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AUTHOR INDEX
Basic Science
Single-Cell ATAC and Single-Nucleus RNA Sequencing Uncovers Cellular Heterogeneity Within Pancreatic Neuroendocrine Tumors

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Background
Pancreatic neuroendocrine tumors (P-NETs) are a rare, understudied form of cancer with few curative options, and their occurrence is rising. Approximately 4,000 new cases are diagnosed per year in the US, and a 5-year relative survival rate of 54%, it’s imperative to understand the molecular mechanisms governing P-NET carcinogenesis. To date, most studies used whole-tumor sequencing to characterize P-NETs, which hampers the discovery of their microenvironment, cellular composition, and cell of origin. In this study, we used single-cell assays on cryopreserved primary PNETs that vary in grade, stage, and metastasis status to characterize the chromatin and transcriptional states of single cells obtained from resected tumors.

Methods
For Transposase Accessible Chromatin sequencing (ATAC-seq) is a robust method to probe areas of accessible chromatin which likely function as regulatory genomic regions called enhancers. We used a novel isolation protocol designed to recover nuclei from cryopreserved tissue for single-cell assays. We performed single-nucleus ATAC-seq and RNA-seq using a 10x genomics multimarker platform. We then used a suite of bioinformatic tools to perform clustering, marker gene identification, and molecular pathway analysis.

Results
We identified several distinct cell populations within P-NETs, including cancer associated fibroblasts, immune cells, and cancer cell populations. Our preliminary analysis suggests there is little to no heterogeneity within individual tumor cells. In contrast, each tumor is significantly different than others with little shared genes. When we compared the tumor samples to normal pancreatic cell profiles, we found that the most aggressive PNETs tend to gain acinar or duct-like identity as they progress in grade.

Conclusions
To date, the mechanisms underlying PNET progression are unknown and there is little known about intra-PNET heterogeneity. The current targeted therapy approved for metastatic PNETs is Lutetium 177 DOTATATE. However, it is affected by tumor heterogeneity and ineffective against metastatic high-grade tumors. Our results provide guidance for development of targeted therapies. Moreover, our study provides new molecular markers that vary between PNETs, allowing to further subtype PNETs. Moving forward, our group aims to use the data from this study to guide the development of an in-vitro PNET tumor progression model.

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DOI: 10.1530/endoboa.89.B1

Development of a Novel Anti-SSTR Bispecific T-Cell Engager (BiTE) Molecule for the Treatment of Neuroendocrine Tumors

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Background
Well-differentiated neuroendocrine tumors (NETs) are characterized by the overexpression of somatostatin receptors (SSTRs). To efficiently engage and activate tumor infiltrating lymphocytes against NET cells, we designed a novel bispecific T-cell engager (BiTE) composed of 2 molecules of somatostatin-14 (SST14), the hormone that physiologically binds SSTRs, linked with a single chain variable fragment (scFv)-based anti-CD3.

Methods
The optimized sequence of the BiTE was subcloned into a vector (p/ACP60) designed for protein expression in insect cells using Baculovirus. Triaplusia-ni (High Five) cells were used to express the recombinant protein, which was isolated from the supernatant using nickel affinity chromatography. Flow cytometry and confocal microscopy were used to determine the binding potential of the BiTE towards CD3 and SST2R. CD3- T cells isolated from the peripheral blood of healthy donors were co-incubated with 293T cells stably transduced to concurrently express SST2R and green fluorescent protein (GFP) in the absence or presence of the BiTE. The SST2R- parental 293T cell line was used as negative control, while anti-CD3/CD28 beads were added as a positive control. The BiTE-induced T cell activation was evaluated measuring the secretion of IFNγ and granzyme B by ELISA and OX40, 41BB and CD69 by flow cytometry.

Results
At a concentration of 100 nM, the BiTE bound the CD3 receptor of approximately 85% of T cells. By confocal microscopy, the BiTE was found to coat SSTR2 + 293T cells. IFN-γ secretion was significantly higher when the T cells were co-cultured with SSTR + 293T cells in the presence of the BiTE as compared with parallel preparations with SSTR- 293T cells or without the BiTE, suggesting that the BiTE-induced T cell activation is specific. At high concentration of BiTE, OX40, CD69 and 41BB on T cells were upregulated regardless of the presence of target cells. However, at the same concentration, the granzyme B concentration increased only in presence of SSTR + target cells.
Conclusions

To our knowledge, this is the first BiTE to incorporate a hormone in one binding site. Its non-antibody-like structure efficiently engaged SSTR2 and T cells enabling the formation of immune synapse.

Abstract ID 21446

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B4

Simultaneous Inhibition of DNA Methylation and Histone Deacetylation for Enhanced SSTR2 Expression In Vitro

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Background

Neuroendocrine tumor (NET) patients with diminished SSTR2 expression are not eligible for any type of SSTR2-specific imaging or treatment. Herein, we propose to epigenetically enhance and enable somatostatin receptor type 2 (SSTR2)-targeted theranostics for patients with NETs. Specifically, we have found that simultaneous inhibition of DNA methylation and histone deacetylation enhanced SSTR2 expression and in vitro binding of $^{68}$GaDOTATATE. Our hypothesis is that epigenetic modifiers with different mechanisms of action, have superior effect in upregulation of SSTR2 when compared to the single drug treatment. Our approach will result in new targeted treatment strategies for patients who currently have very limited therapeutic options.

Methods

To determine the anti-proliferative effects of VPA, Decitabine and the combination of both, all cell lines were treated for 72 hours and an MTT assay concentration of 10 nM for 2 h. After washing, cells were lysed and radioactivity was determined using a gamma counter. Activity was normalized to protein content by BCA assay and expressed as percent added dose per mg protein (%ID/mg).

Results

We have shown that combination treatment with two epigenetic modifiers, both with different mechanisms of action, VPA (HDAC inhibitor) and Deci-tabine (DNMT inhibitor), had superior effect in upregulation of SSTR2 on mRNA, protein and functional levels when compared to the single drug treatment in BON, H727, and MZ cell lines. In contrast and most importantly, neither the fibroblast cell line WE-3 nor the normal thyroid cell line Ht0r-3 showed an increase in $^{68}$GaDOTATATE uptake after treatment.

Conclusions

We have revealed that combination treatment with HDAC (VPA) and DNMT (decitabine) inhibitors potentiated SSTR2 expression in NET cells and exhibited superior $^{68}$GaDOTATATE binding comparing to either single drug. Furthermore, treatment of non-neuroendocrine cell lines exhibited no increase in radiomucide binding. The epigenetic upregulation of SSTR2 expression could improve the efficacy and toxicity profile for targeted radiomucide therapy of NETs with $^{177}$LuDOTATATE.

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B6

Detecting Cell Surface Expression of Calreticulin in Pancreatic Neuroendocrine Tumors Using a Novel [68Ga]Radiolabeled Peptide

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Background

Current theragnostic techniques for pancreatic neuroendocrine tumors (pNETs) exploit the overexpression of somatostatin receptors (SSTRs) on the cell surface. However, approximately 25% of low-grade and most high-grade pNETs do not express SSTRs, requiring alternative theranostics. Calreticulin (CALR) is a protein linked to reticular calcium homeostasis and immunogenic cell death. Upon sufficient cellular insult, CALR translocates from the endoplasmic reticulum (ER) to the plasma membrane. This then promotes phagocytosis of the damaged cell, facilitating an immune response and potentially serving as a biomarker. Herein, we aimed to characterize CALR expression in pNETs and to induce CALR surface translocation in pNETs and to detect surface CALR using a novel radiolabeled peptide.

Methods

Tissue microarrays of human pNETs and normal islets were immunohistochemically stained and CALR expression measured via H-scoring by a pathologist. Surface translocation of CALR was detected by flow cytometry in pNET cells (BON, QGP) treated with either dantrolene or doxorubicin. For peptide radiolabeling, the radiomucide-binding chelator DOTA was covalently linked to a CALR-specific peptide (KLGFPRK). The peptide [DOTA-Bn-SCN$_2$Gal$_2$Asp$_4$KLGFPRK] was labeled with $^{68}$Ga. Samples were analyzed on a HERC with an average radiolabeling efficiency of 95%. For in vitro radiopeptide uptake studies, pNET cells were treated with dantolene for CALR induction and then incubated with 1 μM $^{68}$GaDOTA-Bn-SCN$_2$Gal$_2$Asp$_4$KLGFPRK for 1 hour. For the in vivo biodistribution study, BALB/c mice (n = 4) were injected with ~3 MBq (5 μg) of radiopptide for 1 hour.
Results
Mean H-score of CALR expression was higher in pNETs (241, n=51) compared to normal islets (53, n=17; P<0.001). We found that surface CALR can be significantly induced in pNET cells with the ryanodine receptor antagonist dantrolene or the anthracycline doxorubicin. Our novel [14C]Gal-CALR peptide showed significantly higher binding in pNET cells when surface CALR was induced by dantrolene (n=3, P<0.01). We also performed an initial biodistribution study using non-tumor-bearing BALB/c mice and saw rapid clearance was through the kidneys with no significant uptake in vital organs (n=4).

Conclusions
CALR can be translocated to the cell surface in pNET cells, where it can then be detected by a radiolabeled PET imaging agent. The utilization of an alternative pNET cell surface marker, such as CALR, as a therapeutic target could create new treatment options for the subset of patients with pNETs that have low basal expression of SSTRs.

Abstract ID 21466
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B7
All-Trans Retinoic Acid Radiosensitizes Neuroendocrine Tumor Cells via Peptidyl-Prolyl Cis-Trans Isomerase 1 Inhibition
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Background
Peptide receptor radionuclide therapy (PRRT) is a promising radionuclide-based therapy for metastatic neuroendocrine tumors (NETs) but remains palliative. Peptidyl-prolyl cis-trans isomerase (Pin1) is an evolutionally conserved enzyme that catalyzes the cis-trans isomerization of phosphorylated serine/threonine-proline motifs of its substrates and has recently been involved in DNA double strand break (DSB) repair in BRCA-proficient breast cancer cells. Here we study whether Pin1-inhibition with All-Trans Retinoic Acid (ATRA) radiosensitizes NET cells.

Methods
The pancreatic and lung NET cell lines QGP1, BON1 and NCI-H727 were treated with 10Gy of radiation (IR) and either 50nM or 100nM of ATRA based on dose response curves. The poly (ADP-ribose) polymerase 1 inhibitor (PARP1) Telazaporib (10nM) was added to QGP1 cells to evaluate the additive vs. synergistic effects with ATRA and IR. Pin1 knockdown using siRNA, and BRCA1 and gH2AX western blot were used to determine mechanistic effects. Retinoic Acid Receptor (RAR) alpha status was determined in cell lines using RT-PCR.

Results
ATRA treatment alone showed a significant decrease in tumor cell viability in QGP1 (P<0.013), BON1 (P<0.001), and NCI-H727 (P<0.0003). Combining ATRA + IR yielded further significant decrease in cell viability vs. IR alone (QGP1 (P<0.0001), BON1 (P<0.0001), NCI-H727 (P<0.0003)). ATRA synergized with Telazaporib and IR in QGP1 cells (P<0.0001). Pin1 knockdown with siRNA + IR further decreased cell viability in QGP1 (P<0.0002) and BON-1 (P=0.015) cells when compared to IR alone, suggesting that ATRA radiosensitizes NET cells through Pin1 inhibition. ATRA also decreased BRCA1 mRNA levels in QGP1 cells after IR and increased DNA double strand breaks as evidenced by increased gH2AX mRNA and protein expression after treatment. RAR alpha was highly expressed in all 3 cell lines with an average cycle threshold (CT) value of 20.42, 21.44, and 22.90 in QGP1, BON1, and NCI-H727 respectively.

Conclusions
ATRA radiosensitizes pancreas and lung NET cells through Pin1-inhibition and decreases BRCA1 levels. This ATRA-induced BRCA1-deficient phenotype synergizes with PARP1 inhibition and IR. Further studies will focus on validating these results in animal models.

Abstract ID 21472
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B9
Deletion of Notch1 Signaling in Pancreatic Neuroendocrine Tumors Reduces Metastatic Properties
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Background
The 5-year survival rate for patients with unresectable, metastatic pancreatic neuroendocrine tumors (pNETs) remains less than 30%, emphasizing the need for new and effective treatment options for patients with advanced pNETs. Notch1 signaling is a critical cell-cell communication pathway responsible for regulating differentiation, cell fate determination, and epithelial-mesenchymal transition (EMT). Notch1 plays a critical role in the differentiation state of NE cells and is aberrantly expressed in metastatic pNETs. We hypothesized that Notch1 signaling plays a role in pNET malignancy.

Results
Synergistic effects of MEK inhibitor (Miraximib) and CDK4/6 inhibitor (Palbociclib) were measured by cell proliferation & survival assays, colony formation and immunoblotting. Tumor suppressive effects of drug inhibitors were measured in vivo using 3 pNET mouse models: 1) flank xenografts in immunodeficient mice, 2) tail vein metastasis xenografts in immunodeficient mice, and 3) immune competent, Pdx1-Cre;Men1(+/−)/Pten(+/−) knockout mice that develop insulinoma by 5-6 months of age.

Results
Dual CDK4/6-MEK inhibitor therapy was highly synergistic in vivo in causing pNET cell death and pathway inactivation, as measured by retinoblastoma protein (Rb1) hypo-phosphorylation. In vivo, the CDK4/6-MEK combination significantly slowed the growth of flank pNET xenografts, yielding a 6-fold extension of average survival (~120 days vs 20 days for vehicle control). This combination likewise suppressed (but did not eliminate) pNET growth in a bioluminescence metastasis model and effectively reduced the number of colonized tissues relative to monotherapy controls. Most impressively, dual CDK4/6-MEK inhibition caused dramatic tumor regression associated with a unique B/plasma cell infiltration phenotype in our Pdx1-Cre;Men1(+/−)/Pten(+/−) mouse model of insulinoma.

Conclusions
Combination therapy targeting CDK4/6 and MEK effectively inhibits pNET growth and metastatic colonization. Monotherapies were not effective, in agreement with failed CDK4/6 monotherapy trials in pNET patients. In immune competent Pdx1-Cre;Men1(+/−)/Pten(+/−) mice, CDK4/6-MEK inhibition causes significant tumor regression linked with tumor infiltration of B and plasma cells. These data suggest that the increased efficacy of CDK4/6-MEK targeted therapy against pNETs in immune competent mice is due to activation of an anti-tumor immune response, which we propose may sensitize tumors to immune checkpoint inhibitor therapy.

Abstract ID 21474
DOI: 10.1530/endoabs.89.B8

B8
CDK4/6-MEK Targeted Therapy Causes Regression and Reduced Metastatic Colonization of Pancreatic Neuroendocrine Tumors
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University of Iowa and Holden Comprehensive Cancer Center, 3University of North Carolina, 2Rutgers Cancer Institute of New Jersey

Background
New therapeutics and combinations are needed to improve the survival of patients with advanced, metastatic pancreatic NETs (pNETs). RABL6A is a novel oncopgenic driver of pNET pathogenesis that acts through multiple oncogenic pathways. Kinome and phosphoproteome analyses of proliferation (RABL6A-positive) pNET cells, vs arrested (RABL6A-knockdown) controls, demonstrated that drugable cyclin-dependent kinase 4 and 6 (CDK4/6) and MEK kinases are activated in growing pNET cells. Consistent with those findings, published studies of patient pNETs by immunohistochemistry (IHC) and RNAseq have identified robust activation of CDK4/6 and MEK in the tumors. Studies in other tumor types show CDK4/6 and MEK inhibitors have synergistic antitumor activity linked with heightened CDS T cell and/or natural killer cell activation. This drug combination has not yet been evaluated in pNETs.

Methods
Synergistic effects of MEK inhibitor (Miraximib) and CDK4/6 inhibitor (Palbociclib) were measured by cell proliferation & survival assays, colony formation and immunoblotting. Tumor suppressive effects of drug inhibitors were measured in vivo using 3 pNET mouse models: 1) flank xenografts in immunodeficient mice, 2) tail vein metastasis xenografts in immunodeficient mice, and 3) immune competent, Pdx1-Cre;Men1(+/−)/Pten(+/−) knockout mice that develop insulinoma by 5-6 months of age.

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Conclusions
Combination therapy targeting CDK4/6 and MEK effectively inhibits pNET growth and metastatic colonization. Monotherapies were not effective, in agreement with failed CDK4/6 monotherapy trials in pNET patients. In immune competent Pdx1-Cre;Men1(+/−)/Pten(+/−) mice, CDK4/6-MEK inhibition causes significant tumor regression linked with tumor infiltration of B and plasma cells. These data suggest that the increased efficacy of CDK4/6-MEK targeted therapy against pNETs in immune competent mice is due to activation of an anti-tumor immune response, which we propose may sensitize tumors to immune checkpoint inhibitor therapy.

Abstract ID 21474
DOI: 10.1530/endoabs.89.B8

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Methods
To characterize the role of Notch1, we developed a Notch1-knockout pNET cell line. The resulting cell line was established by deleting Notch1 at exon 3 in BON cells using CRISPR/Cas9. Successful knockout of Notch1 was confirmed by Sanger sequencing and western blot analyses. To confirm the loss of functional Notch1, we measured changes of specific Notch1 downstream genes at both the transcriptional and translational level. Moreover, to have a global view of signaling pathways affected by Notch1, we performed RNAseq analyses comparing wildtype (N1-WT) and Notch1-knockout cells. Reads were aligned to the transcriptome using STAR and differentially expressed genes (DEG’s) determined using DESeq2. Gene set enrichment analysis was then performed using the Hallmark gene sets. Cell migration was measured by a transwell migration assay.

Results
Notch1 knockout was confirmed by a decrease in downstream Hes family genes, and an increase in Acsl1, a gene repressed by Notch. RNAseq results showed an increase in expression of NE differentiation markers in Notch1-knockout cells. NeuroD1, which was also confirmed by RT-qPCR. Further, RNAseq analyses showed that when Notch1 is deleted, there was a significant decrease in EMT-related genes (P=0.015). This finding was confirmed with RT-qPCR, whereby Notch1-knockout cells demonstrated a reduction in expression of Snail (two-sample t(4)= 3.957, P=0.017) and Slug (two-sample t(4)= 1.062, P=0.348) compared to N1-WT, two genes linked to cell migration and EMT. Finally, migration assays revealed that significantly fewer Notch1-knockout cells were able to migrate when compared to wildtype (two-sample t(6)= 5.889, P=0.001).

Conclusions
Knockout of Notch1 signaling in pNET cells inhibits migration and reduces expression of EMT-related genes. Our data suggest Notch1 may confer a more aggressive phenotype in pNET cells by facilitating metastatic spread. Inhibiting Notch1 signaling may be an effective therapeutic strategy in advanced pNETs. Abstract ID 21479
DOI: 10.1530/endoabs.89.B9

B10
Inhibition of Estrogen Receptor Alpha Radiosensitizes Neuroendocrine Tumors
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Background
We hypothesize that estrogen receptor alpha (ESR1) with siRNA and Fulvestrant radiosensitizes NET cells by decreasing expression of DNA repair genes. Further experiments are needed to validate these results and define the exact mechanism by which ESR1 influences DNA repair.

Methods
Increased numbers of viable cells in QGP1 (including RAD51, BRCA1, and BRCA2 following ESR1 knockdown. Using a system of quenching and splitting, we measured changes of expression of genes related to DNA repair.

