cases developed liver metastasis. One of 2 gastrinomas (2.4 cm) presented with liver metastasis at initial diagnosis. Four of 8 cases with liver metastasis showed prominent stromal fibrosis (sclerosing variant), despite the 3 of the four having a tumor size ≤2 cm. Seven cases with liver metastasis showed venous invasion, demonstrated by tumor nodules surrounded by thickened fibrotic septa on H&E stain. All cases with liver metastasis displayed at least focal infiltrating growth pattern. Ki67 index was available in 6 metastatic cases, ranging from 4-27%, with three of them having a Ki67 index >20%.

CONCLUSION: Sclerosing morphology, infiltrating growth pattern and venous

invasion may be associated with liver metastasis in small PanNETs. Further studies are needed to identify biomarkers associated with distant metastasis in these small tumors.

ABSTRACT ID: 113

C-48

Venous Invasion in Resected Pancreatic Neuroendocrine Tumors Is Independently Associated with Disease Free Survival and Overall Survival

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BACKGROUND: Venous invasion (VI) is a well-established independent prognostic indicator in gastrointestinal malignancies; however, the frequency and prognostic significance of VI in resected pancreatic neuroendocrine tumors (PanNETs) is not well established.

METHODS: Institutional approval was obtained for this HIPAA-compliant study. Surgical Pathology Archives at Duke University Medical Center were searched for pancreatectomy specimens performed for PanNET between 01/10/2005 to 12/30/2019. Enucleation specimens of PanNET were excluded. One hundred and forty-five cases with slides available for review and at least one year follow-up were identified. Hematoxylin and Eosin (H&E) slides were reviewed for VI, and Movat's stain was performed when there was suspicious for VI. Pathology reports and electronic medical records were also reviewed.

RESULTS: VI was suspected when there was a circumscribed tumor nodule adjacent to a muscularized artery and was identified in 47 of 145 (32%) cases. While 17 of the 47 (36%) cases with VI showed partially intact venous walls lined by endothelial cells, which could be recognized on H&E stain, Movat's stain was necessary to confirm VI in most cases. VI was correlated with larger tumor size, higher WHO tumor grade, extra-pancreatic extension, lymph node metastasis and liver metastasis ($p<0.05$). In addition, VI was associated with a worse overall and disease-free survival ($p<0.001$). In univariate analyses, tumor grade ($p=0.02$), VI ($p<0.001$), T stage ($p=0.04$) and M stage ($p=0.008$) were associated with overall survival, whereas tumor grade, VI, T stage, N stage and M stage were all associated with disease-free survival ($p<0.0001$). In multivariate analyses, only VI was independently associated with both overall survival ($p=0.02$) and disease-

free survival (p=0.01).

CONCLUSION: VI in resected PanNETs is not uncommon, and is a poor prognosticator. Extra care should be taken to identify VI in pancreatectomies for PanNETs.

ABSTRACT ID: 114

C-49

Importance of Grade in the Surgical Management of Rectal Neuroendocrine Tumors

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BACKGROUND: The incidence of rectal neuroendocrine tumors (NETs) is increasing, and surgery is potentially curative. Current guidelines to proceed with surgical resection depend mainly on tumor size or T stage. We evaluated the role of grade on surgical decision-making and disease trajectory for rectal NETs.

METHODS: Patients with rectal NETs referred to a centralized cancer program between 2004-2015 were reviewed. Baseline characteristics and treatment were recorded. Associations between grade, tumor characteristics, relapse, and survival were determined using Chi-Square, Log-rank, and Kaplan-Meier univariate analyses.

RESULTS: Overall, 65 patients were referred with rectal NETs, with 11% aged ≥70 years and 45% females. Of these, 49%, 26% and 14% had grade 1 (G1), 2 (G2), and 3 (G3) disease, respectively. The rate of procedural intervention declined with increasing grade, ranging from 97% in G1 to 11% in G3 patients ($p<0.001$). Of G1 patients, only 19% of patients had surgical resection after endoscopic polypectomy; all of these patients had transanal excision. Conversely, 92% ($p<0.001$) of G2 patients had surgical resection of which 50% were radical resections. Positive margins were the most common reason for additional procedures (51%). On final pathology, grade was associated with pT stage ($p<0.001$) and lymphovascular invasion (LVI; $p=0.036$)where 42% and 25% of G2 patients had ≥pT2 and LVI, compared to 6% and 0% in G1 patients, respectively. Log-rank test showed that G2 patients were more likely to recur compared to G1 patients (44% vs. 3%; $p=0.003$). Only one G3 patient underwent radical resection as 89% had metastatic disease at diagnosis. Grade was associated with mortality

(p<0.001)with G3 patients having the shortest median survival (4.7 months) compared to G2 (86 months) and G1 patients (median not reached).

CONCLUSION: Grade is an important marker of disease trajectory in rectal NETs and impacts definitive surgical decision-making and disease outcome.

ABSTRACT ID: 115

C-50

Detection Method and Overall Survival in Surgically Resected Pancreatic Neuroendocrine Tumors

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BACKGROUND: Pancreatic neuroendocrine tumors (pNETs) are rare tumors often identified incidentally by imaging or laboratory evaluation. We hypothesized that patients with symptom-detected tumors would present with more advanced disease and have decreased overall survival (OS).

METHODS: Patients with pNETS resected at a single-institution between 01/01/2000-09/30/2019 were analyzed using a prospectively maintained database. OS was calculated using the Kaplan-Meier method. Clinical factors (age, sex, tumor grade, stage, functionality, and resection type) were analyzed using Cox-regression to determine impact on OS. The impact of tumor detection method on stage and OS was analyzed.

RESULTS: 181 patients were included. 95 (59.0%) were classified as stage I, 43 (26.7%) stage II, 3 (1.9%) stage III, and 20 (12.4%) stage IV. Median OS was 139.4 months (IQR 77.2-424.8). 5-year OS was 81.9% for stage I, 83.0% stage II, 50.0% stage III, and 53.9% stage IV. Increasing age (HR=1.04±0.01, p<0.001) and tumor stage (HR=1.44±0.20, p=0.009) were associated with decreased OS. Of 136 patients with information on detection method, 86 (58.5%) tumors were symptom-detected, 11 (7.4%) by incidental laboratory abnormalities, and 50 (34.0%) by incidental imaging findings. Symptom-detection was more common with advanced stage (48.8% stage I, 62.2% stage II, 66.7% stage III, 81.3% stage IV), although not statistically significant (p=0.193). Functional and non-functional tumors were symptom-detected at similar rates (59.7% vs 54.6%, p=0.60). Tumor detection method had no significant effect on OS (HR=1.03±0.21, p=0.889).

CONCLUSION: Most patients with pNETs were diagnosed after noticing

symptoms. Despite symptom-detected tumors having more advanced stage, tumor detection method was not prognostic of stage or OS. This cohort was limited by low patient numbers with advanced disease, and detection method may be prognostic in other cohorts.

ABSTRACT ID: 144

Tumor detection method, sorted by stage and functionality.

Tumor Type	Stage	Detection Type		
		Symptoms	Lab Evaluation	Imaging
Functional	I	8 (42.1)	8 (42.1)	3 (15.8)
	II	2 (50.0	1 (25.0)	1 (25.0)
	III	N/A	N/A	N/A
	IV	2 (66.7)	0	1 (33.3)
Nonfunctional	I	31 (50.8	1 (1.6)	29 (47.5)
	II	21 (63.6)	0	12 (36.4)
	III	2 (66.7)	0	1 (33.3)
	IV	11 (84.6)	0	2 (15.4)

C-51

A Single-Center Experience in Observation of Small Pancreatic Neuroendocrine Tumors: To Operate or Not to Operate?

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BACKGROUND: Management of small (≤2 cm) primary, non-metastatic, non-functioning pancreatic neuroendocrine tumors (pNET) is discretionary. Observation can be recommended for low-grade, <1cm tumors. Our study aims to assess whether surveillance of small, low-grade non-functioning pNETs is appropriate.

METHODS: A retrospective review of patients referred to our high-volume hepato-pancreato-biliary center and diagnosed with pNET was conducted. Eligible patients were identified from pre-existing institutional database and confirmed via chart review.

RESULTS: 126 patients had the diagnosis of biopsy-proven pNET. 8 patients had metastatic disease at time of presentation and were excluded from further analysis. Of the 118 patients analyzed, 26 (22.0%) had functioning lesions and 92 (77.9%) non-functioning lesions. All 26 patients with biopsy-proven functioning lesions underwent surgical resection. Of 92 biopsy-proven non-functioning lesions, 36 had lesions ≤2.0 cm. Of these 36 patients, 31 were observed and 5 underwent an attempt at surgical resection. All 5 operative patients had biopsy-proven Grade 3 lesions. Of the 31 observed patients, 20 (64.5%) were Grade 1 and 11 (35.5%) Grade 2. 10 of the 31 patients (32.2%) had tumor size <1 cm. The mean follow-up time in months for patients who were observed with lesions ≤2.0 cm is 27.24 months. Of 31 patients, 24 presented with consistently stable disease on follow up imaging, 7 presented with decreased disease burden (defined as reduction in size or complete absence) and none presented with disease expansion. Of the 7 patients with decreased disease, 5/7 (71.4%) presented with no evidence of pancreatic disease on imaging,

despite previous biopsy proven and radiographic proven evidence of disease.

CONCLUSION: Our study demonstrates that observation is appropriate for low-grade pNET tumors <1cm. Close observation can be considered for nonfunctioning grade 1 or 2 pNET tumors ≤2cm, while grade 3 lesions should proceed with surgical resection. Further study is needed to guide recommendations.

ABSTRACT ID: 148

C-52

Role of Chromogranin A in the Diagnosis and Follow up of Neuroendocrine Neoplasms: Real World Review

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BACKGROUND: The clinical utility of chromogranin A (CgA) in management of neuroendocrine tumours (NET) is controversial with high rates of false positives and false negatives. We evaluated CgA use at diagnosis, treatment monitoring and recurrence detection.

METHODS: A retrospective review of medical records was conducted of patients with NET who had CgA measured from January 2015 to April 2021. Diagnosis was confirmed by histological means or Gallium-68 DOTATATE scan. For treatment monitoring, CgA was classified as increased, stable or decreased if there was at least a 25% change in levels. Tumour burden was assessed by CT, MRI or Gallium-68 DOTATATE scan. CgA level and imaging performed for contemporaneous assessment were considered paired. Calculations for sensitivity and specificity were made by conventional formulas.

RESULTS: Sixty-seven patients with NET who had a serum CgA level measured were identified. The commonest primary tumour site was pancreas and 64% had metastatic disease. There were 50 paired assessments during diagnostic work up; 33 with elevated CgA representing true positives and 17 with normal CgA representing false negatives. Therefore, the sensitivity is 66%. Sensitivity is higher in patients with symptoms and metastatic disease. There were 320 CgA measurements in follow up; 295 (92%) resulted in no further action, 8 (3%) in further investigation and 14 (4%) had a change in therapy, though 8 were most likely informed by progressive disease seen on imaging. Of 93 paired assessments for treatment monitoring, sensitivity for progressive disease was only 16%. Of 36 paired assessments for watch and wait patients, sensitivity for progressive disease was 64%.

CONCLUSION: Our findings do not support the use of CgA in clinical

decision making. The development of new biomarkers are needed to aid the management of NET.

ABSTRACT ID: 149

C-53

A Prospective Study of Carcinoid Crisis with No Perioperative Octreotide

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BACKGROUND: Octreotide has been used prophylactically to reduce crisis rates as well as therapeutically to treat crises that still occur. However, multiple retrospective studies using prophylactic octreotide still report crisis rates of 24-30%. Average crisis duration with octreotide use range from 8.9-19 minutes and 8-24% last > 10 minutes. A recent prospective study showed there is no massive release of hormones during crisis, greatly weakening the argument for octreotide. Before recommending cessation of octreotide use, the incidence ,duration and complications from crisis need to be studied when it is not used.

METHODS: Patients with NETs undergoing operations between 2017-2020 with no perioperative prophylactic or therapeutic octreotide were prospectively studied. Crisis was declared by agreement of surgeon and anesthesiologist if sudden hemodynamic instability was observed with no plausible alternative explanation. Clinicopathologic data were compared by chi-squared test for discrete and Mann-Whitney U test for continuous variables.

RESULTS: 171 patients underwent 195 operations. Crisis was documented in 49 operations (25%). Median crisis duration was 3 minutes and none lasted >10 minutes (0%). Crises correlated with small bowel primary ($p=0.012$), grade 2 tumor ($p=0.015$), older age ($p=0.021$), and carcinoid syndrome ($p<0.0001$), but there was no significant difference in outpatient long acting somatostatin analog use. Patients with crisis were more likely to receive vasopressors ($p=0.04$), intraoperative transfusions ($p=0.006$), and have major postoperative complications ($p=0.003$). Complication rates were not higher than previous reports using octreotide.

CONCLUSION: Completely eliminating perioperative octreotide did not result in increase rate or duration of crisis, or major complication rates compared to previous studies using it. We conclude that perioperative octreotide use may be

safely stopped due to inefficacy and lack of scientific grounds. Because crisis of even short duration is associated with increased risk of major complications, the search for an effective prophylactic agent should continue.

ABSTRACT ID: 163

C-54

Differences in the Mutation of DAXX, ATRX, and MENIN in Pancreatic Neuroendocrine Tumors from Black and White Patients

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BACKGROUND: Racial disparities in outcomes are known to exist in pancreatic neuroendocrine tumors (pNETs) but have historically been attributed to socioeconomic factors. However, recent studies of racial health disparities have uncovered numerous prognostic differences in the (epi)genetics of various cancers among ethnoracial groups. Such differences have been discovered in breast, prostate, colon, and endometrial cancer, but haven't been investigated in pNETs. The known prognostic epigenetic regulatory proteins DAXX, ATRX, and MENIN are commonly mutated in pNETs (59%, 25-85%, and 18-72% respectively). Most mutations alter the protein and are detectable by IHC. This research aimed to evaluate DAXX, ATRX, and MENIN between Black and White patients for differences in mutation frequency as determined by immunohistochemistry (IHC).

METHODS: Tissue microarrays (TMAs) containing resected primary well-differentiated pNETs from 40 White and 13 Black patients were stained with antibodies specific to DAXX, ATRX, or MENIN. Stains were evaluated by a pathologist as positive or negative based on published guidelines for each respective protein. Frequencies of positive and negative stains between Black and White patients were compared using Fisher's exact test.

RESULTS: 9/40 (23%) White and 2/13 Black patients (15%) were negative for DAXX expression (p=0.711;). 2/40 (5%) White and 1/13 (7%) Black patients were negative for ATRX expression (p=>0.999). 11/40 (28%) White and 0/13 Black patients were negative for MENIN expression (p=0.047; Table 1).

CONCLUSION: The significant difference in loss of MENIN in specimens from

Black patients supports the hypothesis that differential epigenetic modulation may be occurring in pNETs arising in this population.

ABSTRACT ID: 170

Table 1.

Stain	Black (13)	White (40)	P-Value
DAXX Negative	2/13 (15%)	9/40 (23%)	0.711
ATRX Negative	1/13 (7%)	2/40 (5%)	>0.999
MENIN Negative	0/13 (0%)	11/40 (28%)	**0.047***

C-55

Early Onset Well Differentiated Pancreatic Neuroendocrine Tumors: Clinical Presentation, Pathologic Features, and Oncological Outcomes

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BACKGROUND: Young onset of several gastrointestinal cancers is associated with more advanced disease and poor oncological outcomes, however, this association has not been fully investigated for well differentiated pancreatic neuroendocrine tumors (PanNET). Our study aimed to evaluate clinical and pathological differences and disease outcomes between young-onset PanNET (YO-PanNET) and late-onset PanNET (LO-PanNET).

METHODS: Patients with localized PanNET who underwent surgery at MSK between 2000 to 2017 were identified. Those with hereditary syndromes, metastatic disease, and postoperative mortality were excluded. YO-PanNET was defined as <50 and LO-PanNET >50 years of age at time of diagnosis. Family history, clinical and pathology characteristics, were recorded. Fisher's exact test was used to detect difference between the age groups. Kaplan-Meier method was used to investigate age prognostic significance.

RESULTS: A total of 366 patients were identified, 84 (23%) with YO-PanNET. Compared with LO-PanNET, YO-PanNET were less likely to have a personal history of another cancer ($p< 0.001$) and 1st line relative with cancer ($p< 0.015$). We did not observe any significant differences between YO-PanNET and LO-PanNET with regards to pathology features such as tumor grade ($p=0.7$), size ($p=0.5$), nodal metastases ($p=0.8$), and stage of disease ($p=0.7$). With a median follow-up of 68 months (range 0-238), 5-year recurrence-free survival was 76% and 83%, and 10-year RFS was 69% and 78%, respectively, in YO-PanNET and LO-PanNET ($p=0.12$) with similar 5- and 10- year overall survival ($p=0.31$).

CONCLUSION: In this large retrospective surgical series, we found that

YO-PanNET is not associated with an increased rate of personal or familial history of cancer. Pathological characteristics and long-term oncological outcomes do not significantly differ between YO-PanNET and LO-PanNET. Current efforts include next-generation sequencing analysis in the resected surgical specimens to evaluate for genomic biomarkers of recurrence.

ABSTRACT ID: 176

C-56

Comparison of Patients with Small Bowel Neuroendocrine Tumor Liver Metastaseswith and without Carcinoid Syndrome: A Single Institutional Analysis

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BACKGROUND: Carcinoid syndrome is common in patients with small bowel neuroendocrine tumor liver metastases (NETLM) and associated with a spectrum of clinical symptoms. The role for surgery, liver-directed therapy (LDT), hormonal therapy, and peptide receptor radionucleotide therapy (PRRT) for these patients is evolving. We investigated the clinical characteristics and treatment modalities utilized for patients with small bowel NETLM with and without carcinoid syndrome.

METHODS: Clinicopathologic characteristics for patients who were diagnosed with metastatic small bowel NETLM from 1999-2019 were abstracted from a retrospective database at an academic medical center. Patients were stratified by presence of carcinoid syndrome ("non-carcinoid" vs. "carcinoid"). Demographics, treatments, pathologic characteristics, and overall survival (OS__) were compared among groups.

RESULTS: Of 82 patients with small bowel NETLM, 44 (53.7%) had carcinoid symptoms. Presentation with metastatic disease and presence of extrahepatic disease were similar. Patients underwent resection of primary (92.1% non-carcinoid vs. 84.1% carcinoid, p = 0.27) and hepatic resection (47.4% non-carcinoid vs. 54.5% carcinoid, p = 0.62) at similar rates. Of the patients who underwent primary resection, there was no difference in Ki-67 grade, mitotic grade, or nodal positivity. Utilization of LDT was similar (50.0% non-carcinoid vs. 54.5% carcinoid, p = 0.68), and more symptomatic patients received octreotide/lanreotide (81.6% non-carcinoid vs. 97.7% carcinoid, p = 0.01). Treatment with

PRRT was more common in symptomatic patients (2.6% non-carcinoid vs. 31.8% carcinoid, $p < 0.05$). Carcinoid heart disease was identified in 17 (38.6%) of carcinoid patients. While more symptomatic patients were deceased (3 non-carcinoid vs. 13 carcinoid, $p = 0.014$), median OS was similar (not estimable [non-carcinoid] vs. 192 months [carcinoid], $p = 0.146$).