Results
Increased numbers of viable cells in QGP1 (including RAD51, BRCA1, and BRCA2 following ESR1 knockdown. Using a system of quenching and splitting, we measured changes of expression of genes related to DNA repair.

Conclusions
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B11
Patient-Derived Organoids and Their Potential for Precision Medicine in Neuroendocrine Tumors
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Background
Neuroendocrine tumors (NETs) are a heterogeneous group of malignant neoplasms arising from neuroendocrine cells distributed throughout the body. The most common sites of NETs are the gastrointestinal tract, pancreas and lungs. The clinical management of NETs is not standardized, with few FDA-approved therapies. Moreover, drug development has been challenging for NETs due to limited pre-clinical models. To address this unmet need, the NCI Natural History Study of Children and Adults with Neuroendocrine Neoplasms (NCT03739827 and NCT05263394) aims to develop preclinical models, such as in vitro 3-dimensional tissue organoids, to develop more personalized therapies for NET patients.

Methods
From February 2020 – July 2022, 17 surgical specimens were collected for the development of patient-derived organoids. We selected 3 NET organoids (NET16, NET17 and NET18) to test the activity of select drugs: dovitinib (VEGFR inhibitor), visutsertib (mTOR inhibitor), cobimetinib (mitogen-activated protein kinase 1 inhibitor) and TAK243 (ubiquitin activating enzyme inhibitor). NET16 was derived from a 72-year-old male with grade 1 (Ki-67 <3%) small bowel NET. NET17 was derived from a 36-year-old female with grade 2 liver segment metastasis. NET18 was derived from a 66-year-old male, with grade 2 (Ki-67 = 3%) liver segment metastasis. Cell viability assays were performed using Cell Titer Glo after 3 days of drug testing. Chromogranin A, synaptophysin, and Ki67 biomarkers will be assessed in the parental tissues as well as the organoids.

Results
Overall, the activity of the drugs tested was significantly higher in NET16 than NET17 and NET18. TAK243 was the most potent drug in both NET16 and NET18. Dovitinib and vistusertib were more potent in NET16 (IC50 = 0.62 mE) and NET18 (IC50 = 0.62 mE) than NET17 (IC50 = 1.46 mE). Cobimetinib was more potent in NET16 (IC50 = 11.18 mU) and NET17 (IC50 = 16.45 mU) and NET18 (IC50 = 16.45 mU) than NET17 (IC50 = 16.45 mU) and NET18 (IC50 = 16.45 mU).

Conclusions
We have developed an assay for in vitro drug testing in well-differentiated patient-derived NET organoids that will allow for further, large scale drug screening to help predict patient drug responses. Tumor heterogeneity may be contributing to the differences seen in the drug response between the three NET organoids and requires further evaluation. Replication of these studies in a larger subset of patient samples and drug combination studies will be important for the advancement of therapeutics in NETs. Abstract ID 21564
DOI: 10.1530/endoabs.89.B11
B12  
Transcriptomic Influences of Racial Disparities in Black Patients with Pancreatic Neuroendocrine Tumors  
Brendon Herrings1, Rachael Quenters2, Deepith Dhalls3, Herbert Chens1, Clayton Yates1 & J. Bart Rose2  
1University of Alabama at Birmingham Department of Surgery, 21University of Alabama at Birmingham Department of Pathology, 3Tuskegee University Department of Biology.

Results  
Gene set enrichment analysis was then performed using clusterProfiler and the Gene Ontology (GO) consortium gene sets. Ingenuity Pathway Analysis (IPA) was then conducted to determine regulator effect networks.  

Conclusions  
OIdentable structural variants in all mNET samples. Trends towards differences between tumors of different grade and primary site of origin, as well as the presence of potential chromothripsis events, were observed in this small data set. An expanded study evaluating more samples and correlating genomic findings with clinical data and outcomes is ongoing.
Table 1 (Abstract B14). Histopathologic and NGS characteristics of pancreateic mixed acinar neuroendocrine carcinoma patients.

<table>
<thead>
<tr>
<th>Age in years/sex</th>
<th>Tumor site</th>
<th>Type of pathology</th>
<th>Pathology IHC</th>
<th>Presentation</th>
<th>Treatment</th>
<th>NGS assay</th>
<th>Patient status</th>
</tr>
</thead>
<tbody>
<tr>
<td>66/M</td>
<td>Pancreatic head mass</td>
<td>EUS guided biopsy of pancreatic head</td>
<td>Tumor cells positive for trypsin, synaptophysin-1, chromogranin-A, INSM1 and CKAE1/3, negative for beta catenin (negative nuclear stain)</td>
<td>50%</td>
<td>Proficient</td>
<td>Germline invriscienn launched but no evidence of action</td>
<td>Metastatic to liver and regional lymph nodes</td>
</tr>
<tr>
<td>30/M</td>
<td>Pancreatic head mass</td>
<td>EUS guided biopsy of pancreatic head with bilateral reconstruction</td>
<td>tumor cells positive for trypsin and synaptophysin-1 and are negative for IBSL</td>
<td>10%</td>
<td>proficient</td>
<td>Familial adenomatous polyposis (FAP)</td>
<td>Localized tumor. Final pathology staging per AJCC: pT2N0</td>
</tr>
</tbody>
</table>

search of Dartmouth pathology database is ongoing to identify more cases in the last 10 years and to complete genomic analysis on these cases. Abstract ID 21556 
DOI: 10.1530/endoabs.89.B14

B15

Targeting the TCA Cycle with Histone Deacetylase and Nicotinamide Phosphoribosyltransferase Inhibitors Uncovers a Critical Role for YAP1 in Neuroendocrine Cells

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Background More than 12,000 people in the United States are diagnosed with a NET each year and approximately 175,000 people are living with this diagnosis. Little progress has been made in the therapy of NETs over the last two decades, and identification of new vulnerabilities remains a priority.

Methods We used two libraries of compounds selected for potential repurposing and identified agents with the highest cytotoxic activity in neuroendocrine models. FACS analysis was used to examine drug sensitivity; gene expression profiling was performed to gain insight into the molecular mechanisms responsible for drug sensitivity. Immunoblot and metabolic flux analysis were used to confirm observations at molecular and metabolic levels. Cell viability assays for synergy among drug-drug combinations were performed.

Results In the initial screen, nicotinamide phosphoribosyltransferase (NAMPT) and histone deacetylase (HDAC) inhibitors had the highest activity. Hits were validated in an expanded set of neuroendocrine cell lines and their mechanism of action examined. Differential sensitivity to NAMPT inhibitors was documented with gene expression profiles indicating up-regulation of genes involved in hypoxia, glycolysis, gluconeogenesis, and cholesterol homeostasis in NAMPT resistant cells, suggesting increased reliance on glucose and its conversion to pyruvate via glycolysis to meet energy requirements. Furthermore, metabolic flux analysis revealed that in sensitive cells, death following NAMPT inhibition results from a reduction in basal oxidative phosphorylation and energy production. Differential expression of YAP1, the yes-associated protein, between sensitive and resistant cells was indicative of a possible role in the observed drug resistance. Follow-up studies using Kelly cells ectopically expressing YAP1 (Kelly/YAP1), confirmed over-expression of YAP1 increases drug resistance, concurrent with an increase in glycolysis in metabolic flux analysis. Moreover, in resistant cells, interfering with YAP1 function or downregulating its expression increased NAMPT sensitivity, accompanied by a marked reduction in ATP production. Lastly, drug-drug combination using the HDAC inhibitor romidepsin in combination with NAMPT inhibitors showed synergistic activity at low sub-lethal concentrations.

Conclusions Exploiting metabolic vulnerabilities in neuroendocrine cells offers an opportunity for new therapeutic strategies. A double hit on the TCA cycle – depleting acetyl CoA via HDAC inhibition, previously shown, and blocking key intermediate steps dependent on NAD cofactors via NAMPT inhibition could be highly effective and should be pursued with a goal of developing translational clinical trials.

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B16

[212Pb/PSC-PEG2-TOC Therapy for NET Leads to Complete Responses in Mice Bearing SSTR2 Positive Tumors - Comparison to [177Lu]DOTATATE in a Preclinical Model]

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Background Peptide-based targeted alpha-particle radiotherapy has emerged as a promising approach to cancer treatment. 210Po/212Pb is the only elementally identical isotope pair for this application. Tyr3-Octreotide (TOC) peptide ligands targeting SSTR2 have been widely investigated preclinically and clinically. [177Lu]DOTATATE was approved by the US FDA to treat patients with gastroenteropancreatic neuroendocrine tumors. However, the objective response rate (18%) reported in the Phase III trial leaves significant room for improvement. In this study, we modified TOC with a Pb specific chelator (PSC) and PEG2 linker and evaluated the in vivo biodistribution profiles and efficacy of [212Pb/PSC-PEG2-TOC in preclinical mouse model in comparison with [177Lu]DOTATATE. Methods PSC-PEG2-TOC was radiosynthesized with 210Pb and 212Pb by published methods1, 2. [177Lu]DOTATATE was synthesized and radiolabeled using published methods3. Biodistributions were conducted in female athymic nu/nu mice bearing AR42J tumor xenografts following intravenous injection of 74 kBq of 203Pb-labeled PSC-PEG2-TOC at 1, 3, 6 and 24 h post-injection (pi). Single or fractionated doses of [212Pb/PSC-PEG2-TOC (total activity at 4.44 MBq) were administered to mice bearing AR42J tumors for efficacy evaluation. Administered fractionated doses of [212Pb/Lu]DOTATATE were based on previous literature. Tumor volume, body weight, complete blood count, and serum chemistry were monitored.

Results PSC-PEG2-TOC labeled efficiently with 203Pb at high specific activity (50-100 MBq/mmol). 24-h radiochemical purity and maintained near quantitative levels in excipients. In vivo biodistribution studies demonstrated high tumor uptake and rapid renal clearance for [212Pb/PSC-PEG2-TOC. The administration of 4 fractionated doses of [212Pb/PSC-PEG2-TOC produced 100% complete tumor responses at 100 days post therapy initiation and was well-tolerated compared to [177Lu]DOTATATE, which produced improved PFS (28.3 days), but no complete responses. Conclusions These data demonstrate that [212Pb/PSC-PEG2-TOC has the potential to produce a higher rate of objective tumor responses than beta-particle emitting therapeutics for NETs. 

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Clinical – Chemo/SSA/Biologics
C1

Progression-Free Survival in Patients with Bronchopulmonary Neuroendocrine Tumors Treated with Lanreotide or Placebo: Adjustment for Crossover Effects in Placebo Arm

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Background

SPINET was a phase 3 trial (NCT02683941) in patients with well-differentiated, advanced bronchopulmonary neuroendocrine tumors (NETs; typical and atypical carcinoids [TCs and ACs]). During the double-blind (DB) period, patients were randomized (2:1) to receive lanreotide autogel/depot (LAN; 120 mg) or placebo (PBO) every 28 days; in the optional open-label (OL) phase, all patients received LAN. Recruitment was stopped early due to slow accrual; all eligible patients transitioned to OL-LAN. Over the DB or OL phases in patients randomized to LAN, the aim of this post hoc analysis was to compare PFS data during the DB and OL phases between PBO and LAN, adjusting for the crossover using the rank-preserving structural failure time (RPSFT) model.

Methods

RPSFT is one of the most common statistical methods used to adjust overall survival (OS) data for crossover in oncology trials [Jack Ichak, K et al. Pharmacoeconomics 2014;32:533; Bennett I et al. Value Health 2018;21:105] and has been used previously in a post hoc analysis of a phase 3 study in pancreatic NETs (Faire S et al. Ann Oncol 2017;28:339). RPSFT is a non-parametric model that provides a treatment-effect estimate that is corrected for the confounding effect of crossover. Kaplan-Meier estimates were generated and the hazard ratio (HR) estimated using the multivariate Cox proportional-hazards model, stratified for tumor subtype.

Results

Overall, 77 patients were randomized; this analysis accounted for the 19/26 patients (73%) who transitioned to OL-LAN. Over the DB progression-free survival (PFS) during the DB or OL phases in patients randomized to LAN. The adapted primary endpoint was centrally confirmed OS and progression-free survival (PFS) given the promising activity of immunotherapy across several cancer types, our center initiated a phase II trial of pembrolizumab monotherapy in HG-NENs.

Methods

This was an open label, non-randomized phase II study in patients with metastatic extra-pulmonary HG-NEN, K67 > 20%, treated with pembrolizumab following progression on platinum- or temozolomide-based chemotherapy. Primary endpoint was overall response rate (ORR) as measured by irRECIST. Secondary endpoints included clinical benefit rate (CBR), OS, and PFS.

Results

Between December 2017 and December 2018, 6 patients (5 females/1 male) with HG-NEN were enrolled and received at least 1 dose of pembrolizumab. Histology was characterized as poorly differentiated in 50% and well-differentiated in 50%. Ki-67 ranged from 25% to >90%. The majority of patients had primary tumors originating from the rectum (33%), pancreas (16.7%), or liver (16.7%). One patient with small cell cancer of the prostate and one with neuroendocrine breast carcinoma (NEBC) were also included. One patient (16.7%) had stable disease that was maintained for 8.3 months. The remaining 5 (83.3%) patients had progression of disease (POD) by irRECIST at 6 weeks. The ORR was 0% with CBR of 16.7%. Pembrolizumab was well tolerated with 1 grade 3 event and 1 grade 4 event considered to be potentially drug-related.

Conclusions

Pembrolizumab has limited activity as monotherapy in HG-NENs. One patient with NEN-LAN had stable disease for 8.3 months. These findings are consistent with prior publications assessing pembrolizumab in metastatic grade 3 NETs.

Abstract ID 21389
DOI: 10.1530/endoabs.89.C2

C2

Pembrolizumab for the Treatment of Recurrent High Grade Neuroendocrine Neoplasms

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Background

High-grade neuroendocrine neoplasms (HG-NENs) are a heterogeneous and biologically aggressive rare subset of NETs. Few therapeutic options are available to metastatic HG-NENs. To date, first line treatment is platinum- or temozolomide-based chemotherapy which provide modest benefits in overall survival (OS) and progression free survival (PFS). Given the promising activity of immunotherapy across several cancer types, our center initiated a phase II trial of pembrolizumab monotherapy in HG-NENs.

Methods

This was an open label, non-randomized phase II study in patients with metastatic extra-pulmonary HG-NEN, K67 > 20%, treated with pembrolizumab following progression on platinum- or temozolomide-based chemotherapy. Primary endpoint was overall response rate (ORR) as measured by irRECIST. Secondary endpoints included clinical benefit rate (CBR), OS, and PFS.

Results

Between December 2017 and December 2018, 6 patients (5 females/1 male) with HG-NEN were enrolled and received at least 1 dose of pembrolizumab. Histology was characterized as poorly differentiated in 50% and well-differentiated in 50%. Ki-67 ranged from 25% to >90%. The majority of patients had primary tumors originating from the rectum (33%), pancreas (16.7%), or liver (16.7%). One patient with small cell cancer of the prostate and one with neuroendocrine breast carcinoma (NEBC) were also included. One patient (16.7%) had stable disease that was maintained for 8.3 months. The remaining 5 (83.3%) patients had progression of disease (POD) by irRECIST at 6 weeks. The ORR was 0% with CBR of 16.7%. Pembrolizumab was well tolerated with 1 grade 3 event and 1 grade 4 event considered to be potentially drug-related.

Conclusions

Pembrolizumab has limited activity as monotherapy in HG-NENs. One patient with NEN-LAN had stable disease for 8.3 months. These findings are consistent with prior publications assessing pembrolizumab in metastatic grade 3 NETs.

Abstract ID 21389
DOI: 10.1530/endoabs.89.C2

C3

Real World Analysis of Long-Acting Somatostatin Analog (LA-SSA) Treatment and Dose Escalation Among Patients with Neuroendocrine Tumors (NET)

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Background

LA-SSA therapy, including octreotide long-acting release (LAR) and lanreotide depot (LAN), is recommended as first-line therapy for treatment of unresectable or metastatic NETs. Understanding treatment sequencing and dosing patterns of LA-SSAs is essential for clinical decision-making to provide value-based management of NET for both the patients and healthcare system. This study describes treatment patterns of LA-SSA therapy among privately insured patients with NET in the US.

Methods

Claims data for patients with NET who were newly treated with LA-SSAs for ≥3 months were extracted from MarketScan Commercial and Medicare databases between 1/1/2015-10/31/2021 (earliest LA-SSA treatment index date). Treatment patterns were reported during index LA-SSA treatment, including treatment duration, dose, up to 2 dose escalations, use of rescue therapy with short-acting octreotide at any time during treatment, and transition to other LA-SSA. Doses were reported as 28-day doses based on days' supply/drug quantity (for outpatient pharmacy claims) or units of service (for outpatient medical claims). Dose escalation was defined as an increase in quantity administered or frequency of injections (28-day to 21-day cycles). Chi-square tests, two sample t-tests, and log-rank test were used for binary variables, continuous variables, and treatment duration estimated using the Kaplan-Meier approach, respectively.

Results

A total of 762 patients with NET treated with LA-SSAs were identified (241 started on LAN and 521 started on octreotide LAR). Treatment duration was longer for LAN than octreotide LAR (median 3.4 vs. 2.2 years, P-value = 0.004). Compared to octreotide LAR, fewer LAN patients experienced a first and second dose escalation (first dose escalation: 6% vs. 27%; second dose escalation: 1% vs. 5%; all P-values < 0.05). Additionally, fewer LAN patients used rescue treatment (8% vs. 14%, P-value = 0.011). Doses based on days’ supply/drug quantity or units of service were reported for most patients, and 2% of LAN patients received...
an above label 28-day dose (> 120 mg) compared to 14% of octreotide LAR patients (> 30 mg; P-value < 0.05). Amongst patients whose initial treatment ended during follow-up (90 LAN and 274 octreotide LAR patients), fewer LAN patients transitioned to the other LA-SSA compared to octreotide LAR (19% (n = 17) vs. 34% (n = 92), P-value = 0.008).

Conclusions
Compared with octreotide LAR patients, LAN patients were more likely to remain on their initial LA-SSA treatment longer as well as on their starting dose without dose escalation, and less likely to use rescue treatment.

Abstract ID 21424
DOI: 10.1530/endoabs.89.C3

C4
Cisplatin vs Carboplatin in Extrapolumin Poorly Differentiated Neuroendocrine Carcinomas (PD NEC)
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Background
Extrapolumin PD NECs carry a poor prognosis. Some studies suggest cisplatin is more appropriate for younger patients due to its increased potency and nephrotoxicity compared to carboplatin, but randomized trials are lacking. We aim to determine whether there is a difference in outcomes for cisplatin vs carboplatin while adjusting for possible confounding factors.

Methods
We identified PD NEC patients at Mayo Clinic between 2000-2022. Kaplan-Meier method determined overall survival (OS) and progression free survival (PFS). Disease control rate (DCR) was the percentage with complete/partial response or stable disease. Univariate analysis utilized a Cox proportional hazards model.