CONCLUSION: Management of patients with small bowel NETLM is evolving and involves multiple treatment modalities. Presence of carcinoid syndrome may impact these decisions and should be taken into consideration with a multidisciplinary approach to care.

ABSTRACT ID: 182

C-57

HPG_{80}(circulating progastrin), a Novel Blood-based Biomarker for Detection of Poorly Differentiated Neuroendocrine Carcinoma and Well Differentiated Neuroendocrine Tumors

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BACKGROUND: Current blood-based biomarkers for neuroendocrine neoplasms (NENs) lack both sensitivity and specificity. This is especially true for high-grade NENs (small and large cell neuroendocrine carcinomas). Human circulating progastrin (hPG_{80}) is a novel biomarker for NENs and is easily measured in plasma using an ELISA test. This study is the first to explore hPG_{80} in NENs.

METHODS: Progastrin concentrations were quantified in plasma from 95 patients with stage IV NEN using DxPG80technology (ECS Progastrin, Switzerland) and compared with hPG_{80} concentrations in 50-80-year-old healthy donors (n=252) as well as a subgroup comprised of only the 18-25-year-olds (n=137).

RESULTS: The median hPG_{80} in NENs patients was 5.54 pM as compared to 1.5 pM for patients in the 50-80-year-old control group and 0.29 pM for patients in the 18-25-year-old cohort ($p<0.0001$, one-tailed Mann-Whitney U-test). A subgroup analysis of NENs revealed a median hPG_{80} of 3.54 pM in neuroendocrine carcinoma (NEC n=25) vs 5.8 pM in neuroendocrine tumor (NET n=70). Interestingly small cell lung cancer sub cohort (n=13) also showed significant elevation of hPG_{80}(9.09 pM). All the above-mentioned differences were statistically significant as compared to healthy controls.

CONCLUSION: Plasma hPG_{80} in NENs suggests hPG_{80} may be a diagnostic blood biomarker for both low- and high-grade NENs and further study is warranted. A prospective NET trial is ongoing to evaluate its role in monitoring of disease (NCT04750954)

ABSTRACT ID: 194

P-1

Predictors And Outcomes Of Minimally Invasive Surgery For Small Bowel Neuroendocrine Tumors

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BACKGROUND: Open surgical resection with regional lymphadenectomy is the standard of care for small bowel neuroendocrine tumors (SBNETs). There is no consensus on the role of minimally invasive surgery (MIS). This study aims to evaluate the current national trends and determine if MIS is an oncologically appropriate treatment for SBNETs.

METHODS: The National Cancer Database was queried for patients with Stage I-III SBNETs who underwent surgery from 2010-2017. Time trends were examined using the Cochran-Armitage test. Chi-square tests, t-test, and multivariable logistic regression assessed associations of surgical approaches with patient, clinical, and facility characteristics. Propensity score weighted Cox proportional hazards model captured the impact of the surgical approaches on survival.

RESULTS: Of the 9,297 patients with Stage I-III SBNETs, 42.6% (N=3964) and 57.4% (N=5333) underwent MIS and open surgery, respectively. From 2010-2017, the proportion of MIS increased from 32.2% to 53.6% (P<0.001). Patients with Stage I disease (OR =1.37), age <56 (OR=1.12), private insurance (OR=1.37), and receiving care at higher volume centers (OR=1.30) were more likely to undergo MIS (all P<0.001). The average number of lymph nodes (LN) harvested in the MIS cohort was greater than in the open surgery cohort (14.8 vs 13.6 LN, P<0.001). MIS patients had shorter length of stay by 2 days (P<0.001). The MIS approach and LN yield ≥8 were associated with better survival (HR=0.671 and HR=0.780, respectively, P<0.001).

CONCLUSION: With its increasing utilization, superior lymph node yield, and notable survival benefits, a MIS approach should be considered for standard treatment of Stage I-III SBNETs.

ABSTRACT ID: 27

P-2

Incidence of Psychiatric Illness in Patients With Neuroendocrine Tumors - A Comparative Population-Based Analysis

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BACKGROUND: Diversion of tryptophan to hormonal production has been suggested to result in increased prevalence of psychiatric illnesses (PI) in neuroendocrine tumors (NET), but such data are limited to case reports. We measured the occurrence of PI after NET diagnosis compared to matched colon cancer (CC) cases.

METHODS: We linked population-based healthcare data to match adults with NET 1:1 to CC (2000-2019). PI was defined by mental health diagnoses (depression, psychosis, anxiety, schizophrenia) and mental health use after cancer diagnosis and categorized as severe, other, and none. Cumulative incidence functions accounted for death as a competing risk.

RESULTS: 11,223 NETs were matched to CC controls. Median follow-up was 49 (interquartile range - IQR 18-95) months for NETs and 45 (IQR 19-92) months for CC. There was no difference in pre-cancer PI between groups. There was no difference in post-cancer PI by NET primary site or metastases. 5-year cumulative incidence of severe PI for NET vs CC was 7.7% (95%CI 7.2-8.2%) vs 7.6% (95%CI 7.2-8.2%) (p=0.50), and that of other PI was 32.9% (95%CI 32.0-33.9%) vs 31.6% (95%CI 30.8-32.6%) (p=0.0053). In sub-groups of small bowel and lung NETs and of confirmed functional NETs, 5-year cumulative incidences of severe PI and other PI were statistically higher than for matched CC. However, absolute differences were small, with 1.4% for severe and 3.5% for other PI in small bowel and lung NETs, and 1.1% for severe and 3.5% for other PI in confirmed functional NETs.

CONCLUSION: Patients with NETs did not have higher incidence of PI after cancer diagnosis compared to CC, except marginally in sub-groups of small bowel and lung NETs and confirmed functional NETs. These data did not substantiate hypotheses of a relationship between PI and NETs. Future work should examine healthcare use patterns indicating potentially unrecognized illnesses that could go undiagnosed.

ABSTRACT ID: 74

P-3

Incidence and Predictors of Second Cancers in Neuroendocrine Tumors

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BACKGROUND: While long-term follow-up is crucial for neuroendocrine tumors (NET) due to prolonged survival, data on second cancers (SC) are scarce. We evaluated the risk and predictors of SC after NET diagnosis.

METHODS: We performed a population-based retrospective cohort study of gastrointestinal (GI) and pulmonary NET from SEER (2000-2016). Standardized incidence ratios (SIR) were calculated to compare SC incidence among NET to the general US population. Accounting for the competing risk of death, we examined the incidence of SC with cumulative incidence functions (CIF) and predictors of SC were identified with Fine-Gray multivariable models.

RESULTS: Among 58,596 NETs, there was increased incidence of SC for all cancers (SIR 1.35, 95%CI 1.31-1.39), GI cancers (SIR 1.90, 95%CI 1.79-2.00), lung cancers (SIR 1.36, 95%CI 1.26-1.47), and prostate cancer (SIR 1.28, 95%CI 1.18-1.38). Gastric NET had increased incidence of enteric SC, rectal NET had increased incidence of colorectal SC, and appendiceal NET had increased incidence of enteric and colorectal SC (Table 1). Median time to SC was 40 months (IQR 17-77). The 5-year CIF of SC was 5.4% (95%CI 5.2-5.6%) for all NET, 5.9% (95%CI 5.6-6.2%) for GI NET, 3.8% (95%CI 3.3-4.4%) for pancreas NET, and 4.8% (95%CI 4.4-5.2%) for pulmonary NET. Factors independently associated with SC were age 60-69 (sub-hazard ratio [sHR] 5.71, 95%CI 3.90-8.38) and 70-79 years (sHR 5.43, 95%CI 3.69-7.98), and enteric NET (sHR 1.15, 95%CI 1.05-1.25). Factors inversely associated with SC included pancreatic NET (sHR 0.82, 95%CI 0.72-0.93), regional (sHR 0.83, 95%CI 0.77-0.90) or distant NET stage (sHR 0.39, 95%CI 0.35-0.43), and poorly (sHR 0.69, 95%CI 0.58-0.81) or undifferentiated NET (sHR 0.45, 95%CI 032-0.64).

CONCLUSION: There is an increased incidence of SC after NET diagnosis, with different patterns from known NET-related genetic syndromes. These data should

be used to include secondary prevention in surveillance strategies.

ABSTRACT ID: 76

P-4

Secondary Primary Cancers and Survival among Neuroendocrine Tumor Patients

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BACKGROUND: Higher rates of second cancer (SC) are suggested for patients with neuroendocrine tumors (NET), but data on SC are scare and their impact on outcomes is unknown. We evaluates the association between SC after NET diagnosis and survival.

METHODS: We identified gastrointestinal (GI), pancreatic, and lung NET from the SEER registry (2000-2016). Standardized incidence ratios (SIR) established the SC incidence for NET compared to the US population. Multivariable Cox models examined the effect of SC on overall survival (OS) and Fine-Gray accounting for the competing risk of death from other causes assessed the effect on disease-specific survival (DSS), with SC as a time-varying covariate.

RESULTS: Of 58,596 patients, NET had higher than expected incidence of SC for all cancers (SIR 1.35, 95%CI 1.31-1.39), and common cancers, such as GI (SIR 1.90, 95%CI 1.79-2.00), lung (SIR 1.36, 95%CI 1.26-1.47), and prostate cancer (SIR 1.28, 95%CI 1.18-1.38). Median time to SC was 40 months (IQR 17-77). SC was independently associated with worse OS (HR 2.02, 95%CI 1.88-2.17), but better DSS (sub-hazard ratio [SHR] 0.75, 95%CI 0.67-0.83). Stratifying by NET type, SC was independently associated with worse OS (HR 2.92, 95%CI 2.68-3.19) and comparable DSS (SHR 1.01, 95%CI 0.87-1.17) for GI NET, worse OS (HR 1.33, 95%CI 1.17-1.51) and better DSS (SHR 0.66, 95%CI 0.55-0.78) for lung NET, and comparable OS (HR 1.15, 95%CI 0.90-1.48) and better DSS (HR 0.51, 95%CI 0.37-0.69) for pancreatic NET.

CONCLUSION: Observed increased incidence of SC after NET diagnosis negatively impacts OS separately from NET-related survival, as outlined by lower OS but higher DSS with SC. Long-term follow-up strategies for NET should include detection of SC for timely management.

ABSTRACT ID: 77

P-5

Race is an Independent Predictor for Surgery Offer in Patients with Small Bowel Neuroendocrine Tumors But Not Pancreatic Neuroendocrine Tumors

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BACKGROUND: Despite generally accepted guidelines, management of small bowel (SBNETs) and pancreatic neuroendocrine tumors (PanNETs) remains inconsistent; that includes eligibility for/actual offer of surgical interventions. We sought to determine which patient characteristics are predictive of this in NET patients.

METHODS: The Surveillance, Epidemiology, and End Results (SEER) Program database was queried for PanNET/SBNET patients between 1998-2017. Demographic and pathologic data were compared between patients who were offered surgery and those who were not. Multivariate logistic regression was performed to identify independent predictors for patients being offered surgery.

RESULTS: A total of 2618 (56.5%) patients were offered surgery for PanNET and 2017 (43.5%) were not. Patients who were older ($p<0.001$), non-urban ($p=0.001$), had M1 stage disease ($p<0.001$), and high-grade tumors ($p<0.001$) were less likely to be offered surgery. Patients were likely to be offered surgery regardless of sex ($p=0.006$), income ($p=0.038$), T stage ($p<0.001$), and N stage ($p<0.001$). On multivariate analysis, younger age ($p<0.001$), N1 stage ($p<0.001$), M0 stage ($p<0.001$) and low grade (<0.001) were independent predictors for being offered surgery for PanNET. In contrast, 2618 (88.5%) patients had surgery offered for SBNET and 997 (11.5%) did not. Older patients were less likely to be offered surgery ($p<0.001$). Patients were likely to be offered surgery regardless of race ($p<0.001$), urban status ($p=0.011$), T stage ($p<0.001$), N stage ($p<0.001$), M stage ($p<0.001$), or grade ($p<0.001$). On multivariate analysis, younger age ($p=0.003$), white race ($p=0.002$), T3-T4 stage ($p<0.001$), N1 stage ($p<0.001$), and M0 stage

($p<0.001$) were independent predictors for being offered surgery for SBNET.

CONCLUSION: Our study confirmed common factors for surgery offer, but, unexpectedly, white race was an independent predictor for whether a patient was offered surgery for SBNET but not PanNET. This discrepancy could reflect treatment facility related factors and deserves further investigation.

ABSTRACT ID: 117

P-6

Surgical Interventions in Patients with Pancreatic Neuroendocrine Tumors: a SEER-based Survival Analysis

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BACKGROUND: The role of surgery in the management of pancreatic neuroendocrine tumors (PanNET) remains hotly debated. Previous analyses of registry databases compare patients who had surgery to those who did not, but these results have been affected by selection bias. Comparing outcomes in patients who underwent surgery to those who were offered surgery but refused could reduce that bias.

METHODS: The Surveillance, Epidemiology, and End Results (SEER) database was queried for patients diagnosed with PanNET between 1998-2017. Kaplan-Meier curves were constructed to compare survival for patients who were offered surgery and those who were not, as well as patients who underwent surgery to those who refused, by disease stage. Log-rank test was used to examine significance

RESULTS: Patients who were offered surgery for PanNET (N=2256) were associated with higher 10-year survival compared to patients who were not (N=1956, p<0.001). Surgery offer was associated with increased survival for patients at all disease stages: T stage <3 (p<0.001) and T3-T4 (p<0.001), N0 stage (p<0.001) and N1 stage (p<0.001), M0 stage (p<0.001) and M1 stage (p<0.001), low-grade (p<0.001) and high-grade tumors (p<0.001). Patients who had surgery performed (N=1933) had improved 10-year survival compared to those who were offered but refused surgery (N=48) (p=0.001). Sub-analysis comparing patients who had surgery performed to those who refused it was limited by low sample size, but performing surgery was associated with improved survival for patients with T stage <3 (p=0.013), T3-T4 (p<0.001), and M1 stage (p=0.032).

CONCLUSION: Survival analysis suggests improved survival in patients who were offered surgery for PanNET compared to those who were not. Comparing patients who underwent surgery to those who refused it continues to suggest a survival benefit though the existing data are limited. Decreasing selection bias in NET outcomes research can clarify the role of surgery in PanNET management.

ABSTRACT ID: 143

P-7

Prevalence and Presentation of Cushing and Carcinoid Syndromes in Patients with Non-metastatic Primary Lung Neuroendocrine Tumors (NETs)

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BACKGROUND: Carcinoid syndrome and Cushing syndrome are rare in non-metastatic lung NETs. In patients with small bowel NETs, carcinoid syndrome is usually associated with metastatic disease. In lung NETs, biologically active substances may be released directly to systemic circulation without inactivation in the liver or lungs. We aimed to evaluate the prevalence and clinical presentation of these syndromes in patients with lung NETs.

METHODS: Clinical data were collected in patients who underwent surgical resection of primary, well-differentiated lung NETs from Jan 2017 to June 2020 at Mayo Clinic.

RESULTS: Cushing syndrome or carcinoid syndrome was present in 5 of 122 patients, 1.6% and 2.5% respectively. Symptoms of Cushing syndrome lead to evaluation and diagnosis of lung NETs in both cases, but carcinoid symptoms were noted only after diagnosis. Two of 3 patients with carcinoid syndrome and 1 of 2 with Cushing syndrome were diagnosed with intermediate-grade NETs (atypical carcinoid) on pathological evaluation; the other 2 patients were diagnosed with low-grade NETs (typical carcinoid). Nodal metastases were present in 2 of 3 with carcinoid syndrome and none with Cushing syndrome. Elevated ACTH and cortisol levels were present in both with Cushing syndrome. Shared symptoms were moon facies, edema, weight gain, and menstrual irregularity. Other symptoms included new-onset hypertension, diabetes mellitus, macrocytosis, proximal muscle weakness, asymmetric sensorimotor neuropathy, and striae. After resection, both had undetectable ACTH levels and symptom resolution. Two patients with carcinoid syndrome had laboratory

confirmation with 5HIAA or serotonin. All 3 reported diarrhea, flushing, and cough or wheezing, with one presentation consistent with carcinoid crisis. No relapses have been noted to date.

CONCLUSION: Cushing and carcinoid syndromes are uncommon in patients with localized lung NETs. This presentation can aid and lead to diagnostic evaluation and symptoms are expected to resolve following resection.

ABSTRACT ID: 146

P-8

Association Between Hospital Volume and Overall Survival of Pancreatic Neuroendocrine Tumors

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BACKGROUND: Therapeutic advances have altered the natural history of pancreatic neuroendocrine tumors (pNETs) over the last decade. We evaluated the therapeutic and survival disparities of pNETs based on hospital volume using the National Cancer Data Base (NCDB).

METHODS: Patients with pNETs diagnosed between 2004 to 2017 were included and classified into tertiles based on hospital volume. Volume-outcome relationship was determined by using Cox regression after adjusting for patient demographics, comorbidities, tumor characteristics, insurance type, and therapy received. Kaplan Meier estimates of overall survival (OS) were compared using log-rank test.

RESULTS: A total of 7202 pNET patients were treated at 840 facilities. The median annual facility volume was 5 patients/year. Facilities were classified into 3 tertiles (T: mean cases/year) T1:<3; T2:4-8; T3:≥9 cases/year. The unadjusted median OS by facility volume was: T1: 71 months (m), T2: 136 m, and T3: not-reached (p<0.001). On multivariable analysis, compared with patients treated at T3 facilities, patients treated at lower-tertile facilities had a higher risk of death [T2 hazard ratio (HR), 1.17 (95%CI, 1.03-1.33); T1 HR, 1.45 (95%CI, 1.30-1.67), p<0.0001] and the difference was more pronounced in stage IV disease (Table). Patients at T3 facilities (vs T1) were more likely to undergo surgical resection of the primary tumor (75 vs 49%), lymph node dissection performed at the time of surgery (70 vs 42%), and achieve R0 resection (72 vs 46%) (p<0.01).

CONCLUSION: Patients who were treated for pNETs at high-volume centers

(>9 cases/year) had significantly improved OS and were more likely to receive surgical resection along with lymph node dissection and R0 resection.