Results
Thirty-four patients received cisplatin/etoposide and 33 patients received carboplatin/etoposide as first line therapy. Baseline characteristics are in Table 1. The median follow-up was 39.5 months (95% CI: 24.1-39.5) in the carboplatin group (p value 0.17). DCR was 88% in the cisplatin group vs 63% in the carboplatin group (p value 0.001). In univariate analysis, the differences in median OS and PFS were not statistically significant when accounting for age, creatinine, cell morphology, and sex.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Cisplatin Group</th>
<th>Carboplatin Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>(n=34)</td>
<td>(n=33)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>59 (21-84)</td>
<td>66 (31-86)</td>
</tr>
<tr>
<td>Stage 3-4, n (%)</td>
<td>31 (91%)</td>
<td>39 (100%)</td>
</tr>
<tr>
<td>Bilir, n (%)</td>
<td>5 (15%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>10 (29%)</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>Colonectal</td>
<td>6 (18%)</td>
<td>11 (33%)</td>
</tr>
<tr>
<td>Other GI</td>
<td>4 (12%)</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (12%)</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3 (9%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gynaecologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphology, n (%)</td>
<td>7 (21%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>Large cell</td>
<td>12 (35%)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Small cell</td>
<td>15 (44%)</td>
<td>17 (52%)</td>
</tr>
<tr>
<td>Nonspecified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki67, median (range)</td>
<td>84 (0.03-99)</td>
<td>70 (35-90)</td>
</tr>
<tr>
<td>Creatinine, median (range)</td>
<td>0.9 (0.5-1.8)</td>
<td>0.9 (0.58-2.2)</td>
</tr>
</tbody>
</table>

Conclusions
In this study, cisplatin was associated with a favorable DCR and PFS. There was no statistically significant difference in OS between groups, though the median OS for cisplatin was longer by almost 6 months. While PFS for cisplatin was superior, this did not persist when adjusting for other factors. Cisplatin might be favored over carboplatin for young, fit patients, but this study did not confirm a benefit in median OS.

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Endocrine Abstracts (2022) Vol 89

C5
C-MET Expression in MEN1-associated Neuroendocrine Tumors
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Background
Multiple studies have shown that approximately 50-70% of patients with MEN1 die of causes directly related to MEN1 particularly gastroenteropancreatic (GEP) neuroendocrine tumors (NETs). While non-functional GEP-NETs are the most common in the general population, gastrinomas (40%) are the most common functional GEP-NETs in patients with MEN1. C-Met is a proto-oncogene that encodes for c-MET, a tyrosine kinase receptor which promotes tumor cell motility, proliferation, survival, invasion, and metastasis. Studies in patients with sporadic gastrinomas and pancreatic NETs (PNETs) have shown that c-MET expression correlates with decreased survival. While c-met inhibitors are currently in various stages of investigation for treatment of carcinoids and sporadic PNETs, data regarding their efficacy in patients with MEN1-related GEP NETs is lacking. Majority of trials in patients with GEP-NETs exclude or do not report the number of patients with MEN1. Importantly, somatic MEN1 mutations are observed in 20-40% of sporadic NETs (gastrinomas, PNETs, lung NETs, etc.) but correlation of cMET expression with the presence of somatic or germline MEN1 mutations has not been reported. We sought to investigate the expression of c-MET in tumor tissue from germline MEN1 patients with metastatic GEP-NETs.

Methods
We identified subjects with a germline positive MEN1 mutation and pathologically confirmed distant metastasis who had a follow-up visit between 2018-2020. Of these, we selected subjects with available tissue specimens (including either multiple organs or different tumor types). Where available, we identified specimens from multiple organ sources or tumor types. Immunohistochemistry (IHC) to detect c-MET was performed with anti-MET (Cell Signaling) using the DAKO IHC kit (Agilent). IHC slides were imaged and observed to score the level of c-MET staining (-, 1+ to 5+). A score of 3+ or higher was considered consistent with overexpression. We investigated if age at initial GEP-NET presentation, tumor type, tissue source, tumor grade, total number of surgeries for GEP-NET, number of sites of distant metastasis and disease status from overall GEP-NET burden over the preceding 12 months (stable/progressive) predicted c-MET expression.

Results
Eight subjects with available tissue specimens were identified, of which six had tissue from multiple organs while five had tissue from multiple tumor types. Six subjects (75%) showed increased expression of c-MET in one or more tumor specimen(s). The frequency of c-MET overexpression varied with tumor types – carcinoids (n=2/2; 100%), gastrinomas (n=3/5; 60%) and non-functional tumors (n=3/6; 50%). c-MET expression also varied among different tumors in the same patient. Tumor tissue from liver (n=2/2), duodenum (n=3/3), stomach (n=1/1), ovary (n=1/1), pancreas (n=1/5), and lymph nodes (n=1/5), all showed over-expression of c-MET. No clear predictors of c-MET overexpression emerged.

Conclusions
Our finding suggests a role for c-MET expression in personalizing therapy for patients with MEN1-related GEP-NETs with distant metastases.

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DOI: 10.1530/endoabs.89.C5

C6
An Open-Label, Phase 1b/2 study of Surufatinib in Combination with Tidelizumab in Patients with Advanced Neuroendocrine Tumors
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1Department of Medicine, University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA, USA; 2MSCI, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; 3City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; 4Seidman Cancer Center, Case Western Reserve University, Cleveland, OH, USA; 5HUTCHMED International Corporation, Florham Park, NJ, USA; 6MD Anderson Cancer Center, Houston, TX, USA.

Background
Surufatinib, an oral small molecule tyrosine kinase inhibitor, selectively inhibits vascular endothelial growth factor receptor 1, 2, and 3; fibroblast growth factor...
The combination of surufatinib and tislelizumab demonstrated antitumor activity in 6 (20.7%) patients and increased ALT in 5 (17.2%) patients. The most common grade 3 TEAEs were increased aspartate aminotransferase (AST) (34.5%), decreased appetite and fatigue (41.4% each), and increased alanine aminotransferase (ALT) (51.7%), nausea and hypertension (44.8% each), and decreased weight (44.8%). 14 patients (70%) required dose reductions or discontinued one or both medications. Two patients discontinued treatment prior to radiographic assessment. Conclusions The combination of surufatinib and tislelizumab demonstrated antitumor activity in pretreated US patients with thoracic and GEP NETs with a manageable safety profile.

C6 Phase II Study of Pembrolizumab and Lenvatinib in Advanced Well-Differentiated Neuroendocrine Tumors

Taymeyeh Al-Tobah, MPH1, Brian Morse, MD2, Mintallah Haider, MD3, Tiffany Valone, PA4 & Jonathan Strosberg, MD4

Background Immune checkpoint inhibitors have not been shown to be active in well-differentiated NETs, with response rates <5%. Lenvatinib is a multitargeted TKI which targets VEGF and FGF receptors and has been reported to be effective in pancreatic and gastrointestinal NETs (40% and 18.5% ORR, respectively). The combination of antiangiogenic and checkpoint inhibitor therapies can be synergistic in other cancers. We therefore evaluated the combination of lenvatinib and pembrolizumab in well-differentiated GI and thoracic NETs.

Methods A prospective, phase II trial evaluated patients with advanced GI/thoracic NETs (pancreatic NETs were excluded due to high response rate of lenvatinib monotherapy in this patient population), with evidence of progression within 8 months of study entry and at least two prior lines of systemic therapy. Patients received lenvatinib 20 mg daily and pembrolizumab 200 mg IV every three weeks until unacceptable toxicity or progression of disease. Primary endpoint was objective response rate, and an interim analysis was planned once 20 patients were enrolled. 4 ORRs were required to continue enrollment.

Results 20 patients were enrolled on protocol from April 2021 – January 2022 (9 small intestine, 5 lung, 2 thymic, 2 unknown primary, 1 cecal, 1 presacral primaries). Two patients reached an OR with PR (10%) (atyypical lung and small intestinal primaries). Median PFS was 10 months (95% CI 5.9 – 14.1 months). 12 (60%) patients experienced probably- or definitely-associated grade 3 AEs (10 hypertension). 14 patients (70%) required dose reductions or discontinued one of the medications. Two patients discontinued treatment prior to radiographic assessment.

Conclusions The combination of pembrolizumab and lenvatinib did not show sufficient response in patients with NETs to warrant continued enrollment on trial.

C7 Risk of Myelodysplastic Syndrome/Acute Leukemia with Sequential Capecitabine/Temozolomide and 177Lu-Dotatate

Taymeyeh Al-Tobah, MPH, Eleonora Pelle MD & Jonathan Strosberg MD

Background The treatment landscape for neuroendocrine tumors includes alkylating-agent chemotherapy and peptide receptor radiotherapy (PRRT) with 177Lu-Dotatate. The risk of MDS/AML associated with 177Lu-Dotatate is approximately 2-3%. Several small prior studies have suggested substantially higher rates of MDS/AML (approximately 10%) in patients who have also received alkylating agent chemotherapy with streptozocin or temozolomide, either combined with PRRT or sequentially. We designed a study to determine whether sequential treatment with alkylating chemotherapy and PRRT poses an increased risk of developing MDS/AML.

Methods Retrospective study of all patients with advanced NETs treated at the Moffitt Cancer Center between 1/2008 and 9/2019 who received treatment with CAPTEM.

Results 462 patients received treatment with CAPTEM, among whom 49 received also received PRRT. 5 patients developed MDS/AML, all of whom had also received both CAPTEM and PRRT. None of the patients who received CAPTEM chemotherapy without PRRT developed a long-term hematological malignancy. Conclusions 10% of patients who received both CAPTEM and PRRT developed MDS or AML, a risk that is higher than that associated with PRRT alone. This cumulative risk needs to be considered when sequencing treatments in NETs.

C8 Correlation of MEN1 and DAXX Mutational Status with Response to Capecitabine and Temozolomide (CAPTEM) in Pancreatic Neuroendocrine Tumors

Patrick C Lee1, Edik M Blais2, Jun Gong3, Arsen Osipov4, Natalie Moshayed4, Shant Thomassian1, Camille Ng5, Jennifer Chuy5, Lynn M Matrisian6, Emanuel P Petricoin III7, Michael J Pishvaian8 & Andrew E Hendifar9

Background Capecitabine and temozolomide (CAPTEM) is a common regimen for the treatment of metastatic, well-differentiated pancreatic neuroendocrine tumors (PNETs). However, it is unknown whether certain genomic profiles predict response to CAPTEM. PNETs often contain mutations in MEN1, ATRX, DAXX, and the PI3K/AKT/mTOR pathway. We sought to determine whether the mutational status of these genes may correlate with progression-free survival (PFS) on CAPTEM.

Methods A retrospective cohort of PNET cases seen at Cedars-Sinai Medical Center or from Perthera’s Real-World Evidence (RWE) Database (n = 95) included 25 patients who were treated with first- or second-line CAPTEM and had tumor next-generation sequencing (NGS) performed. Relationships between commonly altered PNET genes and PFS on CAPTEM were analyzed using Perthera’s RWE analytics tools. Differences in PFS outcomes by MEN1mut/DAXXmut status and potential confounders (e.g., line of therapy) were analyzed using univariate and multivariate Cox regression.

Results We analyzed 25 PNET patients, 4 (16%) of whom had documented functional tumors. We identified MEN1 mutations as positively associated with CAPTEM.
response, but this effect was less pronounced for the subset with co-occurring DAXX mutations, which are commonly found alongside MEN1 alterations. With and without accounting for line of therapy, we found that PFS on CAPTEM was significantly longer in MEN1-mutated, DAXX-wildtype tumors compared to other mutation profiles (P < 0.01, see Table 1). ATRX and PTEN alterations were also enriched in the MEN1-mut/DAXX-wildtype subset; however, other PI3K/akt/mTOR alterations were common across all MEN1-mutated cases.

Conclusions
We describe a novel, exploratory genomic signature (MEN1-mut/DAXX-wt) that correlates with relative PNET response to CAPTEM. Prospective validation of these associations is warranted while taking into account other therapies, histopathologic factors, and other genomic correlates.

Abstract ID 21458
DOI: 10.1530/endobas.89.C0

C0
ACTH-secreting Pancreatic Neuroendocrine Neoplasms: A Case-Series
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1H. Lee Moffitt Cancer Center and Research Institute, Department of GI Oncology; 2H. Lee Moffitt Cancer Center and Research Institute, Department of Endocrine Oncology.

Background
Pancreatic neuroendocrine neoplasms rarely secrete ACTH resulting in ectopic Cushing’s syndrome. Data are limited to case reports and very small series.

Methods
Cases of ectopic Cushing’s syndrome were identified from a database of pancreatic NENs seen at the Moffitt Cancer Center between 1/2008 and 4/2022. Tumor characteristics, clinical signs and symptoms, therapies and outcomes were evaluated.

Results
13 patients with ACTH-producing pancreatic NENs were seen, ranging in age from 16 to 65 years at time of NEN diagnosis (median 42). 12 of 13 patients had metastatic disease at presentation. Four patients also had ZE syndrome. All tumors were well-differentiated at diagnosis although 2 were described as transformed to poorly differentiated after re-biopsy. Bilateral adrenalectomy was performed in 5 patients for control of Cushing’s syndrome. Tumor responses to therapy were evaluated. Conclusions
Ectopic Cushing’s syndrome is a morbid condition when occurring in pancreatic NENs and is generally associated with aggressive metastatic disease. Bilateral adrenalectomy can be considered for syndrome control.

Abstract ID 21455
DOI: 10.1530/endobas.89.C10

C11
Results from the Phase 1, Randomized, Open-Label, Cross-Over Study to Evaluate Pharmacokinetics of Three Escalating Doses of Oral Octreotide Capsules
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Background
Octreotide capsules (OOC) are approved in the United States for long-term maintenance treatment in acromegaly patients who have previously responded to and tolerated injectable somatostatin analogs (SSAs, octreotide or lanreotide).

Injectable SSAs are also approved and the standard of care in the treatment of carcinoid syndrome associated with neuroendocrine tumors (NET). Compared with acromegaly, patients with NET can require higher average doses of injectable SSAs to achieve adequate symptom control. Prior Phase 1 studies showed the comparability of 20 mg OOC to 0.1 mg Sandostatin SC. Here, single OOC doses up to 80 mg were assessed in healthy subjects for bioavailability, dose proportionality, safety and tolerability.

Methods
Thirty subjects entered an open-label, six-sequence, 3 period cross-over Phase 1 study. Single doses of OOC (20 mg, 60 mg and 80 mg) were administered during the treatment phase. For each treatment period, subjects received a single dose of 1 of the 3 treatments on Days 1, 3 and 5. During each treatment period, serial blood samples for determination of octreotide plasma concentrations were collected pre-dose and through 24-hours following each dose. Approximately 7 days following completion of the last treatment period, subjects returned to undergo safety assessments.

Results
There was a dose-related increase in the geometric mean (gMean) plasma concentrations of octreotide, the gMean values for Cmax, and the AUCs after administration of 20 mg, 60 mg, and 80 mg. Power model exponents ranged from 0.73 (Cmax) to 1.0 for AUC. The 95% confidence intervals for the exponents for all 3 parameters included 1.0, suggesting dose proportionality. Eighteen subjects (18/30, 60%) experienced at least 1 treatment-related adverse event (TEAE). The most common treatment-related TEAEs were diarrhea, abdominal pain, and nausea. All events were recovered/resolved. No TEAEs were assessed as severe in intensity and there were no serious adverse events.

Conclusions
This study demonstrates that doses of OOC up to 80 mg result in dose proportionality with a favorable safety profile, consistent with somatostatin analogs. The results showed that the exposure of 60 mg OOC twice daily should be comparable to 0.6 mg/day of Sandostatin SC (the highest recommended initial SC octreotide dose per US labeling). These results are consistent with a prior pharmacokinetics study undertaken with these higher doses (20 mg, 60 mg and 80 mg) and are comparable with data for injectable SSAs. The data supports dosing requirements for the planned Phase 3 study in patients with carcinoid syndrome associated with NET.

Abstract ID 21458
DOI: 10.1530/endobas.89.C11

C12
Financial Toxicity and Supportive Care in Neuroendocrine Tumor: A Biobank Study
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Background
With the advent of new therapeutic modalities, the overall survival of neuroendocrine tumor (NET) patients has increased. However, the impact of the symptoms, treatments on the quality of life (QoL) of the patients, accessibility to health care, and financial toxicity are underreported in the literature. We have established a prospective NET biobank to capture the burden of the disease on patients’ daily life and the impact on their QoL.

Methods
With Institutional Review Board (IRB) approval, a NET biobank was established in April 2019 at Roswell Park Comprehensive Cancer Center. We have collected patient demographics, symptoms, details regarding access to health care, QoL outcomes through previously developed questionnaires. We have also collected patient samples and analyzed treatment outcomes. Data of 144 patients enrolled to date in the biobank is presented here. The analysis was done with SAS.

Results
Out of the 144 patients, 105 were females and 39 were males. The median age at diagnosis was 55.3 (range: 22 to 81). All the patients were from the United States with majority from New York (41%, n = 59). Majority of the patients had private insurance (62.5%, n = 90), followed by medicare (30%, n = 43), medicaid (3.5%, n = 5) and 3.5% (n = 5) patients had no insurance. Only half of the patients were employed (46.5%, n = 67). 57% (n = 82) of our patients reported that their financial stability is affected by the NET and 27% (n = 38) had to quit their job after being diagnosed with NET. 40.3% (n = 58) of patients had annual household income above $75,000, 7.6% (n = 11) had annual income less than $25,000. 24% (n = 34) patients had income between $25,000-$75,000. 8% of patients (n = 12) reported financial constraints, difficulties in managing the treatment costs with their income. 26% (n = 37) reported that their income is just sufficient to

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meet their treatment and health care expenditure. 67% (n = 7) had functional NETs with diarrhea 63% (n = 61), followed by flushing 51% (n = 49) and sweating 29% (n = 28). Most of our patients have an oncologist, but they have to travel a median of 20 miles for the care (range: 1-1100) and 31% of these patients visit their oncologist monthly. Most of them have surgeon, gastroenterologist, endocrine, nutritionist, and social worker support, and they have to travel a median of 20-30 miles to access the care.

Conclusions
NET diagnosis significantly affects the quality of life and financial stability of patients. A national biobank capturing the QoL parameters including social, emotional, financial well-being would help us to identify and rectify the patient needs promptly.

Abstract ID 21469
DOI: 10.1530/endoabs.89.C12

C13
Serum Serotonin Compared to Plasma 5-HIAA and Chromogranin A as Biomarkers of Response to Hepatic Artery Bland Embolization
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Background
Chromogranin A (CGA) and 5-HIAA are meaningful biomarkers in managing neuroendocrine tumors (NETs). CGA, though nonspecific, can reflect disease bulk and typically decreases after debulking surgery. 5-HIAA is specific to NETs though its measurement may require a special diet, a 24-hour urine collection, or specialized blood collection tubes; but usually decreases after debulking procedures. Serotonin, though useful in diagnosing NETs, is not followed as a biomarker of response as assays before 1995 also measured serotonin release from platelets during blood collection/storage, resulting in wide fluctuations. Serotonin assays now are no longer affected by platelet serotonin release. We hypothesize that by using the current serotonin assay, serial serotonin measurements could predict response similar to CGA and 5-HIAA.

Methods
A retrospective review of clinical, laboratory and radiographic data was performed for all sequential patients who underwent hepatic bland embolization (HAE) from Sept 2016 to Sept 2021 at the University of Kentucky Markey Cancer Center. Inclusion criteria included those patients who had elevated serum serotonin, plasma 5-HIAA, and CGA measurements prior to and post-HAE with concordant changes to the embolization. Percent change in laboratory measurements before and after an HAE treatment was calculated. Measurements closest to procedure dates were used to calculate percent changes. Correlations between percent changes in laboratory measurements were analyzed using Spearman’s rank test. Statistical graphs were used to evaluate the hypothesized correlations.

Results
Fifty-one well-differentiated NET patients underwent 96 HAEs with 23 patients having 28 procedures meeting the inclusion criteria. Nineteen pre-post procedures were included in the serum serotonin and plasma 5-HIAA analysis. Twenty-two pre-post procedures were included in the serum serotonin and CGA analysis. The observed Spearman’s correlation between serum serotonin and plasma 5-HIAA is $r_{s} = 0.72$, p (2-tailed) $<0.001$ (n = 19); and $r_{s} = 0.61$, p (2-tailed) = 0.002 (n = 22) for the correlation between serum serotonin and CGA.

Conclusions
Changes in serum serotonin significantly correlated to changes in plasma 5-HIAA and CGA. Serum serotonin may be a useful biomarker for monitoring the response to therapy. The addition of serum serotonin measurement to future clinical trials as an exploratory biomarker seems warranted.

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Clinical - Nuclear Medicine/Interventional Radiology/Imaging
C14
Cardiac Neuroendocrine Tumor Metastases on 68Ga-DOTATATE PET/CT
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Background
Neuroendocrine tumor (NET) metastases to the heart are found in 1-4% of NET patients and have been reported primarily in the form of individual cases. We investigated the incidence, clinical characteristics, imaging features, and outcomes of NET patients with cardiac metastases on 68Ga-DOTATATE PET/CT.

Methods
The medical records of 406 neuroendocrine tumor patients who underwent 68Ga-DOTATATE PET/CT for their clinical care were individually reviewed to obtain their clinical characteristics and sites of metastatic disease. In patients with cardiac metastases, the cardiac SUVmax was compared to an external cohort of 11 patients with active cardiac sarcoidosis who underwent 18F-FDG PET/CT for research purposes. Clinical follow-up data were reviewed for cardiac adverse events. Overall survival among the metastatic NET patients with and without cardiac metastases was compared with Kaplan-Meier analysis.

Results
There were 9 patients (2.2%) with focal areas of cardiac DOTATATE uptake consistent with metastatic disease. The median age was 61 (range: 54-77) and 78% were male. The most common primary site was the small intestine (7 patients), followed by the colon and pancreas (1 patient each). All patients had well-differentiated tumors, most commonly grade 1 (67%). All 9 patients had extra-cardiac metastatic disease, most commonly in the liver (78%) and lymph nodes (78%), followed by bones (22%). The cardiac metastases were not specifically mentioned in 44% of clinical 68Ga-DOTATATE PET/CT reports. The cardiac SUVmax in the NET cohort (mean ± SD: 18.6 ± 22.3) was significantly higher compared to the cardiac sarcoid cohort (2.4 ± 0.6) without any overlap in values (P<0.05). Similar results were obtained with SUVmax-to-background ratio (26.2 ± 11.4 vs. 2.6 ± 0.4, P<0.05). There were no adverse cardiovascular events attributable to cardiac metastases after a median follow-up of 46 months. Three patients deceased within 3 years and the remaining 6 patients were followed up for 39-61 months, yielding 3-year overall survival of 67%. While the overall survival was slightly lower compared to a cohort of 148 patients with non-cardiac metastatic grade 1-2 gastroenteropancreatic NETs (88% at 3 years), there was no statistically significant difference on Kaplan-Meier analysis (P=0.30 on log-rank test).

Conclusions
Cardiac NET metastases are rare and are found only in the presence of other metastatic sites. Although they do not carry a meaningful prognostic significance, they can often be missed on routine interpretation of 68Ga-DOTATATE PET/CT. A distinguishing feature of cardiac NET metastases is the high degree of DOTATATE uptake compared to focal myocardial inflammation.

Abstract ID 21260
DO: 10.1530/endoabs.89.C14

C15
Effectiveness and Safety of Re-Treatment With 177Lu-DOTATATE in Patients With Progressive NETs in the US: A Retrospective Real-World Study
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Background
Advanced neuroendocrine tumors (NETs) are associated with poor prognoses. A 4-dose regimen of lutetium Lu 177 (177Lu)-DOTATATE has been shown to improve progression-free survival (PFS) and overall disease-free survival (DFS) in patients with advanced NETs. This is the first United States (US) study to evaluate the effectiveness and safety of additional doses in patients with progressive NETs.

Methods
This was a retrospective chart review of 31 adults with advanced NETs who underwent initial treatment with ≤ 4 doses of 177Lu-DOTATATE and who, following disease progression and a period of ≥ 6 months since the end of initial treatment, were re-treated with ≥ 1 additional dose at a single US center (2010–2020). Patient characteristics, treatment patterns, and clinical outcomes were evaluated descriptively. Response was evaluated per RECIST 1.1; toxicity was defined using CTCAE 5.0 criteria. Kaplan-Meier plots were used to evaluate PFS and OS.

Results
Of the 31 patients who received 177Lu-DOTATATE re-treatment, 19 (61%) were male and 29 (94%) were white. Overall, 19 patients received a total of 6 doses (4 initial and 2 re-treatment doses). Mean ± sd administered activity was 41.9±4.4 GBq. Two patients received additional re-treatment (1 and 2 doses, respectively) following a second period of ≥ 6 months and progression after re-treatment. Best responses of partial response and stable disease were observed in 11 (35%) and 20 (65%) patients after initial treatment and 7 (23%) and 14 (45%) patients after re-treatment (Table). Median PFS was 20.2 and 9.6 months after initial and re-treatment, respectively; median OS was 42.6 and 12.6 months. Hematological parameters decreased significantly during both initial and re-treatment but recovered, with no significant difference between the values, prior to initial treatment and re-treatment. Clinically significant hematotoxicity occurred in 1 and 3 patients following initial and re-treatment, respectively. No grade 3/4 nephrotoxicity (based on creatinine levels) was observed.

Conclusions
Re-treatment with 177Lu-DOTATATE after progression appeared to be well tolerated and offered disease control in patients with progressive NETs following initial 177Lu-DOTATATE treatment.

Table 1. Summary of Efficacy and Safety Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Initial Treatment (n=31)</th>
<th>Re-treatment (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>11 (35%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>20 (65%)</td>
<td>14 (45%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (10%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>20.2 (13.5–25.8)</td>
<td>9.6 (5.5–16.2)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>42.6 (31.2–53.8)</td>
<td>12.6 (9.6–18.9)</td>
</tr>
<tr>
<td>Grade 3/4 hematoxicity</td>
<td>1 (3%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abstract ID 21354
DO: 10.1530/endoabs.89.C15

C16
Clinical Utility of Somatostatin Receptor Positron Emission Tomography Imaging Biomarkers for Characterization of Meningioma Among Incidental Central Nervous System Lesions
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Background
Somatostatin receptor (SSTR) PET imaging is utilized with increasing frequency in the clinical management of neuroendocrine tumors. Incidental PET-avid CNS lesions are commonly noted and presumed to be meningiomas. However, SSTR PET lacks specificity for meningioma identification. This study aims to clarify the role of SSTR-based imaging for classification of incidental CNS lesions.

Methods
Patients who had undergone both Ga-68-DOTATATE PET and brain MR imaging and had an incidental CNS lesion identified with a radiographic prediction of meningioma via one (discordant prediction) or both (concordant prediction) imaging modalities were retrospectively analyzed. Imaging indication, semi-quantitative measures, and corresponding clinical history were recorded.

Results
Among 48 patients with a CNS lesion identified on both imaging modalities, most scans were performed for a history of neuroendocrine tumor (64.6%). Cases with concordant lesion type prediction of meningioma via one (discordant prediction) or both (concordant prediction) imaging modalities were retrospectively analyzed. Imaging indication, semi-quantitative measures, and corresponding clinical history were recorded.

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C17 Integration of Radioembolization with CapTem for Liver-Dominant G2 NETs: Long-Term Outcomes

Michael C. Soulen1, Ursina R. Teitelbaum2, Rosemarie Mick3, Jennifer Eads2, Jeffrey I. Mondschein1, Mandeep Dagli1, Diana van Houten1, Nevena Damjanov2, Charles Schneider2, Keith Cengel1 & David C. Metz5

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Background: Capecitabine-Temozolomide (CapTem) is an effective oral chemotherapeutic regimen for NETs. Both drugs are radiosensitizers. A feasibility study of integrated CapTem and Y90 transarterial radioembolization (TARE) in patients with grade 2 neuroendocrine tumor (NET) liver metastases reported encouraging objective response rate (ORR) and progression-free survival (PFS). This study expands that report to a larger cohort with long-term oncologic follow-up.

Methods: Therapy consisted of monthly cycles of capecitabine 600 mg/m² twice daily for 14 days and temozolomide 150-200 mg/m² on day 10-14. Simulation angiography was performed during the initial cycle. The dominant lobe was treated on day 7 of the second cycle of CapTem. Patients with bilobar disease had the other lobe treated on day 7 of the third or fourth cycle. CapTem was continued until progression or intolerance. Subjects were categorized by duration of CapTem into 3-6 mo, 7-12 mo, and >12 mo. PFS was estimated using Kaplan-Meier method and the groups compared by log rank test.

Results: Mean duration of CapTem was 12 months. 10 subjects were on CapTem for 3-6 months, 15 for 7-12 months, and 11 for 13-32 months. 14/36 (39%) stopped CapTem due to toxicities prior to disease progression. Median PFS was >36 months in the 3-6 month chemo group; 23 months for the 7-12 month group, and 30 months for those on chemo >12 months (P = NS).

Conclusions: This limited subset analysis suggests the following hypotheses: 1. Prolonged administration of radiosensitizing chemotherapy does not increase PFS. A limited course of chemotherapy at the time of TARE maybe sufficient to achieve synergy. This could be tested in a prospective trial. 2. Chemotherapy-related toxicities leading to intolerance occur in a substantial proportion of patients, offering an opportunity to investigate de-escalation of chemotherapy to improve quality of life without sacrificing disease control.

Abstract ID 21372
DOI: 10.1530/endobas.89.C18

C19 Transformation of G1-G2 Neuroendocrine Tumors (NETs) to Neuroendocrine Carcinomas (NECs) Following Peptide Receptor Radio-nuclide Therapy (PRRT): a Case Series

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Background: We observed patients with well-differentiated NETs who received PRRT with 177Lu-dotatate and later developed rapid disease progression with biopsy-proven histologic transformation to NECs, an outcome that has not been previously described. In this series, we characterize the clinicopathologic features and outcomes of patients whose tumors underwent poorly-differentiated transformation.

Methods: After obtaining IRB approval, we conducted a retrospective review of all patients with metastatic well-differentiated G1-G2 NETs who received at least one cycle of PRRT with 177Lu-dotatate at our center from January 1, 2019 to December 31, 2020. Patient’s clinical information was extracted from the electronic medical record and a refined search for “transformation”, “high-grade” and “neuroendocrine carcinoma” was performed for each patient chart.

Results: Among 152 patients (primary sites: 82 small bowel, 39 pancreas, 14 lung, 17 unknown) the median number of PRRT cycles delivered was 4. Among these, we identified 7 patients whose NETs transformed to NECs following PRRT. All had pancreatic primary site (7/7 [100%]; P = 0.0009). Median time from start of PRRT to transformation was 256 days (range 79-432 days). Five patients (71%) received treatment with platinum and etoposide after transformation with partial response as best response. All patients with transformation died from progressive disease with median overall survival (OS) after transformation of 3.3 months (95% CI: 2.1-4.4). Median OS from start of PRRT for patients with transformation was 11.9 months (95% CI: 4.2-19.5) compared to 31.1 months.

Abstract ID 21355
DOI: 10.1530/endobas.89.C16

C18 Radiosensitization for TARE: Does Duration of Chemotherapy Affect PFS?

List of participants and their roles in the submission
Michael C. Soulen1, Ursina R. Teitelbaum2, Rosemarie Mick3, Jennifer Eads2, Jeffrey I. Mondschein1, Mandeep Dagli1, Diana van Houten1, Nevena Damjanov2, Charles Schneider2, Keith Cengel1 & David C. Metz5

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Background: Capecitabine and temozolomide (CapTem) are classic radiosensitizers used in combination with radiation therapy for many cancers. A feasibility study of integrated CapTem and Y90 transarterial radioembolization (TARE) for neuroendocrine tumors (NETs) suggests synergy with PFS of 31 months exceeding historical controls. The impact of duration of chemotherapy after TARE on PFS is not known.

Methods: 36 subjects with liver-dominant grade 2 metastatic NET were treated with 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 simultaneous angiography with Tc99m-MAA SPECT. 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 bilateral disease had the other lobe treated on day 7 of the third or fourth cycle. Clinical and laboratory assessment was done monthly and imaging performed every 3 months. CapTem was continued until progression or intolerance. Subjects were categorized by duration of CapTem into 3-6 mo, 7-12 mo, and >12 mo. PFS was estimated by Kaplan-Meier method and the groups compared by log rank test.

Results: Mean duration of CapTem was 12 months. 10 subjects were on CapTem for 3-6 months, 15 for 7-12 months, and 11 for 13-32 months. 14/36 (39%) stopped CapTem due to toxicities prior to disease progression. Median PFS was >36 months in the 3-6 month chemo group; 23 months for the 7-12 month group, and 30 months for those on chemo >12 months (P = NS).

Conclusions: This limited subset analysis suggests the following hypotheses: 1. Prolonged administration of radiosensitizing chemotherapy does not increase PFS. A limited course of chemotherapy at the time of TARE maybe sufficient to achieve synergy. This could be tested in a prospective trial. 2. Chemotherapy-related toxicities leading to intolerance occur in a substantial proportion of patients, offering an opportunity to investigate de-escalation of chemotherapy to improve quality of life without sacrificing disease control.

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(95% CI: 26.3-35.9) in patients without transformation (hazard ratio, 8.1, 95% CI: 3.5-18.8; \( P < 0.001 \)). No differences in the incidence of transformation were observed according to gender (\( P = 0.43 \)), race (\( P = 0.78 \)), or original tumor grade (G1 vs G2) (\( P = 0.86 \)). Among those with pancreatic NETs, all transformed cases had primary tumors located in the pancreatic tail (0% vs 32%; \( P = 0.01 \)). All transformed cases had prior chemotherapy with alkylating agent temozolomide. The number of prior lines of therapy were similar between those without and with transformation (mean, 3.5 vs 3.7; \( P = 0.81 \)). No differences in the incidence of transformation among pancreatic NET patients were observed according to prior everolimus (\( P = 0.91 \)), sunitinib (\( P = 0.55 \)), and streptozocin (\( P = 0.97 \)).

Conclusions

This single-institution case series describes seven cases of poorly differentiated transformation among pancreatic NET patients with prior PRRT occurred among patients with pancreatic tail primary site and had prior therapy with alkylating agent temozolomide. Further investigation is necessary to determine best treatment sequence in this patient population.

Abstract ID 21416

DOI: 10.1530/endobas.89.C19

C20  
Quality of Life Assessments for Advanced Pheochromocytoma and Paraganglioma Patients that Received High-Specific-Activity I-131 MIBG: Results from a Pivotal Phase 2 Clinical Trial  
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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 (PPG). We have previously described pivotal pilot study efficacy data that served as the basis for HSA I-131 MIBG approval demonstrating improvements in blood pressure control, objective tumor responses, and biomarker responses. Here we provide the results from a European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 v3) developed and validated to assess the quality of life (QoL) of cancer patients.

Methods

Patient with iobenguane-avid PPG, who were ineligible for surgery, failed prior therapy or not candidates for chemotherapy were eligible to receive treatment. Patients received up to two therapeutic doses, each at ~500 mcI (18.5 GBq), administered ~90 days apart. QoL assessments, designed to measure cancer patients’ physical, psychological, and social functions, were measured by patient reporting of the EORTC QLQ-C30 v3. Questionnaires were administered at screening/baseline before the first therapeutic dose, at Weeks 3, 6, 10, 12, 15, 18, and 22, and monthly at Months 6 to 12 following the first therapeutic dose. Best response within 12 months post-therapeutic dose 1 was determined. A high score (scale of 0 to 100) for overall global health status/QoL represents a high QoL. A high score (scale of 0 to 100) for the functional scales represents a high/high level of functioning. A high score (scale of 0 to 100) for a symptom scale/item represents a high level of symptomatology/problems.

Results

An improvement in mean ± SD and median Global Health Status/QoL, from baseline (n = 57) compared with best response was observed (59.8 ± 19.8 vs. 77.8 ± 17.7 (+18.0)); and 58.3 vs. 83.3 (+25.0), respectively). For each parameter of the five functional scales, mean scores after baseline (n = 58) suggest an improvement in function that was sustained for at least 12 months: Role (64.3 ± 29.9 vs. 86.2 ± 19.8 (+21.9)); Social (67.7 ± 29.2 vs. 90.2 ± 20.0 (+22.5)); Physical (72.3 ± 20.7 vs. 88.7 ± 14.1 (+16.6)); Emotional (73.7 ± 21.7 vs. 93.1 ± 11.7 (+19.4)); and Cognitive (80.8 ± 21.9 vs. 96.8 ± 8.39 (+16.0)). For symptom scales (fatigue, pain, financial difficulties, insomnia, dyspnea, constipation, appetite loss, nausea and vomiting, and diarrhea), the best response mean scores after baseline suggest an improvement for all symptoms ranging from -26.5 (pain) to -6.2 (diarrhea).

Conclusions

In a pivotal clinical study, advanced PPG patients’ physical, psychological, and social functions were all improved over baseline consistent with improvements in reported efficacy outcomes when treated with HSA I-131 MIBG.

Abstract ID 21417

DOI: 10.1530/endobas.89.C20

C21  
Characterizing Bone Metastases in Patients with Well-Differentiated Neuroendocrine Neoplasms Utilizing Ga68-DOTATATE PET  
Tucker W. Coston, MD, D1, Himil J. Mahadevia, MBBS2, Marie M. Plante, MD2, Joseph M. Accurso, MD2, Akash Sharma, MD, MBA3, Geoffrey B. Johnson, MD, PhD4, Jonathan B. Ashman, MD, PhD5, Ayse Tuba Kendi, MD6, Mohamad Bassam Sonbol, MD6, Timothy J. Hobday, MD,7 Thorvardur R. Halfdanarson, MD,8 & Jason S. Starr, DO1  
1Mayo Clinic Florida, Division of Hematology & Medical Oncology; 2University of Missouri-Kansas City, Division of Internal Medicine; 3Mayo Clinic Florida, Division of Internal Medicine; 4Mayo Clinic Florida, Division of Nuclear Medicine; 5Mayo Clinic Florida, Division of Radiology; 6Mayo Clinic Arizona, Division of Radiation Oncology; 7Mayo Clinic Minnesota, Division of Nuclear Medicine; 8Mayo Clinic Arizona, Division of Hematology & Medical Oncology; 9Mayo Clinic Minnesota, Division of Medical Oncology.

Background

Tumors of neuroendocrine origin are a rare, heterogeneous group of neoplasms. Neuroendocrine neoplasms (NENs) are categorized by site of origin, differentiation status, and by grade (Ki-67 expression and/or mitotic rate), with significant prognostic variability accordingly. These tumors frequently metastasize to bone, with reported incidence between 6-12% by older SSTR imaging. Our study evaluates patients with well-differentiated tumors of neuroendocrine origin to determine the incidence of osseous metastases when evaluated with higher-sensitivity Ga68 DOTATATE PET scans. The study characterizes the clinical features therein.