ABSTRACT ID: 153

Facility wise 1-, 3- and 5-year overall survival in stage IV pNETs

	Survival (%)	Survival (%)	Survival (%)
Facility	1-year	3-year	5-year
Low-volume	49	31	21
Intermediate-volume	68	47	34
High-volume	78	54	41

P-9

The Impact of Sociodemographic Factors on Overall Survival for Patients with Adrenocortical Carcinomas in California

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BACKGROUND: Adrenocortical carcinomas (ACC) are rare, aggressive endocrine malignancies with few known predictors of mortality beyond disease-specific variables like stage. We sought to characterize the ACC burden in California and to investigate associations between sociodemographic factors and mortality.

METHODS: Using the population-based California Cancer Registry, we identified all incident diagnoses of ACC in California from 1992-2017 (ICD-O-3 histology code 8370/3 and ICD-10 codes C74.0-C74.9). We used Kaplan-Meier time-to-event survival analysis and compared overall survival (OS) by demographic factors with the log-rank test. Cox proportional hazards regression was used for multivariable survival analysis, adjusting for sociodemographic, disease, and treatment variables.

RESULTS: From 1992-2017, there were 865 cases of ACC in California (median age at diagnosis 55 years; 59% women; 63% non-Hispanic White, 4% non-Hispanic Black, 22% Hispanic, and 9% Asian/Pacific Islander; 55% married/partnered; 74% residing in urban counties, 23% suburban, and 3% rural). Median OS for each subgroup is shown in the Table. In univariate analyses, survival differed by sex (p<0.001), race/ethnicity (p=0.029), marital status (p=0.032), and county of residence (urban, suburban, or rural; p=0.026). In multivariable analyses, women had lower all-cause mortality than men and married/partnered cases had improved mortality compared with unmarried (Table). In addition, younger age at diagnosis, localized stage, smaller primary tumor size, and surgical resection were independently associated with improved survival (all p<0.05). Differences by county type and race/ethnicity were no longer significant after adjustment for other demographic, treatment, and tumor characteristics.

CONCLUSION: We report that sex and marital status are associated with mortality in ACC independently of disease-related factors. Additional research is needed to clarify whether survival differences reflect disparities in access to care, support mechanisms, and/or hormonal effects.

ABSTRACT ID: 169

P-10

Covid-19 in Patients with Neuroendocrine Tumors (NETs): the Mayo Clinic Experience

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BACKGROUND: Coronavirus Disease 2019 (COVID-19) has been linked with increased morbidity and mortality in cancer patients. NETs are rare and there is paucity of data about COVID-19 outcomes. We aim to report outcomes in patients with NETs treated at Mayo Clinic who developed COVID-19.

METHODS: Adult patients with active NETs (diagnosed within the last 5 years and/or on active treatment) and a positive nasopharyngeal SARS-CoV-2 PCR were included. Data were analyzed with descriptive statistics.

RESULTS: 38 patients met criteria for inclusion. Median age was 64 years with 55% males and a median of 3 (0-7) risk factors for severe COVID. Majority had metastatic disease 66% (25/38). Pancreas was the most common origin site (12/38). 21 out of 38 had received cancer directed treatment (CDT) within 90 days of COVID-19 diagnosis: Cytotoxic chemotherapy (5), somatostatin analogues (15) and immunotherapy (1). Most common symptoms were cough, fever and fatigue (12/38). 12 (32%) patients required hospitalization. Median length of hospital stay was 5 days. COVID specific treatment included steroids (6), remdesivir (3) and convalescent plasma (2). Mortality was 3% (1/38). One death was attributed to COVID related encephalitis. None of the patients required ICU care or ventilatory support. All patients were able to resume CDT after recovery. 20 out of 38 patients subsequently had confirmed COVID-19 vaccination with one requiring admission for fever.

CONCLUSION: In our cohort of patients with NETs with COVID-19, we have observed relatively favorable outcomes with no requirement of ICU care despite significant risk factors and recent CDT. Baseline characteristics of NET patients with mild vs moderate-severe COVID-19.

ABSTRACT ID: 171

P-11

The Epidemiology of Mixed Acinar Neuroendocrine Carcinoma of the Pancreas in the United States

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BACKGROUND: Mixed acinar neuroendocrine carcinoma of the pancreas (MANEC-P) is a rare malignancy with a poor prognosis. However, MANEC-P epidemiology is not well defined. Therefore, this study aimed to estimate and compare the incidence, prevalence, and cancer-specific survival (CSS) of MANEC-P in the United States (US).

METHODS: Between 2000-2017, MANEC-P patients were identified in the Surveillance, Epidemiology and End Results and the National Program of Cancer Registries databases. The outcomes evaluated were the age-adjusted incidence rate, limited-duration prevalence, and CSS.

RESULTS: Six-hundred thirty patients were identified for the incidence analysis and 149 patients for prevalence and CSS analyses. MANEC-P incidence-rate was 0.011/100,000 populations, significantly higher in male, black and peaked at 75-79-years of age and was highest in the Northeast region (0.013) and lowest in the Midwest (0.009) region ($p<0.01$). A decreasing trend in MANEC-P incidence was observed (average annual percentage change=-0.71), with a significant difference between 2001-2010 and 2010-2017 (7.89 vs. -11.13, $p<0.05$). The 17-year prevalence was 0.00005%, with a projected 189 patients alive at the beginning of 2018. Median CSS was 44 (95% CI, 23-69) months. One-hundred and nine patients (73.2%) received curative-intent surgery. The median follow-up was 73 months for the surgery group vs. 42 months for the no-surgery group. Minorities (HR=0.56) were associated with better CSS ($p<0.05$). Getting older (HR=1.02), tumor grade III-IV (HR=2.4) and metastatic disease (HR=4.25) were associated with worse CSS (each $p<0.05$). Although chemotherapy and radiotherapy were not significantly associated with CSS, surgery was associated

with improved CSS (HR=0.37, p<0.001).

CONCLUSION: MANEC-P are rare malignancy with a steady incidence-rate and poor prognosis over the last two decades in the US. Surgery may be associated with better MANEC-P survival. MANEC-P grade and metastasis are associated with poor CSS. Further investigation is warranted as no standard of care is available for this fatal pancreatic cancer.

ABSTRACT ID: 192

P-12

MDT Experience in Argentina in Nets in Times of the Covid19 Pandemic

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BACKGROUND: The ongoing COVID-19 pandemic caused 4,470,374 total cases in Argentina, and 94,304 deaths have been reported from March 2020 to June 2021. To maintain high standards of care, the ARGENTUM Group decided to strengthen decision-making through multidisciplinary virtual workshops including patients with NETs treated in different centers in Argentina.

METHODS: A Retrospective study based on multicenter series experience was conducted.

RESULTS: From March 2020 to May 2021, 12 MDT virtual meetings were conducted , including 47 patients , and 57 presentations. Total participants median: 23(DS: +/-7.9) Specialties: Oncology: 8 (DS: +/-1.3), Gastroenterology:

3 (DS: +/-1.5), Nuclear medicine: 3(DS: +/- 1.2) Endocrinology: 2 (DS: +/-2.8), Surgery: 2 (DS: +/- 1.4), Pathology: 2 (DS: +/-0.7), Radiology: 2(DS: +/- 0.6), others: 3 (DS +/-0.8) Centers: Autonomous City of Buenos Aires: 41 patients, Province of Buenos Aires: 4. Others provinces: 2. Median Age: 50 (DS: +/- 14.53), 28 Female (60%). COVID19 Infection: 5 patients (10%), no deaths by COVID19 were recorded. Vaccination: First dose: 12, Second: 3. Tumor localization: Pancreas 17(36%), Small bowel 11(23%), Colorectal 6(13%), Gastric 3(6%), Appendix 4(9%), Others: 5(10%), unknown 1(2%). Histology: NET 34(72%) NEC 6(13%) MiNEM 3(6%), others: 2(4%) unknown 2(4%). Objective presentations: Medical treatment: 28 (43%) Surgery: 8(12%) Second opinion: 7(11%) Others: 14(23%). Multidisciplinary decisions: Analogous 9(15%), Chemotherapy 9(15%), ITK 3(5%), PRRT 4(6.6%), Evaluation of Images 13(21.6%), Biopsy and/or mutations testing 6(10%), Follow-up 7(11.6%), Surgery 4(6.6%), Regional treatment 3(5%), Radiotherapy 1(1.6%), Evaluation for transplant 1(1.6%).

CONCLUSION: Given the delay in both diagnosis and treatment of malignancies due to the transportation and travelling restrictions established during the pandemic, the ATENET (Multidisciplinary Athenaeum of NET) meetings were speedily adapted to the virtual modality. This proved to be a safe, viable and effective option, removing barriers that facilitate an interdisciplinary vision useful to make complex decisions in patients with NETs.

ABSTRACT ID: 151

O-1

A Systematic Survey of Two Decades of Clinical Trials in Neuroendocrine Neoplasms (NENs)

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BACKGROUND: NENs have historically been grouped homogenously in clinical trials, despite their heterogeneity. Given the adoption of an advanced pathologic classification system, dissemination of trial design recommendations from the 2011 National Cancer Institute (NCI) Neuroendocrine Tumor (NET) Clinical Trials Planning Meeting and approval of several targeted therapies over the last decade, in this analysis, we sought to assess whether there had been changes in study design, eligibility, accrual and outcomes between NEN trials which began enrollment between 2000-2009 or between 2010-2020.

METHODS: We conducted a systematic survey of completed therapeutic phase II, III NEN trials published (including abstracts) between January 1, 2000- December 31, 2020. Trials were identified through a database search of Medline, EMBASE, Web of Science, Cochrane Database of Systematic Reviews, ClinicalTrials.gov, EU Clinical Trials Register and NCI Clinical Trials. Frequencies and relative frequencies were used to describe the categorical variables; proportions between the two enrollment periods were compared using Pearson chi-squared tests.

RESULTS: Of 3243 identified studies, 119 met criteria for inclusion. Eligibility differences between the two enrollment periods are described in Table 1. With regards to design differences, trials which began enrollment after 2010

increasingly utilized progression-free survival (35% vs 18%, P = .04) and decreasingly utilized objective response rate (30% vs 53%, P = .01) as a primary endpoint compared to trials which began enrollment before. Other study characteristic differences between the enrollment periods will be detailed at the meeting.

CONCLUSION: NEN trials enrolling over the last decade have become more focused on select tumor populations. Despite this trend, 21% of studies still included all NENs. Studying novel agents in specific disease populations may further drug development in the field.

ABSTRACT ID: 45

Table 1

	Category	2000-2009 N(%)	2010-2020 N(%)	P-value
	NEN Types Specified in Inclusion Criteria			
	All NENs	34(63%)	13(21%)	<.001
	Gastrointestinal NETs	11(20%)	25(40%)	.02
	Pancreatic NETs	16(30%)	32(51%)	.02
	Neuroendocrine Carcinomas	1(2%)	11(17%)	.006
	Tumor Features Specified in Inclusion Criteria			
	Tumor Differentiation	34(63%)	59(98%)	<.001
	Ki-67 Index	5(9%)	23(38%)	<.001

O-2

The Feasibility and Acceptability of Health and Wellness Coaching for Neuroendocrine Tumor Patients and Their Caregivers

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BACKGROUND: Neuroendocrine tumor (NET) patients and caregivers report significant negative psychosocial consequences from living with this rare, insidious cancer. Nonetheless, limited wellness interventions have been tailored to this population. As a nonprofit that provides education and support, LACNETS (Los Angeles Carcinoid Neuroendocrine Tumor Society) launched the first health and wellness coaching (HWC) program for NET patients and caregivers. The objective of this study to assess feasibility and acceptability of HWC for NET patients and caregivers.

METHODS: NET patients (n=22) and caregivers (n=10) were offered 8 HWC sessions (45-60 min) funded by LACNETS and an optional two sessions subsidized for a fee of $20 each. Sessions were delivered telephonically or virtually by nationally board-certified HWCs. Feasibility was assessed through enrollment and retention. Program acceptability was assessed through 4 Likert questions at program completion.

RESULTS: Thirty-two participants requested information; 28 enrolled, and 21 have completed at least 6 sessions thus far (4 still enrolled). Eighteen (12 NET patients, 6 caregivers) attended all 8 sessions, with the mean (SD) = 7.0 (1.86). Thirteen opted for additional sessions [mean (SD) = 1.0 (1.00)], bringing the mean (SD) sessions completed to 7.9 (2.58) . Sixteen of 17 (94%) who have finished the program provided acceptability ratings on a 5-point scale. All participants (100%) rated HWC at 4 or 5 for “helping [them] make positive changes in [their] overall health and wellness,” and all “would recommend HWC to another NET patient/caregiver.” (87.5% = 14 out of 16) Eighty-seven percent rated HWC at 4 or 5 as

"a valuable investment" through which they "gained new insights and/or skills that helped them better thrive while living with NET."

CONCLUSION: Enrollment met projections; retention surpassed them. Strong program acceptability was also demonstrated in this compromised population with high psychosocial needs. Further research on this innovative approach is warranted.

ABSTRACT ID: 61

O-3

Patient-reported Cognitive and Psychological Screening in Neuroendocrine Tumors (NETs) - a Prospective Cohort Study

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BACKGROUND: An association between neuroendocrine tumors (NETs) and neuropsychological symptoms has been suggested, but objective data is limited. We aimed to assess neuropsychological symptoms in NETs using validated patient-reported outcomes (PROs).

METHODS: We prospectively administered the Beck Depression Inventory (BDI-II) and the Functional Assessment of Cancer Treatment Cognitive domain (FACT-Cog), in addition to routine screening with the Edmonton Symptom Assessment System (ESAS), to adults with grade 1 or 2 NETs at a specialized NETs clinic (2017-2018). BDI-II and FACT-Cog scores were correlated to ESAS symptom scores with Spearman correlation test.

RESULTS: Of 276 patients, 45.9% were metastatic and 30.1% functional. Median time from NETs diagnosis to PROs measure was 50 (inter-quartile range - IQR 27-83) months. Using the BDI-II, 40.6% patients had mood disturbances, including 22.1% above the level of clinical depression and 4.7% with severe depression. FACT-Cog assessment revealed moderate perceived cognitive impairment (median 63, IQR 50-68, possible range 0 to 72), considerable reduction in perceived cognitive ability (median 20, IQR: 15-23, possible score 0 to 28), severe effect regarding comments received from others (median 16, IQR 14-16, possible score 0-16) and quality of life (median 15, IQR 11-16, possible score 0-16). BDI-II and FACT-Cog components did not correlate with ESAS for individual symptoms or total scores.

CONCLUSION: Using validated PROs, one out of 5 NETs patients presented signs of clinical depression and perceived cognitive ability was impaired with impact on quality of life, beyond the initial diagnosis period. The BDI-II and FACT-Cog did not correlate with routine symptom screen with ESAS; thus, specific cognitive and psychological PROs screen should be added to the management of NETs to identify patients with potential depression and cognitive impairment for further assessment and intervention in order to improve patient-centred care.

ABSTRACT ID: 75

O-4

Neuroendocrine Tumor Treatments and Follow-up Disease Management - Comparative Perspective (U.S. and Canada vs. Global)

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BACKGROUND: The Survey of Challenges in Access to Diagnostics and Treatment for Neuroendocrine Tumor (NET) Patients (SCAN) assessed global delivery of healthcare to NET patients.

METHODS: During Sept-Nov 2019, 2359 NET patients from 68 countries completed an online self-reported survey, available in 14 languages, disseminated by INCA and its partner organizations.

RESULTS: 22% of NET patients were from the United States (US) (511/2359), 9% from Canada (CA) [208/2359]. Almost half of NET patients on treatment used

somatostatin analogues (SSA; Global: 45%, 1022/2274, US: 44%, 214/492; CA: 52%, 105/202), about one-fifth underwent surgery (Global: 19%, 432/2274, US: 24%, 118/492; CA: 20%, 41/202), about 10% received PRRT, more in CA (Global: 11%, 250/2274, US: 9%, 43/492; CA 19%, 39/202, p<0.0001). More patients in the US and especially in CA were monitored by conventional imaging (e.g. CT, MRI, ultrasound; Global: 71%, 1617/2273, US: 76%, 100/508; CA: 91%, 185/203); about half by CgA (Global: 48%, 1086/2273, US: 50%, 255/508; CA: 55%, 112/203). Other blood tests were administered more frequently in the US and CA vs. Global (Global: 33%, 749/2273, US: 40%, 204/508; CA: 40%, 82/203). Gallium 68 SR-PET CT was used more in the US (Global: 31%, 704/2273, US: 38%, 32/508; CA: 16%,29/203), and 5-HIAA more in CA (Global: 27%, 603/2273, US: 24%, 123/508; CA: 49%,99/203). Availability of all these treatments and monitoring tools was similar or higher in the US and CA vs. Global. Gallium 68 SR-PET/CT had significantly higher availability in the US according to patients (Global: 60%, 1364/2273, US: 73%, 371/508; CA: 58%, 117/203).

CONCLUSION: The divergence between the treatment and follow-up approaches used globally, in CA and the US clearly demonstrate the differences in providing NET care, both globally and within advanced economies. Follow-up disease management strategies vary significantly and a consensus on the optimal standard follow-up is still lacking.

ABSTRACT ID: 101

O-5

Outcomes of Initial Treatment in Early Stage Neuroendocrine Carcinoma of the Uterine Cervix (NCUC)

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BACKGROUND: Neuroendocrine carcinoma of the uterine cervix (NCUC), which accounts for 1-2% of cervical cancers, remains a deadly subtype. In this study, we combine data from Mayo Clinic (MC) and the University of Iowa Hospitals and Clinics (UIHC) to provide information on tumor characteristics, treatment, and outcomes.

METHODS: The electronic medical record was reviewed for patients with NCUC from MC and UIHC. Primary endpoints included progression-free survival (PFS) and overall survival (OS). Secondary endpoints included median survival for those with stage I/II disease who received surgery in initial treatment.

RESULTS: There were 61 patients (MC: 25, UIHC: 36) with FIGO stage I: 29, stage II: 9, stage III: 6, stage IV: 14, and unknown: 3. 46 were small cell (76%), 9 were large cell (15%), and 6 were unknown (9%). In patient with stage I/II: 6 patients received neoadjuvant chemotherapy or radiation prior to surgery, and an additional 14 patients received chemotherapy after surgery. There was a significant difference in OS between those who received surgery and those that did not in stage I/II (OS 44.3 vs 16.4 months, p = <0.001). There was a significant difference in OS between those who received surgery + adjuvant/neoadjuvant chemoradiation vs those who received chemoradiation without surgery as initial therapy (OS 50.0 vs 16.4 months, p= 0.001).

CONCLUSION: Our study is consistent with others showing that NCUC is aggressive and usually progressive despite multimodal therapy. We demonstrate a survival benefit for patients with NCUC stage I/II disease who receive surgery as part of initial therapy. Our study supports the use of radical hysterectomy in

combination with adjuvant therapy as first line treatment for early stage NCUC disease.

ABSTRACT ID: 121

38 patients with stage I/II NCUC divided by subtype of initial treatment and PSF/OS in months.