Methods

This study was performed at a single tertiary-care institution with 3 sites in the US. IRB approval was obtained. An automated data extraction tool was used to mine the electronic medical record by searching all performed positron emission tomography (PET) studies for keywords. Identified scans had to include a combination of the following keywords: “DOTate” AND “m68” or “lesion” AND “bone” or “osseous” or “skel”1. The individual medical records identified from the generated report were then reviewed to include only patients with 1) well-differentiated NENs of GI and pancreatic origin, lung carcinoid, paragangliomas/phaeochromocytoma, or other/unknown primary site, and 2) patients with confirmed osseous metastatic disease. Patient data was then entered into a database and evaluated in aggregate.

Results

1,948 PET scans of 1,473 patients were extracted from the EMR, from which 424 patients were identified for inclusion; scans were performed between 5/2018 and 5/2021. Calculated incidence of bone metastasis by Ga68 DOTATATE PET was 28.8%. Median age of included population was 61 years (range 14-92), 49.5% being male. Site of origin was 47.2% bowel NET, 18.9% pancreatic NET, 10.8% lung carcinoid, 10.6% paraganglioma/phaeochromocytoma, 2.1% other site, and 10.4% unknown primary. Majority of patients were asymptomatic (64.0%), had sclerotic appearance (76.7%), Krenning 4 (71.4%), and ≥3 sites (68.3%) of osseous disease. 94.6% of the population had disease of the axial skeleton; 65.6% of appendicular. Only 57 patients with osseous disease (13.4%) suffered a fracture, despite high proportions of patients having metastasis at high-risk sites. Fracture occurred at disproportionately low rates in NETs originating in bowel (22.8% of fractures), with proportionately higher rates among pancreatic NETs and paragangliomas/phaeochromocytomas (31.6% and 22.8%, respectively).

Conclusions

Osseous metastatic disease in well-differentiated NENs are evident at much higher rates when imaging with Ga68 DOTATATE PET compared with previously reported data. Nevertheless, fracture occurred at a low rate, suggesting that these patients are at a relatively low risk for skeletal-related events

Abstract ID 21449

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C22  
The Role of 68Ga-DOTATATE PET/CT in the Management of Gastrointestinal and Pancreatic Neuroendocrine Tumors  
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Background

Despite the superiority of 68Ga-DOTATATE PET/CT in the detection of neuroendocrine tumors, the clinical impact of using this imaging modality in surgical and medical oncology practices in the United States is not well established. Here we evaluate the impact of 68Ga-DOTATATE PET/CT imaging
in the diagnosis and management of patients with GI and pancreatic NETs at the University of Rochester Medical Center.

Methods
Single-center retrospective evaluation of patients with a diagnosis of GI or pancreatic NET who received a 68Ga-DOTATATE PET/CT scan between January 2019 and December 2020 as identified by an automated data collection system (Hyperion). The patient’s clinical history and imaging were reviewed to ascertain if 68Ga-DOTATATE PET/CT had an impact in their clinical management as well as new lesion detection when compared to conventional imaging.

Results
A total of 105 patients had a median age of 65 had a diagnosis of GI or pancreatic neuroendocrine tumor and underwent a 68Ga-DOTATATE PET/CT scan. Of these, only 66 patients had conventional imaging within 90 days available for comparison. The primary sites of disease from the most common to least were small bowel (50.4%), pancreas (25.7%), unknown but likely GI (8.6%), appendix/colon (6.6%), gastric (5.7%), mesentery (2.9%). Most NETs were historically moderately/well differentiated. Following 68Ga-DOTATATE PET/CT, 38 patients (36.2%) had a change in management. Of these, 27 patients had a change in medical management with 26 patients starting systemic therapy such as PRRT, chemotherapy or somatostatin and 1 patient being down-staged and taken off somatostatin. 9 patients had a change in surgical management with 7 patients undergoing a surgical resection due to primary or metastatic lesion detection and 2 patients having cancellation of planned primary tumor resection. Amongst patients who underwent conventional imaging such as CT or MRI within 90 days of PET, 32 patients (48.4%) had new lesions identified on 68Ga-DOTATATE PET/CT.

Conclusions
Our retrospective study demonstrates that 68Ga-DOTATATE PET/CT resulted in a change in therapeutic management in 36.2% of patients with GI or pancreatic NET and improved lesion detection over conventional imaging in 48.4% of patients. This supports its use in the care of patients with GI and pancreatic NETs.

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C24

MIBG and DOTATATE Therapy for Pheochromocytoma and Paran-glioma: A Single Institution Experience
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Background
Since the FDA-approval of Lu-177-DOTATATE and I131-MIBG radiophar-maceutical therapies in 2018, there is emerging real-world experience with their use. Only a few institutions in the US have both therapies available. Here, we describe our experience with these agents for patients with pheochromocytoma and paraganglioma (PPGL).

Methods
This is a retrospective evaluation of all patients with progressive, metastatic, PPGL referred for radiopharmaceutical therapy at our institution since 2018. Parameters evaluated include therapy eligibility, side effects and toxicity, and outcomes to date. At our institutions, the choice of treatment is first guided by the degree of uptake on functional imaging, followed by the FDA-label for the therapy.

Results
A total of 17 PPGL patients have been referred to date (all but two with paraganglioma). Five were not treated with a radiopharmaceutical due to a variety of factors such as stable or limited disease, rapid progression, insufficient uptake on imaging, or patient choice. Six were treated with Lu177-DOTATATE (average age 60 (range 30-80)) due to higher SSTR-expression compared to MIBG uptake. All had paraganglioma (three with SDHx mutations, others unknown). Five completed 4 cycles of therapy with minimal side effects and transient, cytopenias. Of those five, three have stable disease or partial response, and two had progression within 6 months. Two had marked improvement in quality of life and/or decrease in hypertensive medications. The last patient is currently receiving active therapy. Five were treated with I-131 MIBG (average age 56 (range 31-68)). All had similar SSTR-expression and MIBG uptake, thus were treated with the FDA-approved therapy. Four had paraganglioma, and 2 had pheochromocytoma (3 SDHx mutations, others unknown). Four completed 2 cycles, and two only 1 cycle. Four patients had transient cytopenias, and two had clinically significant thrombocytopenia. One had a complete response, two with partial response, one with stable disease, and 2 with progression within 6 months. Three patients had an improvement in quality of life and/or decrease in hypertensive medications.

Conclusions
Real-world data show that both DOTATATE and MIBG therapies have a role in the systemic therapy of patients with progressive, metastatic PPGL, with similar outcomes with regard to efficacy and toxicity. Pre-therapy functional imaging can be used to guide the therapeutic choice. Additional data is needed for confirmation of the findings from this small cohort.

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C25

Evaluation of 68Ga-DOTATATE PET After Two Cycles of Peptide Receptor Radionuclide Therapy (PRRT) in Neuroendocrine Tumors (NET)
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Background
We aimed to evaluate the added information provided by 68Ga-DOTATATE PET after two cycles of peptide receptor radionuclide therapy (PRRT) in patients with somatostatin receptor (SSTR)-expressing neuroendocrine tumors (NET).

Methods
In this retrospective study, 105 patients (54 women and 51 men, 62.5 ± 10.5-year-old) with progressive NET treated with at least two cycles of 177Lu-DOTATATE were included. All patients had 68Ga-DOTATATE PET/CT or PET/MRI at baseline, after two cycles, and upon completion of PRRT. RETIST and change in SSTR-density were used to evaluate the scans and assess treatment response. Change in tumor marker chromogranin A was recorded. Patients were surveyed regarding their stance on the additional scan midway through the treatment.

Results
All patients considered the additional 68Ga-DOTATATE PET contributing to their quality of life as it provided important peace of mind. After two PRRT cycles, 0/105 patients considered the additional 68Ga-DOTATATE PET contributing to their quality of life as it provided important peace of mind.
Pre-therapy Functional Imaging with MIBG and DOTATATE to Guide Radiopharmaceutical Therapy for Pheochromocytoma and Paraganglioma: A Single Institution Experience

Nadine Mallak, Laszlo Szidonya, Guillaume Pegna, Rodney Pommier & Erik Mittra
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Background
Since their FDA-approval in 2018, both Lu177-DOTATATE and I131-MIBG radiopharmaceuticals are available at our institution for the treatment of pheochromocytoma and paraganglioma (PPGL). Tumor uptake of the radiopharmaceutical on pre-therapy imaging is a requirement for treatment. Here, we describe our experience with pre-therapy imaging, and how it relates to the tumor genotype and the therapeutic choice.

Methods
This is a retrospective evaluation of pre-therapy imaging of all patients with progressive, nonresectable or metastatic, PPGL referred for radiopharmaceutical on pre-therapy imaging is a requirement for treatment. Here, we describe our experience with pre-therapy imaging, and how it relates to the tumor genotype and the therapeutic choice.

Results
A total of 17 PPGL patients have been referred to date. Five were not treated with a radiopharmaceutical due to a variety of factors such as stable or limited disease, rapid progression, insufficient uptake on imaging, or patient choice. Paragangliomas: n=4, pheochromocytomas: n=1:
- SDHC mutation (n=1): MIBG: Negative, DOTATATE: Heterogeneous uptake.
- SDHB mutation (n=3): 1. Imaging not performed due to rapid progression.
- SDHAf mutation (n=1), SDHAF2 mutation (n=1), HRAS mutation (n=1): MIBG: Negative, DOTATATE: Positive.
- Six were treated with Lu177-DOTATATE, all paragangliomas:
- SDHB mutation (n=1), mutation unknown (n=2): MIBG: Heterogeneous, DOTATATE: Positive.
- SDHD mutation (n=1), SDHAF2 mutation (n=1), HRAS mutation (n=1): MIBG: Negative, DOTATATE: Positive.
- Six were treated with I131-MIBG. Paragangliomas: n=4, pheochromocytomas: n=2:
- SDHB mutation (n=2), RET mutation (n=1), SDHx mutation (by IHC on biopsy, no genetic testing performed) (n=1), mutation unknown (n=1): MIBG: Positive, DOTATATE: Positive.

Conclusions
We describe an experience with pre-therapy DOTATATE PET imaging at our institution. Pre-therapy functional imaging with MIBG and DOTATATE were performed in a comprehensive manner, guided by the choice of peptide receptor radionuclide therapy (PRRT) in metastatic PPGL. The results of our experience are consistent with the literature, and we have identified cases of pseudo-progression and true progression.
Diagnostic Performance of PET or PET/CT Utilizing 18F-DOPA, 68Ga-DOTATATE, 18F-FDG, and CT and MRI in Supporting \( {\text{MEN2A-related-pheochromocytoma}} \)

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Background

Pheochromocytoma (PHEO) is a rare neuroendocrine tumor arising from chromaffin cells of adrenal gland that can cause life-threatening complications due to overproduction of catecholamines. Per EANM/SNMMI guidelines, 18F-DOPA PET or positron emission tomography (PET) is recommended as a positron emission tomography (PET) imaging modality with the highest detection rate (18F-DOPA). This study was performed in a small cohort of patients with MEN2A-related PHEO. The purpose of this prospective study was to evaluate and compare the detection rates of 18F-DOPA, 68Ga-DOTATATE, 18F-FDG, and 18F-fluorodopamine in the detection of \( {\text{VHL-related pheochromocytoma}} \).

Methods

Between October 2007 and October 2021, twelve patients (eight males, four females, mean age, 27.9 ± 13.6 years) prospectively underwent 18F-DOPA PET (n = 2) or PET/CT (n = 7), 68Ga-DOTATATE PET/CT (n = 6), 18F-FDG PET/CT (n = 2), and 18F-fluorodopamine PET/CT (n = 2) with VHL-related PHEOs. Additionally, these patients also underwent CT (n = 10) and MRI (n = 5) with VHL-related PHEOs. The mean duration between CT and PET/CT was 10 ± 15 days, between CT and 18F-DOPA PET/CT was 5 ± 10 days, and between CT and 68Ga-DOTATATE PET/CT was 2 ± 4 days.

Results

Nineteen patients had 26 PHEOs [12 unilateral (7 right, 5 left) and 7 bilateral] on histopathologic diagnosis served as a reference standard. PET/CT scans were evaluated by a nuclear medicine physician and body radiologist. All but one patient underwent surgical resection of PHEOs, and the histopathologic diagnosis served as a reference standard. PET/CT scans were evaluated by a nuclear medicine physician and body radiologist.

Abstract ID 21581

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Clinical - Surgery/Applied Pathology
C30
Liver-Directed Therapy of Neuroendocrine Liver Metastases
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Background
The optimal therapy sequencing for metastatic neuroendocrine tumors (NETs) remains undefined. Recent advances in systemic therapies may have changed approaches. Better understanding in patterns of care is necessary to assess and design treatment strategies. We examined the use of factors associated with liver-directed therapy over time.

Methods
We conducted a population-based study of metastatic NETs over 2000-2019. Outcomes were use of liver-directed therapy, sub-divided into liver resection and embolization. Bi-yearly incidence rate of use in eligible patients (alive and no prior liver-directed therapy) was assessed. Multivariable Poisson models examined factors associated with use of liver-directed therapies.

Results
Of 5,159 metastatic NETs, 922 patients (16.7%) received liver-directed therapy (461 embolizations, 329 resections, 132 dual therapy) at median of 35 days (IQR:0-490) after metastatic diagnosis. Incident use of liver embolization increased after 2013 to reach 72% in 2018-2019. Incident use of liver resection followed a similar trajectory up to 94% in 2018-2019. Gastro-entero-pancreatic primary NET (relative risk - RR 5.69, 95%CI 3.76-8.60), female sex (RR 1.25, 95%CI 1.05-1.48), year of diagnosis (RR 1.32, 95%CI 1.04-1.68 for 2007-2015), and lower socioeconomic status (RR 0.87-0.98 by incremental material deprivation quintile) were independently associated with liver resection. Gastro-entero-pancreatic primary NET (RR 2.8, 95%CI 2.2-3.7), socioeconomic status (RR 0.94, 95%CI 0.89-0.99 by quintile) and year of diagnosis (RR 0.71, 95%CI 0.59-0.85 for 2007-2015 and RR 0.61, 95%CI 0.50-0.75 for 2016-2020) were independently associated with risk of liver embolization.

Conclusions
Receipt of liver-directed therapies for metastatic NETs has increased over time in unadjusted analysis. However, there was lower risk of liver embolization in most recent time periods, but higher risk of resection. Socio-economic status represented an independent factor for lower likelihood of liver-directed therapies. Further characterization of timing and outcomes of liver-directed therapy with an equity lens, is warranted to define the optimal sequencing.

Abstract ID 21263
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C31
Goblet Cell Adenocarcinoma (GCA) of the Appendix: Interrogating Proteomics to Identify Potential Actionable Targets
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Background
Appendiceal GCA is a tumor which has been misunderstood for decades. GCAs are comprised of goblet-like mucinous cells, with variable numbers of neuroendocrine and Paneth-like cells and lie on the spectrum between appendiceal adenocarcinoma and neuroendocrine tumors. Prognosis depends on the stage and tumor grade; 30% of patients with low-grade and 50-70% of high grade GCAs present with metastatic disease. Currently, there are limited systemic therapy options and definitive therapy such as cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are applicable to only a small number of patients. In this clinicopathologic study, we aimed to interrogate tumor proteomic profiles to identify possible actionable targets for future therapeutic interventions.

Methods
We identified GCAs of the appendix from our institutional pathology cohort after obtaining IRB approval. Demographic details and survival data were recorded. We performed immunohistochemical staining for claudin-18.2, somatostatin receptor 2 (SSTR2), PD-1, PD-L1, and human epidermal growth factor 2 (HER-2) expression. Chi-squared tests and log-rank tests were used when comparing groups.

Results
We identified 15 patients with appendiceal GCAs (10 female, 5 male) with a median age of 57.5 years at diagnosis. Of 14 patients with T category information available, 13 (92.8%) possessed T3 or T4 primary tumors. Six (42.8%) patients presented with metastatic disease while 3 patients developed metastatic disease. None (0%) of the patients possessed tumors with any degree of SSTR2, PD-1 or PD-L1 expression. Only 2 patients (13.3%) possessed tumors with weak claudin 18.2 expression. Eight (57.1%) patients possessed tumors with HER-2 overexpression by immunohistochemistry (3+ membranous staining, > 10% of tumor cells in 4 patients). Patients with GCAs with HER-2 overexpression had median survival of 46.9 months (95% confidence interval (CI) 5.5-not reached) compared to a median survival of 26.5 months (95% CI 15.7-not reached) in patients with HER2 unamplified disease (Log-rank test 𝑃= 0.2). There were no statistically significant clinicopathologic differences between patients with HER2 2+/3+ and HER2 1+ tumors though patients with HER2 overamplified disease were more likely to recur compared to patients with HER2 unamplified disease (43% vs 0%, Chi-squared test 𝑃= .39).

Conclusions
For the first time we have demonstrated that HER-2 is overexpressed in a significant proportion of patients with GCAs, suggesting that this can be a potential therapeutic target to explore clinically. Furthermore, the absence of SSTR2 in GCAs suggests that the tumor is much more akin to an adenocarcinoma than low grade NET.

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C32
Surgeon Management of G3 Gastroenteropancreatic Neuroendocrine Neoplasms: A Systematic Review and Meta-Analysis
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Background
Grade 3 (G3) gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs) are rare, aggressive tumors with poor prognosis. The WHO 2017 classification further subdivided G3 NENs into G3 neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs). Current guidelines favor medical management in most of these patients, and the role of surgical management is not well-defined. We performed a systematic literature review and meta-analysis of surgical management vs non-surgical management for G3 GEP NENs.

Methods
A PRISMA-compliant systematic review of the MEDLINE, EMBASE, Scopus, and Cochrane Library databases (end-of-search date: July 16th, 2021) was conducted. Individual patient survival data were reconstructed, and random-effects meta-analyses were performed.

Results
Fourteen studies comprising 1,810 surgical and 910 non-surgical patients were systematically reviewed. Publication bias adjusted meta-analysis of 12 studies (1,788 surgical and 857 non-surgical patients) showed increased overall survival (OS) after surgical compared with non-surgical management for G3 GEP NENs (HR: 0.40, 95%CI, 0.31-0.53). Subgroup meta-analyses showed increased OS after surgical management for both pancreatic and gastroentero-pancreatic primary tumors separately. In another subgroup meta-analysis of G3 GEP NETs (not NECs), surgical management was associated with increased OS compared with non-surgical management (HR: 0.26, 95%CI, 0.11-0.61) (Table).
15th Annual Multidisciplinary NET Medical Symposium NANETS 2022

Table. Comparison of Survival in GEPNENs treated Surgically or Non-Surgically.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Studies, n</th>
<th>Patients, n (surgery vs non-surgery)</th>
<th>Hazard Ratio (&lt;1 favors surgery)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3 GEP NEN (NET &amp; NEC)</td>
<td>12</td>
<td>1,798 vs 807</td>
<td>0.49</td>
<td>0.31-0.63</td>
</tr>
<tr>
<td>G3 Pancreatic NEN (NET &amp; NEC)</td>
<td>8</td>
<td>451 vs 370</td>
<td>0.31</td>
<td>0.24-0.40</td>
</tr>
<tr>
<td>G3 Gastrointestinal NEN (NET &amp; NEC)</td>
<td>3</td>
<td>1,207 vs 379</td>
<td>0.42</td>
<td>0.34-0.52</td>
</tr>
<tr>
<td>G3 GEP NET (not NEC)</td>
<td>3</td>
<td>62 vs 25</td>
<td>0.26</td>
<td>0.11-0.61</td>
</tr>
</tbody>
</table>

Conclusions
Surgical management of G3 GEP NENs may provide a potential survival benefit in well-selected cases. Further research is needed to define which patients will benefit most from surgical vs non-surgical management. The current literature is limited by inconsistent reporting of survival outcomes in surgical vs non-surgical groups, tumor grade, differentiation, primary tumor site, and selection criteria for surgical and non-surgical management.

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C33
High-Grade Pancreatic Neuroendocrine Neoplasms: Interobserver Diagnostic Accuracy and Relationship with Clinicopathological and Molecular Characteristics
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Background
The pathogenesis, biologic behavior, and treatment of well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC) are different. The diagnosis relies on multiple factors, but pathologic assessment is crucial. Based on currently available diagnostic criteria, the distinction between NET G3 and NEC are made on morphologic assessment, without taking Ki-67 proliferative index into consideration. This study looks at the concordance rates among experienced gastrointestinal pathologists following published guidelines (current WHO criteria and additional morphologic criteria based on a recent international consensus study) and how it compares to clinical parameter-based retrospective categorization.

Methods
32 cases of NET G3 and NEC were selected from a retrospective search of cases for pancreatic neuroendocrine neoplasms, with tumor slide availability in-house, including Ki-67 stain. A morphologic review was performed by 8 GI pathologists (blinded to all other information, including proliferative indices), practicing at a tertiary cancer center for a median of 20 years. A “clinical” diagnosis was separately formulated based on information collected from electronic medical records focusing on special imaging results (octreotide/gallium scan, FDG-PET), molecular data (if available), and clinical course of the disease, including survival and response to treatment received. Reliability assessment and correlations were studied using standard statistical software.

Results
The cases evaluated by all eight pathologists and showed only a fair interobserver agreement on diagnosis (kappa = 0.334). There was a majority agreement of ≥ 5/8 pathologists on 30 (90.1%) cases. The most discordant case (only 2/8 observers agreed with the clinical diagnosis) demonstrated some morphologic features similar to NEC. The highest consensus on morphologic criteria was noted for the absence or presence of geographic necrosis (κ = 0.497 moderate). The “clinical” diagnosis formulated based on multiple clinical parameters correlated strongly with overall survival (2017 +/- 13 days for NET and 720 +/- 386 days for NEC; P = 0.006) as well as Ki-67 proliferative index (33 +/- 17 for NET and 53 +/- 22 for NEC; P = 0.011). Ki-67 proliferative index also independently showed negative correlation with survival (P = 0.027).

Conclusions
The distinction between NET G3 and NEC solely based on morphology, as is the current recommendation, is challenging, especially in a small biopsy. Ancillary studies (immunohistochemistry and/or molecular studies) and correlation with clinical datapoints such as special imaging (octreotide, 68-Gallium DOTATATE, and/or FDG PET) and clinical course and tumor response to therapy is probably warranted.

Abstract ID 21411
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C34
Grade Creep and the Importance of Tissue Sampling: Changes in Ki-67 and Grade in Serial Neuroendocrine Tumor Samples
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Background
Neuroendocrine tumor (NET) grade, which utilizes Ki-67 expression, is a useful prognostic tool and aids in treatment decisions. However, it is not well known how these measures evolve over time. This retrospective review evaluates changes in Ki-67 and grade over time in patients with multiple NET tissue samples.

Methods
77 patients were included (44M; mean age 58 ± 9.5 years at first sample). Primary NET sites included 46 small bowel, 21 pancreatic, 3 rectal, 2 colonic, 2 lung, 1 appendiceal, 1 biliary, and 1 unknown. Surgical resection and biopsy histology, including Ki-67 immunohistochemistry, were reviewed. NETs were graded using the 2017 WHO classification. Statistical analysis was performed using the paired Student t test.

Results
Among 77 initial samples, 69% were from biopsy and 31% from surgical resection: 75% were from metastatic and 25% from primary tumor. Median Ki-67 was 4% (range 1-20%), with 39% grade 1 and 61% grade 2. Second samples were obtained a median of 0.6 (range 0-7.6) years after initial pathology. 68% were from surgical resection and 32% from biopsy; 57% from metastatic disease and 43% from primary tumor or resection bed recurrence. Median Ki-67 was 5.2% (range 1-64%), with 39% grade 1, 51% grade 2, and 10% grade 3. No significant increase in Ki-67 was observed between first and second samples (P = 0.1); grade increased in 26%. Thirty-two patients had third samples a median of 3.0 (range 0-11.3) years after initial pathology. 53% were from biopsy and 47% from surgical resection; 81% from metastasis and 19% from primary site. Median Ki-67 was 6.9% (range 1-36%), with 25% grade 1, 66% grade 2, and 9% grade 3. No significant increase in Ki-67 was observed between second and third samples (P = 0.172); grade increased in 28%. Six patients had fourth samples and two patients had fifth samples a median of 3.6 (range 0.5-5.4) years after initial sampling, all from metastasis. Five of 8 samples were grade 3 (63%). Among all patients, grade increased between initial and final samples in 31% (n = 24). A statistically significant increase in Ki-67 was seen between initial and final samples (P = 0.004). Ki-67 increased at an overall rate of 1.2% annually.

Conclusions
Serial NET sampling demonstrates an increase in Ki-67 over time, resulting in grade increase in 31%. Improved understanding of these changes may have important diagnostic and therapeutic implications, including guidance for frequency of re-biopsy.

Abstract ID 21415
DOI: 10.1530/endoabs.89.C34

C35
Liver Directed Therapy is Associated with Improved Survival in Metastatic Gastroenteropancreatic Neuroendocrine Neoplasms with Concurrent Bone Metastasis
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Background
Bone metastasis from gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) was once considered rare, but prevalence has recently been reported as high as 12%. Although bone metastasis has been associated with poor prognosis, the most frequent cause of mortality in this population remains liver failure when liver metastases are present. Thus, it remains unclear whether patients with concurrent liver and bone metastasis who receive liver directed therapy (LDT) would derive survival benefit.

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Methods
The California Cancer Registry (CCR) dataset merged with the California Office of Statewide Health Planning and Development (OSHPD) was used to perform a retrospective study of patients diagnosed with GEP-NENs metastatic to both liver and bone between 2000 and 2012. Univariate analysis was performed using Student’s t-test, Pearson chi-square, and Mann-Whitney U test. Median overall survival (OS) was compared using the method of Kaplan and Meier and log-rank test.

Results
Two hundred and three patients were identified. Seventy five (36.9%) patients underwent LDT including resection, ablation, or embolization, of whom 30 (14.8%) received LDT after diagnosis of bone metastasis and 45 (22.1%) prior to that diagnosis. 128 (63.1%) never received LDT. Twenty-eight patients had a stomach primary tumor (8.9%), 88 (43.3%) pancreatic, 33 (16.3%) small bowel, and 64 (31.5%) colorectal. There were no significant differences in age, sex, race, primary site, grade, or proportion of patients with additional sites of metastasis between these groups, although those who underwent LDT after a diagnosis of bone metastasis were more likely to have a higher Charlson comorbidity score when compared with those that had had LDT prior (60.0% vs 24.4%, P = 0.001) and also were more likely to have received radiation therapy (33.3% vs 8.9%, P = 0.001). Median OS from time of initial diagnosis was significantly longer in patients that received LDT compared to those who did not (29.9 vs 15.5 months, P = 0.004). There was no significant difference in OS between those who never received LDT and those who received it only after diagnosis of bone metastasis (13.5 vs 18.6 months, P = 0.638). However, when calculated from time of bone metastasis diagnosis, median OS was significantly longer in those that received LDT after that diagnosis than those that never received LDT (9.3 vs 2.3 months, P = 0.005) and was not significantly different in those that had received LDT prior to diagnosis (9.3 vs 5.6 months, P = 0.256).

Conclusions
LDT is associated with improved median OS in GEP-NENs, even after diagnosis of concurrent bone metastasis.

Abstract ID 21421
DOI: 10.1530/endoabs.89.C35

C37
Is There a Role for Surgical Resection of Grade 3 Neuroendocrine Neoplasms?
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Background
Grade 3 (G3) gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs) are aggressive tumors with poor survival outcomes for which medical management is usually recommended. This study sought to evaluate outcomes of surgically treated G3 GEP-NEN patients.

Methods
A single-institutional prospective NEN database was reviewed. Patients with G3 GEP-NENs based on World Health Organization (WHO) 2019 definitions were included. Clinicopathologic factors remained stable 436.14/100,000 in 2019 (APC 2.19, P = 0.001). The G3 cohort included 39 G3NETs and 28 G3NECs. Clinicopathologic factors were compared between groups. Overall survival from G3 diagnosis was assessed by the Kaplan-Meier method.

Results
Surgical resection was performed for 463 patients (211 G1, 208 G2, 44 G3), including 276 from small bowel, 157 from pancreas, and 30 from stomach/duodenum/right colon. Most had metastatic disease at presentation (54% G1, 69% G2, 91% G3, P < 0.001). The G3 cohort included 39 G3NETs and 5 G3NECs, 22 of pancreatic and 22 of midgut origin. Median overall survival (mOS; in months) was 268.1 for G1NETs, 129.9 for G2NETs, 50.5 for G3NETs, and 28.5 for G3NECs (P < 0.001). Over the same period, 31 G3 patients (12 G3NETs, 19 G3NECs) were treated non-surgically, with mOS of 19.0 for G3NETs and 12.4 for G3NECs. On multivariable cox-analysis grade and TNM-stage correlated with survival, with better survival in resected than non-resected G3NETs (Table).

Conclusions
Surgical resection of G3 GEP-NENs remains controversial due to poor prognosis, and surgical series are rare. This large, single-institutional study found significantly lower mOS in patients with resected G3NETs than those with G1/G2 tumors, reflecting more aggressive tumor biology and a higher proportion with metastatic disease. The mOS for resected G3NETs and G3NECs exceeded historical non-surgical G3NET series (mOS 11–19 months), suggesting surgery should be considered in carefully selected patients with G3NECs, especially those with well-differentiated G3NECs.

Abstract ID 21440
DOI: 10.1530/endoabs.89.C37

C38
Increased Incidence, Prevalence, and Surgical Management of Enteropancreatic Neuroendocrine Tumors Is Associated with Improvements in Survival - A Contemporary Analysis
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Background
Neuroendocrine tumors (NETs) are increasing in incidence and prevalence. Small intestine, rectum, pancreas and appendix are the most common enteric sites of NETs, and when identified early, surgical resection can be curative. We hypothesized that observed increases in incidence and prevalence of NETs are primarily driven by earlier detection of loco-regional tumors. In turn, increases in incidence of early-stage tumors is associated with increases in resection and overall improved survival duration.

Methods
Patients with NETs were identified in the Surveillance, Epidemiology and End Results (SEER) Program data, spanning 2000–2019. Age-adjusted incidence, 20-year limited duration prevalence, surgical resection and 5-year survival rates were calculated. Annual percent changes (APC) were calculated for each.

Results
Overall incidence of NETs continued to increase from 4.83/100,000 in 2000 to 8.24/100,000 in 2019 (APC 3.30, P = 0.001), whereas incidence of all malignancies remained stable 436.14/100,000 in 2019 (APC P > 0.05). Incidence of small intestine (APC 2.82, P < 0.001), rectum (APC 2.41, P < 0.001), pancreas (APC 8.32, P < 0.001), and appendix (APC 15.7, P < 0.001) NETs increased from 2000 to 2019. Overall increased incidence was primarily driven by localized and regional NET for small intestine (localized APC 2.75, regional APC 3.01 P < 0.001), pancreas (localized APC 15.66, regional 7.13, P < 0.001), and appendix (APC 18.28, regional 13.68 P < 0.001) NET. Rectal NET showed increased incidence of local, but not regional disease (APC 1.97, P < 0.001). The prevalence of localized (0.004% to 0.04%), regional (0.001% to 0.01%) and metastatic (0.001% to 0.006%) NET increased significantly, likely due to the indolent nature of NET. Overall rate of patients undergoing resection increased significantly from 2000 to 2019, 4.06/100,000 to 7.38/100,000. Rates also increased for each disease site; small intestine (APC 2.19, P < 0.001), rectum (APC 2.25, P < 0.001), pancreas (APC 10.21, P < 0.001), and appendix (APC 16.05, P < 0.001). Overall improvement in survival was associated with more recent diagnosis from 2000 to 2019 (HR 0.95, P < 0.001), when controlling for sex and tumor grade, more recent diagnosis was associated with improvements in survival; small intestine (HR 0.97, P < 0.001), rectum (HR 0.92, P < 0.001), pancreas (HR 0.97, P < 0.001), appendix (HR 0.94, P < 0.001), though this may represent significant lead time bias in a relatively indolent tumor.

Conclusions
Continued increases in incidence and prevalence of locoregional NETs has been accompanied by a rise in surgical resection rates and is associated with
improvements in survival. These trends may be due in part to greater detection of early-stage tumors, and in turn an earlier window for curative surgical intervention. Abstract ID 21444 DOI: 10.1530/endoabs.89.C38

C99

Have We Accounted for Asians? A Critical Analysis of Racial Cancer Disparity Amongst Asian Pancreatic Neuroendocrine Tumor Patients

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Background
Pancreatic neuroendocrine tumors (pNETs) are slow growing, malignant tumors that show different survival outcomes by race. They are often diagnosed in late stages, with few treatments available. pNETs are the second most common pancreatic cancer and are rapidly increasing in incidence. Current size-based guidelines were largely developed in White patients and recently have been called into question for Black patients. We investigated differences of primary tumor size (PTS) and incidence of lymph node metastasis (LNM) between White and Asian pNET patients to evaluate generalizability of established guidelines.

Methods
A multi-institutional analysis of patients with low grade, resected, nonfunctional, sporadic, non-metastatic pNETs was performed using the National Cancer Database. A Chi-squared test was utilized to determine correlation between PTS and incidence of LNM as well as patient racial group and incidence of LNM. A logistic regression model was utilized to determine correlation between LNM, tumor size, and patient racial group. Overall survival was assessed using the Kaplan-Meier method.

Results
A total of 4,977 pNET patients (205 Asian and 4772 White) were analyzed in the dataset. Both White and Asian patients had low incidence of lymph node metastasis (26.9% and 19.0%, respectively, P<0.05). Within both populations, tumor size (<2 cm, 2-3 cm, and >3 cm) positively correlated with incidence of LNM (11.5%, 24.6%, and 39.1%). No difference in LNM rate was noted between the two racial cohorts with PTS £3 cm, however Asian patients are less likely to exhibit LNM at PTS >3 cm (28.2% and 39.5%). Overall survival was not shown to be significantly different between Asian and White pNET populations (P=0.68).

Conclusions
Current surveillance recommendation for pNET primary tumor size less than 2 cm is based on data derived from primarily White patients populations, but Asian patients are less likely to exhibit LNM at larger tumor sizes. Asian patients are less likely to exhibit LNM at larger tumor sizes. Asian patients are less likely to exhibit LNM at larger tumor sizes. Conservation methods are needed in larger cohort.

Abstract ID 21447 DOI: 10.1530/endoabs.89.C39

C40

TP53 Mutation Portends a Worse Overall Survival in Patients with Advanced Grade 3 Well-Differentiated Neuroendocrine Tumors

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Background
The well-differentiated grade 3 neuroendocrine tumor (G3NET) category was introduced in the 2017 WHO classification as a new category of high-grade neuroendocrine neoplasm (NEN). G3NET is thought to have worse overall survival (OS) than lower grade NET, but better OS than poorly differentiated neuroendocrine carcinoma (NEC). However, challenges in pathologic diagnosis and changes in terminology have limited our understanding of the G3NET category. We compared outcomes in patients with high-grade gastroenteropancreatic NEN and assessed whether specific mutations had an impact on outcomes.

Methods
We performed an IRB-approved retrospective chart review of 134 patients with high grade metastatic NEN. Formal pathology review at UCSF, and tumor DNA sequencing performed in the context of clinical care. Pathology reports and clinical histories were re-reviewed by a single pathologist and cases were best re-classified as NEC, NET or ambiguous G3NEN. OS, defined from the time of high grade and metastatic NEN diagnosis to death or last follow-up, is measured using Kaplan-Meier methods, and log-rank test is used to compare across G3NET, NEC, and ambiguous G3NEN.

Results
Of the 134 patients, 56 (42%) had NEC, 33 (25%) had G3NET, and 45 (34%) had ambiguous NEN. The median age was 61 and 41% were female, with no differences in NEC vs G3NEN vs ambiguous G3NEN. Site of origin was pancreas (n = 46, 34%), colorectum (n = 30, 22%), other gastrointestinal (n = 24, 18%) and unknown (n = 34, 25%). The most common recurrently altered genes in NEC were TP53 (75%), RB1 (39%), KRAS (29%), APC (25%), MYC (11%), and CDK2A2 (9%). G3NET demonstrated frequent alterations in MEN1 (49%), DAXX (21%), ATRX (9%), TSC1 or TSC2 (18%) SETD2 (18%), CDKN2A (18%), and TP53 (21%). Ambiguous G3NEN had frequent alterations in TP53 (33%), RB1 (31%), CDKN2A (29%), APC (18%), MEN1 (13%), KRAS (9%), and ARID1A (9%). Median OS among G3NET (20 months, 95% CI 10-not calculable), NEC (17 months; 95% CI 10-21), and ambiguous G3NEN (15 months, 95% CI 12-40) was not statistically different (log-rank P=0.411). However, patients with G3NET harboring mutation in TP53 had significantly worse OS (6 months, 95% CI 2-NC) than those without mutation in TP53 (25 months, 95% CI 16-NC; P=0.021). Conclusions
There is potential to use TP53 mutation status for prognosis of advanced G3NEN. Validation of these findings in a larger cohort is needed. Ongoing work is focused on investigating the prognostic value of other mutated genes in this cohort of high grade NEN.

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C41

SSTR-2 Expression in Solid Tumors: An Immunohistochemistry Analysis

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Background
Somatostatin receptor (SSTR) expression has been characterized in well-differentiated neuroendocrine tumors (NET). However, the understanding of receptor expression in various non-neuroendocrine solid tumors is limited. This study was performed to evaluate STR-2 in various cancers to provide a rational basis for SSTR-2 targeted anti-cancer therapies.

Methods
Formalin-fixed paraffin, paraffin-embedded tissue was obtained from pathology archives after institutional review board approval. Tumor blocks were prospectively stained with an anti-SSTR-2 antibody via immunohistochemistry (IHC). The following tumor types were studied: small cell carcinoma (Code 0; n=14), medullary thyroid carcinoma (Code 1, n=10), melanoma (Code 2, n=10), Merkel cell carcinoma (Code 3, n=10), head and neck p16 positive squamous cell carcinoma (Code 4, n=10), well-differentiated NET (Code 5, n=10), paranganglioma and pheochromocytoma (Code 6, n=20), poorly differentiated neuroendocrine carcinoma (Code 7, n=9), and p66 negative squamous cell carcinoma (Code 8, n=4). IHC was scored as follows: SSTR2 Intensity (0 = none, 1 = weak, 2 = moderate, 3 = strong); SSTR2 Localization (1 = membranous; 2 = cytoplasmic; 3 = mixed); SSTR2 % Positivity (5% increments).