Initial Treatment	Number of patients	Median PFS (months)	Median OS (months)
Surgery Alone	3	20.3	117.3
Surgery + Neo- or Adjuvant Chemotherapy	6	NA	59.4
Surgery + Chemoradiation	11	35.1	50.0
Surgery + Radiation	3	NA	23.9
Chemoradiation	12	16.5	16.4
All who had surgery	24	44.3	44.3
All without surgery	12	16.5	16.4

O-6

Evaluating the Association Between Family History and Overall Survival Among Patients with Gastrointestinal and Pancreatic Neuroendocrine Tumors

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BACKGROUND: Although family history of cancer has been associated with risk of developing neuroendocrine tumors (NETs), the prognostic impact of family history is unknown. We evaluated the association between family history of cancer in a first-degree relative and overall survival (OS) in patients with gastrointestinal and pancreatic NETs (GEP-NETs).

METHODS: We conducted a retrospective cohort study involving patients with GEP-NETs evaluated at the Dana-Farber Cancer Institute between 2003-2015. Patients with familial NET syndromes and poorly differentiated histologies were excluded. Primary exposure was first-degree family history of malignancy, as self-reported on a questionnaire administered at the time of first appointment. Primary outcome was OS; recurrence-free survival (RFS) was also assessed for patients with non-metastatic disease. Kaplan-Meier survival analysis and log-rank tests were used. Cox proportional hazards models were applied to adjust for covariates.

RESULTS: Among 572 patients, 214 (37%) had a first-degree relative with cancer. Family history was positive in 168/404 (42%) patients with metastatic disease and 46/168 (27%) of those with non-metastatic disease. There was no difference in OS according to family history in both patients with metastatic disease (HR 0.99, 95% CI 0.75-1.33) and non-metastatic disease (HR 0.81, 95% CI 0.17-3.90). Among patients with non-metastatic disease, there was also no difference in RFS based on family history (HR 1.02, 95% CI 0.44-2.37). There remained no association between family history and OS in patients with metastatic disease after adjusting

for primary site, stage, age, sex, smoking, alcohol use, and time-period of diagnosis.

CONCLUSION: There was no difference in OS and RFS in patients with sporadic GEP-NET with and without a family history of malignancy. Although there may be an association between family history and risk of developing NET, there do not appear to be differences based on family history affecting patient outcomes.

ABSTRACT ID: 134

O-7

Succinate Dehydrogenase Pathogenic Variants are Not Associated with Non-canonical Cancers

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BACKGROUND: Germline succinate dehydrogenase (SDHx) pathogenic variants (PVs) are associated with pheochromocytoma (PCC) and paraganglioma (PGL), gastrointestinal stromal cell tumors, and renal cell carcinomas. Associations with other cancers have not been studied systematically. The goal of this study was to determine associations between SDHx PVs and cancer in a cohort of patients undergoing testing for cancer predisposition genes.

METHODS: Subjects who underwent multigene panel testing of cancer predisposition genes between 2013 and 2016 (Ambry Genetics) were included. Demographic data and histories were obtained from clinical documentation. Logistic regression was used to assess the association between SDHx (SDHA, SDHB, SDHC, SDHD,andSDHAF2) PVs and 11 common cancer types. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

RESULTS: Of 8510 unrelated individuals undergoing testing of SDHx genes, 5% had germline SDHx PVs. The mean age at testing was 48 yo (SD: 15.3). The majority of subjects were female (79%). 77% of the study cohort had a personal history of cancer, most commonly breast cancer (n=2746), followed by kidney cancer (n=1629) and PCC/PGL (n=894). By gene subunit, SDHB was associated with the highest risk of PCC, while SDHD had the highest risk of PGL. In subjects tested for all SDHx genes, the presence of any SDHx PV was significantly associated with a personal history of cancer (OR:2.3, 95% CI:1.2-4.0). When evaluated by cancer type, SDHx PVs correlated with risk of PCC (OR:17.7, 95% CI:7.4-37.4) and PGL (OR:75.4, 95% CI:40.4-139.3) but not with breast, colorectal, kidney (all histologies), melanoma, pancreatic, prostate, ovarian, thyroid, or uterine/endometrial cancer, in patients tested for all SDHx genes.

CONCLUSION: SDHx PVs were strongly associated with PCC/PGL, but not with increased risk of other canonical human cancers. Future population-based studies are required to confirm these findings.

ABSTRACT ID: 187

O-8

Understanding Neuroendocrine Tumour Patient Preferences for Medical Management of Midgut NETs Using Discrete Choice Experiments: a DIRECT NETs Study

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BACKGROUND: Neuroendocrine tumours (NETs) are heterogenous in terms of prognosis, symptom burden, and quality of life impact. Understanding the heterogeneity in NET patient preferences, perspectives and values is therefore essential for providing patient centered care. The DIRECT NETs (DIRect Experience with Choice of Therapy for NeuroEndocrine Tumours) studies, conducted by CommNETs, are discrete choice experiment (DCE) surveys that model clinical scenarios where advanced NET patients have several treatment options. We present results from a DCE modelling treatment options for advanced midgut NETs following progression on first line somatostatin analogues (SSA).

METHODS: Peptide receptor radionuclide therapy (PRRT), SSA dose escalation, and everolimus were the treatments modeled. Attributes included progression free survival (PFS), method of treatment administration, and key differentiating adverse event rates reported in randomized control trials. The DCEs employ the 'potentially all pairwise rankings of all possible alternatives' (PAPRIKA) method as implemented by the 1000minds platform. Participants self-enrolled to complete an online, self-reported, anonymous survey, which was disseminated by CommNETs and NET patient advocacy groups. Key outputs included part-worth utilities for individual attribute levels, ranking of attributes, and ranking of

attribute profiles matching specific treatments.

RESULTS: 110 NET patients completed the survey. Attribute importance in descending order was as follows: PFS, mucositis, diarrhea, secondary malignancy, and method of treatment. 64.5% of participants placed the greatest importance on longer PFS. Amongst treatment profiles, 60.9% preferred attribute levels matching PRRT, 30.0% SSA dose escalation, 7.3% everolimus. Patients reporting non-functional tumours were more likely to prioritize PFS than those with functional tumours (78.1% vs 57.9%; Chi-square P = 0.046).

CONCLUSION: Most NET patients may prefer treatments that maximize PFS, however more than a third place more importance on other treatment attributes such as adverse event rates. Discussion of treatment options with NET patients should balance quality of life impacts with achieving disease control.

ABSTRACT ID: 195

T-1

Safety, Pharmacodynamic, and Antitumor Activity of Tidutamab, an SSTR2 x CD3 Bispecific Antibody, in Subjects with Advanced Neuroendocrine Tumors

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BACKGROUND: Somatostatin receptor 2 (SSTR2) is overexpressed in neuroendocrine tumors (NETs), gastrointestinal stromal tumors (GIST), and other cancers. Tidutamab is a humanized, anti-SSTR2 x anti-CD3 bispecific antibody that directs T-cell-mediated cytotoxicity to SSTR2+ cells.

METHODS: This Phase 1 study (NCT03411915) investigates the safety/tolerability and maximum tolerated dose (MTD) of tidutamab, administered as weekly infusions in 28-day cycles, in parallel cohorts of advanced NET and GIST subjects. We report updated safety, pharmacodynamic, and response (RECIST 1.1) data for NET cohorts.

RESULTS: As of 16 Jun 2021, 41 subjects (median age, 64 years; 46% male) were treated: 21 in dose escalation and 20 in expansion at the MTD (first dose, 0.3µg/kg, 1.0µg/kg thereafter); 1 subject remains on treatment. Grade 3 treatment-related adverse events in ≥2 subjects included nausea and vomiting (14.6%); diarrhea (9.8%); anemia (7.3%); and fatigue, malnutrition, oesophagitis, esophageal dysmotility, and cytokine release syndrome (4.9%). Grade 3/4 treatment-related laboratory abnormalities (≥3 subjects) included lymphopenia (29.3%); transaminase elevation and GGT increase (19.5%); hypophosphatemia (9.8%); and lipase increase (7.3%). Among 41 subjects, median progression-free survival was 8.2 months (95% CI 2.7, 14.3). The KM estimate of median overall survival (OS) was 15.5 months; OS at 12 months was 77%. The best response was stable disease (11/20 evaluable subjects; 55%). Among 11 subjects with stable disease, median duration was 3 months. Tidutamab induced acute/sustained T-cell activation and cytokine release. Higher baseline CD4 central memory cells were positively associated with stable disease >6 months, while higher baseline intratumoral PDL1 and on-treatment increases in peripheral T-cell PD1 expression were associated with shorter time on study.

CONCLUSION: Tidutamab was generally well tolerated with disease control in >50% of evaluable NET subjects. Additional studies in other tumors that express SSTR2 are warranted, and poor outcomes in subjects with higher PD(L)-1 expression suggest combinations with checkpoint inhibitors should be considered.

ABSTRACT ID: 109

T-2

Dose Selection for Paltusotine, a Once Daily Oral Nonpeptide, Somatostatin Receptor 2 Ligand, for the Treatment of Patients with Carcinoid Syndrome (CS)

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BACKGROUND: Long-acting somatostatin receptor ligands (LA-SRLs) are first line therapy for neuroendocrine tumor (NET) syndromes including acromegaly and the carcinoid syndrome (CS). In acromegaly, usually caused by a benign growth hormone-secreting pituitary tumor, two phase 2 studies (NCT 03789656 and 03792555) suggested that patients injected with SRLs can switch to once daily oral paltusotine (CRN00808), a nonpeptide, small molecule, somatostatin type 2 (SST2) receptor ligand (SRL) with 70% bioavailability, while maintaining stable serum IGF-1 levels. However, CS patients may require higher doses of an orally administered drug due to malabsorption and/or maldigestion commonly associated with the syndrome or its treatment and the pharmacokinetics (clearance and volume of distribution) of paltusotine may differ between CS and acromegaly because of differences in metabolic capacity of the liver and body composition.