Results
64% of SCLC samples stained positive for SSTR-2, and 35.7% of SCLC samples stained strongly positive for SSTR-2. 60% of Head and Neck carcinoma samples stained positive for SSTR-2, and 40% of these were of moderate intensity. As expected, 100% well-differentiated NET samples stained positive for SSTR-2. Only 33% of poorly differentiated neuroendocrine carcinoma samples were stained positive for SSTR-2, out of which only 11% stained strongly positive for SSTR-2. Conclusions
The understanding of receptor expression in various non-neuroendocrine solid tumors is limited. This study was performed to evaluate SSTR-2 in various cancers to provide a rational basis for SSTR-2 targeted anti-cancer therapies.

Endocrine Abstracts (2022) Vol 89
Small Intestinal NET Recurrence – When Why and How?
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Background
Through this study, we hoped to better understand the factors affecting recurrence-free survival in patients who have undergone curative intent resection for small bowel neuroendocrine tumors (SB-NETs). Extensive literature exists on recurrence predictors for pancreatic NETs but not for those of the small bowel. We hope to bridge this gap.

Methods
We retrospectively evaluated patients who had received their index curative-intent operation for a small bowel neuroendocrine tumor at the Mayo Clinic (Rochester) from 2013-2017. Patients with distant metastases and those who had residual disease after resection were excluded. Descriptive statistical analysis was performed. Recurrence-free survival was estimated using Kaplan-Meier analysis and groups compared using log-rank test.

Results
Inclusion criteria were met in 122 patients. TNM stage was 1 or 2 (localized disease) in 25 patients (20.5%) and 3 (regional disease) in 97 patients (79.5%). Multifocal disease was present in 55 patients (45.1%). Symptomatic disease was present in 80 patients (65.6%). The most common symptoms were obstruction and GI bleeding, which were seen in 16 (13.1%) and 21 (17.2%) patients, respectively. Overall, 5-year recurrence-free survival was 87% (95% CI 81-93). When stratified by extent of disease, 5-year recurrence-free survival was 95% (95% CI 87-100) for localized (stage 1-2) disease and 84% (95% CI 77-92) for regional (stage 3) disease (P = 0.07). When stratified by tumor size, 5-year recurrence-free survival was 94% (95% CI 89-99) for tumors <2 cm and 66% (95% CI 50-86) for tumors >2 cm (P < 0.001).

Conclusions
In this preliminary study, recurrence risk after curative-intent resection of small bowel neuroendocrine tumors was low and was associated with tumor size and extent of disease. This data can be used to accurately counsel our patients in the future and provide optimal follow-up recommendations after curative intent resection.

Post-Operative Biochemical Surveillance Thresholds Can Be Used to Monitor for Sympathetic Pheochromocytoma/Paraganglioma Recurrence and Metastasis
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DOI: 10.1530/endoabs.89.C44

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Background
Sympathetic pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors associated with excess catecholamine production. Routine biochemical and imaging surveillance to monitor for recurrence and metastasis is recommended. However, there is limited data describing optimal surveillance approaches and post-operative biochemical thresholds for detecting recurrences or metastases. This study sought to correlate biochemical and imaging surveillance with recurrences or metastases.

Methods
Patients who underwent surgery for PPGLs at a tertiary-care cancer hospital between 2000-2021 were retrospectively reviewed. Patients with <3 years of post-operative biochemical surveillance or with early locoregional recurrence (LRR) or metastasis at presentation were excluded. Surveillance catecholamine values and imaging were compared between patients with and without LRR/metastasis.

Results
Eighty patients treated for PPGLs met inclusion criteria. Median follow-up was 72 months (IQR 48.5-98.5). Seventy-one patients (89%) had genetic testing, with 40 patients (50%) having a PPGL-susceptibility mutation. Thirteen patients (16%) developed recurrence (local n = 8, contralateral de novo n = 2, metastasis n = 3). LRR/metastases were predominately from pheochromocytomas (n = 12); one paraganglioma developed diffuse metastases. Nine of 13 patients with LRR/metastasis had an identified PPGL-susceptibility mutation (RET 6, VHL 2, SDHD 1). Patients with LRR/metastasis were younger at presentation than those without LRR/metastasis (22 years vs 48 years, P = 0.025). No difference in gender, tumor size, or surgical approach was observed between groups. All patients with LRR/metastasis had evidence of biochemical excess preoperatively. Median time to identification of LRR or metastasis was 38 months (IQR 20-71.5). Biochemical surveillance was the most commonly used surveillance modality (91% of patients at 1 year). Only 45 patients (56%) had both biochemical and imaging surveillance at 1 year. Nine LRR/metastases were initially identified by biochemical surveillance vs 4 LRR/metastases identified by imaging first. All 4 recurrences/metastases identified by imaging first were patients who had undergone cortical-sparing adrenalectomy in the context of a PPGL-susceptibility mutation. Eleven patients with LRR/metastasis had normetanephrine levels ≥ 2 times the upper limit of normal (ULN). Although patients without LRR/metastasis intermittently had minimally-elevated metanephrine levels, none exceeded twice the ULN.

Conclusions
Routine postoperative biochemical surveillance in patients with functional PPGL may be adequate to detect development of LRR/metastasis. Normetanephrine levels ≥ 2 times the ULN are suggestive of LRR/metastasis. Elevated post-operative metanephrine levels are observed but did not exceed ≥ 2 times the ULN in patients without LRR/metastasis. Surveillance metanephrines were commonly the sole modality needed in identifying LRR/metastasis, except for in cases of cortical-sparing adrenalectomy. This data may be helpful in determining optimal modalities for long-term surveillance.

15th Annual Multidisciplinary NET Medical Symposium NANETS 2022
Population Science
Further studies are needed to better understand the biological underpinnings to SCC and AC, conferring dismal prognosis in patients with cervical neoplasms.

Conclusion

of type), was significantly associated with prolonged OS in the CNECs cohort analysis, when adjusted for other significant clinicopathologic factors, including or NEC NOS was independently associated with shorter OS in the multivariate and AC (NR, 95% CI; NR, NR), all

Magee-Women’s Hospital, Pittsburgh, PA, 15213, USA.

We used the National Cancer Database to identify patients diagnosed with islet cell carcinomas (ICD-O-3 histology code 8150/3) between 2004-2019. Chi-squared tests were used for comparative analysis and Cox proportional hazards model for identifying clinical covariates associated with OS.

Results

53,370 patients fulfilling inclusion criteria were identified; 868 patients (2%) with CNECs (547 SCNEC, 80 LCNEC, and 241 NEC NOS), 41,764 (78%) with SCC, and AC, with the topography codes C67.0-C67.9 (cervix) and the morphologic codes 8246, 8013, 8042 for NECs (small cell - SCNEC, large cell – LCNEC, NEC not Otherwise specified - NEC NOS), 8052, 8070-76 and 8064 for SCC, 8140, 8145, 8147, 8260, 8310, 8480-82 for AC. Demographic/ciopathologic/treatment/survival data were extracted. SEER earmark staging system (localized, regional, distant) was utilized. Overall survival (OS) from cancer diagnosis to death from any cause was estimated with the Kaplan-Meier method. Chi-squared tests were used for comparative analysis and Cox proportional hazards model for identifying clinical covariates associated with OS.

Background

Cervical neuroendocrine carcinomas (CNECs) are a rare and heterogeneous group of cervical neoplasms, with very limited data regarding epidemiology and survival. In this study, we explored clinicopathologic factors and oncologic outcomes of patients with CNECs derived from the Survival, Epidemiology and End Results (SEER) database, in comparison to cervical squamous cell carcinoma (SCC) and adenosquamous carcinoma (AC).

Methods

The SEER database (18 registries/November/2020) was queried for patients with CNECs, SCC, and AC, with the topography codes C67.0-C67.9 (cervix) and the morphologic codes 8246, 8013, 8042 for NECs (small cell - SCNEC, large cell – LCNEC, NEC not otherwise specified - NEC NOS), 8052, 8070-76 and 8064 for SCC, 8140, 8145, 8147, 8260, 8310, 8480-82 for AC. Demographic/ciopathologic/treatment/survival data were extracted. SEER earmark staging system (localized, regional, distant) was utilized. Overall survival (OS) from cancer diagnosis to death from any cause was estimated with the Kaplan-Meier method. Chi-squared tests were used for comparative analysis and Cox proportional hazards model for identifying clinical covariates associated with OS.

Abstract 21380

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Factors Impacting Survival Outcomes of Islet Cell Carcinoma

P2

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Islet cell carcinomas are low-grade tumors originating from the islets of Langerhans. Despite the indolent nature of these tumors, metastasis is often detected upon initial diagnosis, at which point the mean survival is approximately 2 years. In this study, we aim to investigate disparities that exist in these patients and how facility variables, patient demographics, and palliative care (PC) utilization contribute to differences in survival outcomes.

Methods

We used the National Cancer Database to identify patients diagnosed with islet cell carcinoma (ICD-O-3 histology code 8150/3) between 2004-2019 (n = 2364). Differences in socioeconomic factors were determined using Pearson’s chi-squared test with post-hoc Bonferroni adjustment. Survival was evaluated using Kaplan-Meier curves, log-rank tests, and Cox proportional hazards modeling.

Results

Socioeconomic Factors, Treatment Modality, and Survival in Islet Cell Carcinoma: A National Cancer Database Analysis

Robert W. Hu, Tiffany Chu & Peter T. Silberstein
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Islet cell carcinoma is a rare cancer of neuroendocrine origin. There has yet to be a study analyzing the treatment type and survival outcomes in this cancer. In this study, we utilized a national database to understand the correlations between patient demographics, socioeconomic factors, modality of treatment, and survival.

Background

Islet cell carcinoma is a rare cancer of neuroendocrine origin. There has yet to be a study analyzing the treatment type and survival outcomes in this cancer. In this study, we utilized a national database to understand the correlations between patient demographics, socioeconomic factors, modality of treatment, and survival.

Methods

The National Cancer Database was queried to identify patients diagnosed with islet cell carcinoma (ICD-O-3 histology code 8150/3) between 2004-2019 (n = 2364). Chi-squared test was utilized to analyze healthcare disparities that exist in these patients and how various socioeconomic variables contribute to the treatment modality received. Descriptive statistics, Kaplan-Meier, log rank test, and multivariate Cox proportional hazards analyses were used to study correlations in treatment modality and survival.

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Methods

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Results

Of the patients studied, 53.7% were male and 46.3% were female; 84.3% were White, 10.7% African American, and 4.9% other. Median age at diagnosis was 59 years. Chi-squared testing demonstrated that facility type, facility location, insurance status, high school degree (HSD), and medium income quartile were significantly associated with treatment modality. Kaplan-Meier analysis demonstrated that those who received surgery had significantly higher mean survival time (152 months) compared to all other modes of treatment. Furthermore, those who received any form of treatment had a significantly higher mean survival time (98 months) compared to those without treatment (51 months). Cox regression indicated that age, insurance status, HSD, comorbidities,
Comparison of Demographics and Overall Survival (OS) Among Patients with Young-Onset(YO) and Late-Onset(LO) GI Neuroendocrine Tumors/Carcinomas (NETs/NECs) in the United States

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Background

More than 12,000 people are diagnosed with neuroendocrine malignancies each year in the US. There are limited data on YO-NETs/YO-NECs. In the present study, we seek to evaluate clinical characteristics/trends of patients with GI-YO-NETs and GI-YO-NECs.

Methods

Using the National Cancer Database, NCDB, we identified 124,081 GI-NETs and 52,063 GI-NEC cases 18 or older, diagnosed between 2004 and 2019. Histology codes to identify NETs and NECs were 8150-8153, 8155-8157, 8240-8244, 8249 for NETs and 8246 for NEC. YO was defined as age <50 and LO was defined as age ≥50. Logistic regression was used to associate factors with YO status. OS, estimated by Kaplan-Meier methodology, was compared using log rank test.

Results

YO-NETs comprise 21% of GI-NETs and YO-NECs comprise 17% of GI NECs. NETs/NECs most frequently arose from small intestine, colon, rectum, pancreas, and stomach. Females had higher proportion of YO-NETs and YO-NECs vs males: 23.4% vs 19%; P < 0.0001 for YO-NET and 19% vs 15.8%; P < 0.0001 for YO-NEC, respectively. The proportion of YO-NETs was lowest for non-Hispanic Whites (19.6%), highest for Hispanics (32.6%) and intermediate for Asians (24.7%) and African Americans (22.1%). Same trend was observed for YO-NECs. A majority of YO-NETs/YO-NECs presented as stage I-III disease, 86.6% and 59.7%, respectively, although stage was unavailable in a large fraction of patients. Consistent with prior data and unlike other cancers, YO-NETs/NECs had significantly better OS than LO-NETs/NECs in both surgical and non-surgical groups. Seventy-three percent of YO-NETs had private insurance and 19.3% had government-based insurances. While the proportion of YO-NECs decreased over time, the proportion of YO-NETs stayed the same. Differences in rates of YO-NETs and YO-NECs were within 2% across income, level of education, and geographical location.

Overall Survival for GI-YO-NETs w/wo surgery

<table>
<thead>
<tr>
<th>NET</th>
<th>5-year survival</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>YO-No Surgery vs LO-No Surgery</td>
<td>75% vs 54%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>YO-Surgery vs LO-Surgery</td>
<td>94% vs 81%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YO-No Surgery vs LO-No Surgery</td>
<td>31% vs 20%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>YO-Surgery vs LO-Surgery</td>
<td>83% vs 66%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions

Our NCDB analysis suggests the proportion of GI-YO-NETs/NECs is higher among females and Hispanics and lowest among White non-Hispanics. In addition, GI-YO-NETs/NECs have higher 5-year survival compared to GI-LO-NETs/NECs. These data may have biologic or environmental explanations and will need further investigation, but one must be careful in interpreting results in diseases such as NETs, that are often chronic and whose incidence rises with age.

Abstract ID 21409

DOI: 10.1530/endoabs.89.P5
Background
Targeted therapies for somatostatin receptor-positive NETs have seen significant developments in recent years. Approved and investigational somatostatin analogs for GEP-NETs are changing the treatment landscape for these cancers allowing for better management of difficult-to-treat tumors. To improve competence in applying these advances and to consider patient perspectives in treatment selection, an educational initiative was designed in collaboration with the Healing NET Foundation.

Methods
A 1-hour CME activity was broadcast live-online in October 2021 and remains on-demand through October 2022 at OMedLive.com. The first module of the CME activity focused on real-world and quality-of-life data, and consensus guidelines related to somatostatin analogs (SSA) and peptide receptor radiotherapies (PRRT). The second module of the CME activity highlighted patient perspectives based on interviews of real patient with SSA and PRRT experience. This second section was distributed via social media through the Healing NET Foundation. Knowledge and competence questions were administered pre-, immediate post-, and 2 mos. post-activity. McNemar tests compared paired responses (pre/post & pre/post 2 mos) with Cohen’s d for effect size.

Results
As of 01/28/22, 238 clinicians have participated in the activity, 80% of whom are physicians, advanced practitioners (NP/PA), and nurses. Through social distribution, the patient perspectives were viewed by 300 patients/caregivers. Across the four CME test questions low baseline knowledge/competence was observed when selecting treatment with SSA based on reported progression-free survival and time to deterioration of quality of life from clinical trial data. Clinical considerations based on patient perspectives and prophylactic regimens with PRRT also revealed low baseline knowledge/competence. Statistically significant improvements were seen for pre/post paired responses across all four CME questions with gains ranging from 25% to 53%. The greatest challenge managing a patient with GEP-NET was identified as adherence to treatment schedules. At 2-mos. follow-up, 90% and 95% reported improved behavioral impact on both clinical practice and patient experience/outcomes, respectively. Qualitative data including clinician write-in examples of behavioral impact and patient perspectives from the interviews will be shared.

Conclusion
Assessments reveal a positive impact of live-online education on clinical practice when sharing patient perspectives in context of clinical updates. Open-ended responses to behavioral impact questions illustrated clear improvements in clinician-reported patient experience and outcomes, clinical practice management, and knowledge of SSA and PRRT for patients with GEP-NETs.

Table. Participant Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (n=196), median [range]</td>
<td>65 years [28, 83]</td>
</tr>
<tr>
<td>Biological sex (n=196)</td>
<td>Female 115 (68%) Males 54 (32%)</td>
</tr>
<tr>
<td>Race (n=170)</td>
<td>White 156 (92%)</td>
</tr>
<tr>
<td>Hispanic ethnicity (n=170)</td>
<td>Asian 6 (4%)</td>
</tr>
</tbody>
</table>

Conclusion
We demonstrate preliminary feasibility of a novel direct-to-participant, web-based research tool in NENs. The data and feedback from this pilot are being used to develop a larger quality of life cohort study called NET Voices, which will inform subsequent intervention studies. Ongoing efforts are also focused on increasing participant diversity.

Abstract ID 21430
DO: 10.1530/endoabs.89.P7

P8
Multivisceral Surgical Resection of Locally Advanced Pancreatic Neuroendocrine Tumor is Associated with a Survival Benefit
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City of Hope National Medical Center, Department of Surgical Oncology, Duarte, California.

Background
In patients with locally advanced pancreatic neuroendocrine tumors (PNET), surgical resection is associated with improved survival. There is a paucity of data whether there is a benefit for mutivisceral resection for locally advanced PNET compared to pancreatectomy alone. This study investigated the association of surgical resection on overall survival comparing pancreatic specific and multivisceral resection for PNET.

Methods
The Surveillance, Epidemiology and End Results Program (SEER) database was utilized to identify patients with PNET between 1/1/2000 and 12/31/2018. Survival was modeled using Kaplan-Meier analysis and multivariable Cox proportional hazards models.

Results
A total of 8605 patients were analyzed. Stage included localized (3147, 36.5%), regional (1685, 19.5%), distant (3474, 40.3%) and missing (299, 3.7%). Tumor size correlated with stage: localized 1.9 cm [IQR 1.2-3.1], regional 3.5 cm [IQR 2.4-5.5], and distant 4.5 cm [IQR 3.0-6.4], P = 0.001. Among these patients, 4403 (51.2%) did not undergo surgery, 3624 (42.2%) underwent pancreatectomy, 178 (2.0%) underwent surgery and distant metastasis, and 197 (2.3%) underwent surgery and multiple metastases. The Surveillance, Epidemiology and End Results Program (SEER) database was utilized to identify patients with PNET between 1/1/2000 and 12/31/2018. Survival was modeled using Kaplan-Meier analysis and multivariable Cox proportional hazards models.

Conclusion
Overall survival was similar in patients who underwent multivisceral and pancreatic specific surgery for PNETs. When feasible, multivisceral surgery should be considered for selected patients within the confines of multidisciplinary strategies.

Abstract ID 21439
DO: 10.1530/endoabs.89.P8
P9 Lifestyle and Neuroendocrine Tumor (NET) Development Within the European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort

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Background
There has been increasing interest in the relationship between lifestyle and NET. Results from previously published small observational studies indicate that smoking, alcohol and diabetes may contribute to NET development, but the reported data is conflicting. Additionally, little data is available on diet and physical activity. The aim of the current study is to investigate the association between lifestyle factors and NET development in a large prospective cohort.