METHODS: To design a PK/PD study evaluating the use of once daily oral paltusotine to control symptoms and inhibit functional tumor markers in patients with CS, we analyzed data from the capsule formulation used in the acromegaly patient studies to determine dose- and exposure-response and from a new tablet formulation evaluated in healthy volunteers.

RESULTS: The dose- and exposure-response data from NCT 03789656 and 03792555 will be presented. These data suggest that a dose range of 40 to 60 mg once daily results in consistent IGF-1 suppression in patients with acromegaly.

CONCLUSION: We propose a similar starting dose for paltusotine in CS as in

acromegaly. This dosing range (40-80 mg once daily) is further supported by clinical experience with LA-SRL therapies in gastro-entero-pancreatic NETs for which the approved doses are the same as acromegaly. Therefore, we will evaluate in an exploratory trial a paltusotine dose range from 40 to 80 mg/day with the potential, if required, for up titration to higher doses.

ABSTRACT ID: 127

T-3

[^{177}Lu]Lu-DOTA-TATE as First-line Therapy for Patients with Grade 2 and 3 Advanced Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): the NETTER-2 Study

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BACKGROUND: The NETTER-1 study demonstrated that [^{177}Lu]Lu-DOTA-TATE, a radioligand therapy selectively targeting somatostatin receptors (SSTRs), plus 30 mg octreotide long-acting release (LAR), provided significantly increased progression-free survival (PFS) compared with 60 mg octreotide LAR in patients with GEP-NET who previously progressed on octreotide (HR, 0.21 [95% CI, 0.13-0.33]). However, the NETTER-1 population predominantly consisted of patients with grade 1 (G1) NET, and G3 patients were excluded. Five-year survival declines by ~44% for patients with G3 NET versus G1, with limited data and few therapy options available. The ongoing NETTER-2 study is evaluating [^{177}Lu]Lu-DOTA-TATE plus 30 mg octreotide LAR as a potential first-line radioligand therapy option in patients with advanced GEP-NET (G2 and G3) who have a high-risk profile and significant unmet medical need.

METHODS: This multicenter, randomized, open-label, phase III study (NCT03972488) is enrolling adult and adolescent patients (aged ≥15 years and body weight >40 kg) with SSTR-positive, high proliferative rate (G2 with Ki67 index ≥10% or G3 with Ki67 ≤55%), advanced GEP-NET diagnosed within 6 months

before screening. Patients are randomized 2:1 to receive [^{177}Lu]Lu-DOTA-TATE (7.4 GBq/200 mCi every 8 weeks [Q8W] x 4 cycles; cumulative dose: 29.6 GBq/800 mCi) plus octreotide LAR (30 mg Q8W with [^{177}Lu]Lu-DOTA-TATE then Q4W after last [^{177}Lu]Lu-DOTA-TATE treatment) or 60 mg octreotide LAR (Q4W). Both somatostatin analogue (SSA)-naïve and patients previously treated with SSAs without progression are eligible. Patients are excluded if other first-line therapies are considered more appropriate per investigator. Stratification factors are tumor grade and origin (pancreatic versus other NET). The primary endpoint is PFS (centrally assessed according to RECIST v1.1). Secondary endpoints include objective response rate, quality of life, overall survival, disease control rate, and safety. Cross-over is allowed for patients in the control arm who have centrally confirmed progression.

RESULTS: Study is in progress.

CONCLUSION: Study is in progress.

ABSTRACT ID: 138

T-4

A Phase II Trial to Evaluate the Safety and Dosimetry of [^{177}Lu]Lu-DOTA-TATE in Adolescent Patients with Somatostatin Receptor (SSTR)-positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs), Pheochromocytomas and Paragangliomas (PPGLs)

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BACKGROUND: In the pediatric population, limited approved therapies exist for patients with GEP-NETs and PPGLs. SSTR subtype-2 is overexpressed by GEP-NET and PPGL tumors; therefore, it is a relevant target for peptide receptor radionuclide therapy with [^{177}Lu]Lu-DOTA-TATE. [^{177}Lu]Lu-DOTA-TATE is approved for the treatment of adult patients with SSTR-positive GEP-NETs. It has shown efficacy in several studies evaluating adult patients, but there have been no Advanced Accelerator Applications-sponsored pediatric clinical trials in GEP-NETs and PPGLs to date. The treatment of adolescents with GEP-NETs and PPGLs represents a significant unmet need, providing a strong rationale to evaluate [^{177}Lu]Lu-DOTA-TATE in these patients.

METHODS: This multicenter, phase II, open-label, single-arm study is designed to evaluate the safety and dosimetry of [^{177}Lu]Lu-DOTA-TATE in adolescent patients (12 to <18 years old) with advanced, inoperable, SSTR-positive GEP-NETs (grade 1 or 2, well differentiated) in the primary cohort and PPGLs in the exploratory cohort. Eligible patients will receive 4 cycles of [^{177}Lu]Lu-DOTA-TATE (activity per cycle: 7.4 GBq), administered every 8 weeks. After the last dose,

patients will be followed for 5 years. Radiation dosimetry and pharmacokinetic (PK) assessments will be done after the first [^{177}Lu]Lu-DOTA-TATE administration. Safety assessments will be performed regularly after each cycle. Primary endpoints are target organ absorbed radiation dose and incidence of adverse events (AEs) after the first cycle. Secondary endpoints are incidence of AEs within 6 months (short-term follow-up) and 5 years (long-term follow-up) after the last dose, and PK and dosimetry compared with predicted values. Efficacy will be assessed as an exploratory objective, including objective response rate, progression-free survival, and overall survival in both cohorts. This study will enroll at least 8 patients with GEP-NETs and as many patients with PPGLs as possible across multiple sites in Europe and North America (NCT04711135).

RESULTS: Study is in progress.

CONCLUSION: Study is in progress.

ABSTRACT ID: 139

T-5

ETCTN 10388: a Phase 1 Trial of Triapine and Lutetium 177 Dotatate in Well-differentiated Somatostatin Receptor-positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

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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 Lu 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 17% 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.

METHODS: This study is an investigator initiated, NCI sponsored, multicenter phase 1 trial of triapine and Lutathera in GEP-NET patients after the failure of at least one line of prior systemic treatment. A total of 29 patients are being enrolled in the dose escalation with help of Bayesian optimal interval design (BOIN) and dose expansion cohorts. Patients are being treated with 177 lutetium dotatate in combination with triapine. Triapine will be administered orally from D1-14 with each dose of PRRT [200 mCi]. Primary endpoint is to evaluate recommended phase II dose (RP2D). Secondary endpoints are to evaluate safety,

pharmacokinetics, and clinical activity (ORR and PFS).

RESULTS: Trial is currently enrolling patients. NCT04234568

CONCLUSION: Ribonucleotide reductase (RNR) is the only enzyme responsible for conversion of ribonucleoside diphosphate to deoxyribonucleotide diphosphate (dNDP), the key building blocks for DNA synthesis. Radiation is a potent inducer of DNA double-strand breaks (DSBs), and RNR is the rate-limiting enzyme in the repair of DNA in this setting. Triapine is an inhibitor of RNR. This study will test the hypothesis that radiation sensitizer triapine can be safely combined with peptide receptor radionuclide therapy and ultimately may improve antitumor activity of Lutathera.

ABSTRACT ID: 196

T-6

ETCTN 10450: a Phase 1 Trial of Peposertib and Lutetium Lu 177 Dotatate in Well-differentiated Somatostatin Receptor-positive Neuroendocrine Tumors

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BACKGROUND: Radiation is a potent inducer of DNA double strand breaks (DSBs). Targeting signaling networks involved in DSB repair is a promising approach for enhancing cellular radiosensitivity. The primary repair mechanism of radiation-induced DSBs is the non-homologous end joining (NHEJ) pathway, in which the DNA-PK complex plays a pivotal role. Upregulation of DNA-PK promotes repair of DSBs leading to tumor radioresistance. Thus, DNA-PK is an important molecular target for inhibiting DSB repair and enhancing the cytotoxicity of radiation. Peposertib is a selective inhibitor of DNA-PK that targets tumor cell DNA damage repair and survival by blocking NHEJ.

METHODS: This study is an investigator initiated, NCI sponsored, multicenter phase 1 trial. A total of 29 patients will be enrolled in the dose escalation with help of Bayesian optimal interval design (BOIN) and dose expansion cohorts. The study will be open through the NCI ETCTN (National Cancer Institute Experimental Therapeutics Clinical Trials Network) program. Peposertib will be administered orally from D1-21 with each dose of PRRT [200 mCi]. Primary endpoint is to evaluate recommended phase II dose (RP2D). Secondary endpoints are to evaluate safety, pharmacokinetics, and clinical activity (ORR and PFS). We are also evaluating hPG80 (Progastrin), baseline somatostatin receptor density, somatic tumor mutations, germline mutations and dosimetry.

RESULTS: Peposertib is a potent and selective small-molecule adenosine triphosphate (ATP)-competitive inhibitor of DNA-PK that targets tumor cell

growth and survival by inhibiting the critical DNA damage repair mechanism in solid and hematological malignancies. DNA-PK inhibition in combination with radiation has demonstrated a synergistic tumor inhibition in preclinical NET studies.

CONCLUSION: Trial is currently enrolling patients. NCT04750954

ABSTRACT ID: 199