Methods
A cohort of in total 450,111 participants from 9 participating countries was established from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Information on lifestyle and diet was obtained at baseline through questionnaires. For this study, lifestyle factors including smoking, alcohol consumption, Mediterranean diet score, body mass index and Cambridge Physical Activity Index were assessed.

Results
193 lung and gastroenteropancreatic (GEP) NET cases were diagnosed. Smoking was significantly associated with all NET development in multivariable analysis in all NETs (HR 1.46, 95% CI 1.02 – 2.11) and GEP NETs (HR 1.58, 95% CI 1.04 – 2.41). Alcohol consumption was not associated with NET development. Hazard ratios for medium (7-10 points) and high adherence (11-18 points) to the Mediterranean diet were 0.71 (95% CI 0.51 – 0.98) and 0.39 (95% CI 0.25 – 0.62) for all NETs, 0.47 (95% CI 0.25 – 0.90) and 0.36 (95% CI 0.15 – 0.86) in lung NETs, and 0.80 (95% CI 0.55 – 1.16) and 0.40 (95% CI 0.23 – 0.69) in GEP NETs. Obesity and physical activity were statistically not significantly associated with NET development.

Conclusion
This is the largest prospective cohort study looking at the relation between lifestyle and NET development. Smoking is strongly associated with NET development in both the entire NET population and GEP NETs in the EPIC cohort. Body mass index increases the risk of NET development. Increased adherence to the Mediterranean diet has a protective association with NETs. The observations from our study provide support for further research into lifestyle and NETs with regard to natural course, disease stage and treatment response, eventually contributing to preventive measures.

Abstract ID: 21459
DOI: 10.1530/endobests.89.99

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P10 Environmental Pollution and GEP-NETs – Is There an Association?

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Background
Incidence of gastroenteropancreatic neuroendocrine neoplasms (GEP-NETs) is increasing, but etiology of sporadic, non-familial disease remains obscure. Behavioral risk factors like smoking and alcohol consumption may be associated with GEP-NETs, yet environmental factors potentially associated with GEP-NENs remain unexamined. We regressed age-adjusted incidence rates for GEP-NENs cases in California (CA) on county-level pollution data to determine if an association between GEP-NEN incidence and environmental pollutants exists.

Methods
GEP-NEN cases were obtained from the CA Cancer Registry for the years 2000-2012 and age-adjusted for each of 54 of 58 CA counties. Pollution scores were obtained from the Cal EnviroScreen 3.0 (CES3) database which contains census-tract level measures of exposure to several types of pollution, including air (diesel and fine particulate matter 25 ppm; ozone; residential proximity to areas of high traffic), water (drinking water quality; groundwater toxins), proximity to hazardous and solid waste sites, pesticide exposure, and an overall pollution burden score. CES3 census tract scores were averaged for each county; county-level GEP-NEN incidence rates and average pollution scores were then analyzed by linear regression. Incidence rates for gastrointestinal NENs (GI-NENs) and pancreatic NENs (P-NENs) were calculated and analyzed separately.

Results
There were 8,580 GI-NENs and 1,491 P-NEN cases. Median age at diagnosis was 58 for GI-NENs and 59 for P-NENs. GI-NENs were evenly distributed by sex, and a majority of cases were white race (GI-NENs 50%; P-NENs 59%). Weak or zero correlations were observed between GI- or P-NEN incidence rates and pollution burden score (R2 = 0.02) but a nearly zero R2 for pollution burden score (R2 = 0.02). Similarly, GI-NEN incidence regressed on air pollutants yielded low R2s (0.004) and other categories of pollutants.

Conclusion
We observed a slight association between age-adjusted GI- or P-NEN incidence rates and county-level scores for exposure to diesel particulate matter, and exposure to air from heavy vehicular traffic. Future studies with more fine-grained measurements of air pollution exposure and GEP-NEN incidence rate may uncover a stronger association between GEP-NENs and the environment.

Abstract ID: 21468
DOI: 10.1530/endobests.89.P10
Other
Efficacy and Toxicity of Anti-Vascular Endothelial Growth Factor (VEGF) Receptor Tyrosine Kinase Inhibitors (TKIs) in Neuroendocrine Tumors (NETs) – A Systematic Review and Meta-Analysis

Satya Das, MD, MSC1, Sharon Phillips, MSPH2, Cody M Lebeck Lee, MD3, Rajiv Agarwal, MD, MSC4, Emily Bergslan, MD5,6, Jonathan Strosberg, MD, Jennifer A. Chan, MD, MPH5,6, Heather LaFerriere, MLIS6, Robert A. Ramirez, DO7, Jordan Berlin, MD7,8 & Arvind Dasari, MD, MS7,8

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Background
Although anti-VEGF RTKIs have been tested in patients with NETs over the last 2 decades, no study to date has benchmarked efficacy and toxicity of these drugs in this patient population.

Methods
A literature search was performed to identify all phase II and phase III studies of anti-VEGF RTKIs in patients with NETs published between January 1, 2000 – July 31, 2021. Major trial databases (e.g. Medline, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Cochrane Database of Reviews and others) were searched in August 2021 for relevant studies. The primary objectives of the meta-analysis were to compare objective response rate (ORR) and progression-free survival (PFS) between patients with pancreatic (p) NETs and extra-pancreatic (ep) NETs and the incidence rate ratio (IRR) of adverse events (AEs) between patients receiving anti-VEGF RTKIs vs control drugs.

Results
Of 92 potentially relevant studies, 17 studies with 8 distinct anti-VEGF RTKIs were included in the meta-analysis. A total of 1611 patients were available for the analysis; 1194 received anti-VEGF RTKIs. ORR in pNETs was 18% (95% CI 13-25%) while ORR in epNETs was 8% (95% CI 5-12%); test for differences between pNETs and epNETs (x² = 8.47, P < .01). Median PFS in pNETs was 13.9 months (95% CI 11.43-16.38 months) while median PFS in epNETs was 12.71 months (95% CI 9.37-16.05 months); test for differences between pNETs and epNETs (x² = 32, P < .005). With regards to common grade 3/4 AEs, patients who received anti-VEGF RTKIs were more likely to experience hypertension (IRR 3.04, 95% CI 1.63-5.65) and proteinuria (IRR 5.79, 95% CI 1.09-30.74) relative to those who received control. There was no difference in IRR for rare serious AEs (e.g. cardiac dysfunction, cerebrovascular accident, myocardial infarction, non-central nervous system emboli and gastrointestinal tract perforation) between patients who received anti-VEGF RTKIs and those who received control.

Conclusion
Anti-VEGF RTKIs demonstrate anti-tumor effect and safety in both pNETs and epNETs, supporting their development in both patient populations. The true determining factor for efficacy of agents within this drug class may be the baseline disease characteristics of the tested population in a randomized clinical trial; a treasured including patients with more aggressive baseline disease will demonstrate greater benefit from the anti-VEGF RTKI given poorer outcomes anticipated in the control arm.

Abstract ID 21373
DOI: 10.1530/endobs.89.01

Germline Pathogenic Variants in Patients with High-Grade (G3) Metastatic Gastroenteropancreatic (GEP) Neuroendocrine Neoplasms (NENs)

Farhana Moon1, Bryan Khuong Le1, Alan Paciorek2, Amie Blanco3, Adrienne Wakeling4, Claire K. Mulvey4, Li Zhang5, Nancy M. Joseph6 & Emily Bergslan4,6

1Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; 2Department of Epigenetics and Biostatistics, University of California San Francisco, San Francisco, CA, USA; 3Cancer Genetics and Prevention Program, University of California San Francisco, San Francisco, CA, USA; 4Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA, USA; 5Department of Pathology, University of California San Francisco, San Francisco, CA, USA.

Background
The incidence of germline pathogenic/likely pathogenic variants (PLPV) is relatively well described in low grade well differentiated neuroendocrine tumors (NENs). However, germline findings in G3 NENs including grade 3 NETs (G3NET) and poorly differentiated neuroendocrine carcinoma (NEC) is gravely understudied, and guidance related to germline testing in G3NEN is lacking.

Methods
An IRB approved, single institution, retrospective chart review was performed in patients with metastatic G3NEN of gastroenteropancreatic (GEP) origin and unknown primary in whom both tumor DNA sequencing and germline testing were performed as part of clinical care. Pathology reports and clinical history were reviewed by one pathologist to best reclassify as G1NENs, NECs or ambiguous G3NEN. Data were collected from germline and tumor molecular sequencing reports. In patients harboring a germline PLPV, somatic PLPV were evaluated.

Results
Among 88 UCSF patients with G3NEN, 15 (17%) had germline PLPV (14 patients with one and 1 with 2); see Table for details. Median age at the time of metastatic G3NEN was 58 years (range 26-84). Primary tumor sites: pancreas

Abstract ID 21401
DOI: 10.1530/endobs.89.02
In vitro clinical response correlates. The exact effect of somatostatin analogs (SSAs) in inhibitory effect of lanreotide on tumor cells proliferation is due to binding to SSTR1-5. Lanreotide is clinically effective in advanced neuroendocrine tumors (NETs).

\[ \text{Lanreotide has a significant effect on CD8}^+ \text{ cytotoxic T cells.} \]

**Table: Germline P/LPV in G3NENs**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutated in germ line</th>
<th>Mutated in tumor</th>
<th>Differentiation</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUTHY</td>
<td>4</td>
<td>2</td>
<td>1 NEC</td>
<td>2 Pancreas</td>
</tr>
<tr>
<td>BRCA1</td>
<td>2</td>
<td>1</td>
<td>3 Ambiguous</td>
<td>1 Unknown</td>
</tr>
<tr>
<td>APC</td>
<td>2</td>
<td>1</td>
<td>1 NEC</td>
<td>1 Pancreas</td>
</tr>
<tr>
<td>BRCA2</td>
<td>1</td>
<td>1</td>
<td>Ambiguous</td>
<td>CR</td>
</tr>
<tr>
<td>MLH1</td>
<td>1</td>
<td>1</td>
<td>NEC</td>
<td>CR</td>
</tr>
<tr>
<td>NTHL1</td>
<td>1</td>
<td>1</td>
<td>Ambiguous</td>
<td>Pancreas</td>
</tr>
<tr>
<td>ATM</td>
<td>1</td>
<td>1</td>
<td>NEC</td>
<td>GI</td>
</tr>
<tr>
<td>CHEK2</td>
<td>1</td>
<td>1 (CHEK2 &amp; MEN1)</td>
<td>NET</td>
<td>Pancreas</td>
</tr>
</tbody>
</table>

**Conclusion**

Germline P/LPV were identified in 17% of patients with GEP G3NENs, with 67% present at high maf in the tumor-supporting a role in G3NEN pathogenesis and with potential therapeutic implications in some cases. The findings suggest a role for germline genetic testing in all patients with G3NEN.

Abstract ID 21410

DOI: 10.1530/endobas.89.03

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**O4**

**Immune Cell Molecular Pharmacodynamics of Lanreotide in Relation to Treatment Response**

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**Background**

Lanreotide is clinically effective in advanced neuroendocrine tumors (NETs). The inhibitory effect of lanreotide on tumor cells proliferation is due to binding to somatostatin receptors (SSTR1-5). It has been demonstrated that immune cells express SSTR1-5 differentially: the exact effect of somatostatin analogs (SSAs) on T cell function is not understood.

**Methods**

In vitro and in vivo effects of lanreotide on immune cells were investigated, with clinical response correlates. In vitro, SSTR1-5 expression was measured on CD4+ T helper cells, CD8+ cytotoxic T cells, and CD4+CD25+ regulatory cells from healthy donors (HD), and lanreotide effect on key functional immune response parameters were studied. To assess in vivo effects of lanreotide on immune cells of NET pts, peripheral blood mononuclear cells (n=17) obtained pre and 3 months post treatment were studied for gene and protein expression profiles in sorted T cell subsets using NanoString immune cell panel.

**Results**

HD T cells had high expression of SSTR2 and low/no expression of other SSTRs. In vitro, lanreotide had no effect on functional immune response parameters investigated. For the in vivo study, the patient cohort consisted of 9 responders and 8 non-responders. Clinicopathological features, see table. Pretreatment immunological competence of responders was greater than non-responders, indicated by upregulation of TCR signaling (in CD4+ and T reg). Irrespective of clinical response, lanreotide had most significant effect on CD8+ T cells, downregulating WNT, TCR, and NF-kB signaling. Compared to non-responders, responders had downregulation of cytokine and chemokine signaling but upregulation of ubiquitination and proteasome degradation associated genes. Several myeloid specific genes were significantly changed in the CD4 T helper population, possibly due to co-isolated myeloid cells interacting with T cells during sorting.

**Conclusion**

The in vivo immune effects of lanreotide seen in the absence of in vitro effects reflect the relevance of environmental parameters such as interactions with myeloid components of the immune system not accounted for under the experimental in vitro conditions.

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**05**

Implementation of a Patient Advisor Program for Neuroendocrine Tumor Patients: Acceptability, Benefits and Potential Challenges

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**Background**

Multiple unmet needs of patients diagnosed with a neuroendocrine tumor (NET) have been described in the literature, especially informational and psychological needs. A multidisciplinary approach has been suggested to improve overall care of NET patients. Trained patient advisors (PA) could complement the healthcare team, by providing a personalized accommodation to patients based on their experiential knowledge, therefore helping to bridge this current gap. The aim of this study was to explore the acceptability, perceived advantages and limits of a PA program for NET patients.

**Methods**

For this mixed methods study, thirteen patients with a diagnosis of small bowel or pancreatic NET were recruited. Participants first completed an online questionnaire to collect sociodemographic data and information regarding their diagnosis. Semi-structured interviews were then conducted with patients alone, or accompanied by their spouse, to collect their opinions on the implementation of a PA program focused on NET patients. Questions explored the patients’ interest in the program, the potential benefits and challenges perceived, as well as practical considerations for implementation. Interviews were transcribed verbatim and analyzed following principles of grounded theory.

**Results**

A total of thirteen patients and four spouses were interviewed, with an average interview length of 64.5 minutes. The creation of a PA program was supported by 85% of the patients, who believed this resource could be an interesting source of information for NET patients, and could provide them with moral support, as well as a meaningful social network. Participants suggested that the possibility of being paired with a PA should be introduced at the moment of diagnosis, but the timing of the initial contact should be left to the patient’s discretion. Patients should also be referred to a PA whose trajectory of care is as similar to theirs as possible. Anticipated challenges included incompatible personalities, discomfort and logistical considerations such as time and transport.

**Conclusion**

The implementation of a PA program would be positively received by NET patients. Envisioned benefits included access to experiential knowledge as a source of information, provision of moral support and creation of a social network, which could possibly address current unmet needs. Further studies are needed to implement this program.
Invasive approach to disease monitoring and treatment response assessment in a variety of cancers (1,2). Consequently, in GEP-NETs, ctDNA could have the potential to guide management and reduce the burden of disease monitoring for patients. However, the feasibility of measuring ctDNA in patients with GEP-NETs has not yet been assessed.

Methods
Whole exome sequencing was conducted on tumor samples and matched normal whole blood samples from patients with metastatic well-differentiated grade 1-2 GEP NETs. Patient-specific clonal somatic mutations were used to build personalized tumor-informed multiplex PCR assays, which were used to assess ctDNA by next generation sequencing of plasma samples. Patients were included if measurable disease by RECIST was present on scans and primary tumor specimen was also available for analysis. Patient and tumor characteristics were then compiled through chart review.

Results
Between 2020 and 2022, plasma ctDNA was measured for 15 patients. ctDNA was detected in 60% of patients (9/15), with levels ranging from 0.05 to 214.8 MT/mL of plasma. Longitudinal ctDNA measurements were obtained in 2 patients with negative baseline ctDNA, both of which remained negative. Of the 15 total patients, 12 out of 15 had stable or responding disease at time of testing. Two out the 3 patients with progressive disease, had negative ctDNA. Additionally, 67% of the patients with detectable ctDNA (10/15) had metastatic disease involving >25% of the liver or other features of bulky disease (3).

Conclusion
ctDNA can be detectable in patients with metastatic GEP-NETs. Further studies are needed to determine the role of ctDNA in treatment response monitoring and surveillance of these patients.

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variants are more common in Non-Caucasian Patients with Neuroendocrine Neoplasms (NENs)

variants occur in approximately 10% of NEN patients with recent data suggesting a higher frequency in pancreatic NENs or paraganglioma/pheochromocytoma (PPGL). However, identification of VUS can complicate interpretation of germline results, particularly when diverse populations are under study and the optimal gene panel size for testing remains unclear.

Methods
A single-center retrospective chart review was performed in consecutive NEN patients referred for possible germline testing at UCSF. Information was collected on demographics and tumor characteristics (site of origin, differentiation). If germline testing was performed, gene panel size and test results were recorded (P/LP, negative, or VUS).

Results
435 NEN patients were referred for a discussion of germline testing at UCSF between 2004-2022. 64% of referred patients (n=277) proceeded with genetic counseling; 239) of these patients underwent germline testing which included reporting of VUS. The test population was 53% (n=128) female; 11% (n=27) Hispanic; 73% White (n=175), 12% Asian (n=29), 3% African American (n=7), 2% American Indian/Alaska origin and Native Hawaiian (n=4), 3% Mixed race (n=8) and 7% Unknown race (n=16). Tumors included well-differentiated (WD) neuroendocrine tumors (NET) in 72% (n=173), 12% Asian (n=29), 3% African American (n=7), 2% American Indian/Alaska origin and Native Hawaiian (n=4), 3% Mixed race (n=8) and 7% Unknown race (n=16). Tumors included well-differentiated (WD) neuroendocrine tumors (NET) in 72% (n=173), 8.3% (n=20) poorly differentiated neuroendocrine carcinoma (NEC), 5.4% unknown differentiation (n=13), plus 13.8% PPGL (n=34). Overall, 25% (n=48) of tested patients harbored a P/LP mutation variant, 33.2% (n=79) had a negative result and report was missing in 2 cases. 46% (n=110) had at least one VUS identified, with Hispanics significantly more likely to harbor a VUS compared to non-Hispanics- 77% (n=21/27) vs 42% (n=88/207) [OR 4.73, 110)
Leveraging Transcriptomics to Grade Pancreatic Neuroendocrine Neoplasms (NENs) and Assess Molecular Alterations Associated With Somatostatin Receptor (SSTR) Subtype Expression

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Background

SSTR subtypes are collectively expressed in the majority of NENs. However, SSTR subtype expression is not routinely assessed for clinical decision-making.

Methods

A total of 55 patients with PanNENs were evaluated. Median age was 56.1 years, 49.1% were male, 87.3% were white. Most patients (69%) had pancreatic primary and 18% had a small bowel primary. Most patients (96%) had well-differentiated NEN. Thirty-four (61.8%) patients had metastatic disease at presentation. Family history of cancer, ethnicity, or age.

Results

We undertook a prospective study of germline genetic testing using a > 80 gene next-generation sequencing panel among PanNEN patients receiving care at Mayo Clinic Cancer Center (3 sites) between April 1, 2018, and June 20, 2022. Patients were not selected based on cancer stage, family history of cancer, ethnicity, or age.

Conclusion

A total of 55 patients with PanNENs were evaluated. Median age was 56.1 years, 49.1% were male, 87.3% were white. Most patients (69%) had pancreatic primary and 18% had a small bowel primary. Most patients (96%) had well-differentiated NEN. Thirty-four (61.8%) patients had metastatic disease at presentation. Family history of cancer, ethnicity, or age.
9% of patients which highlights the importance of germline testing for familial counseling and treatment selection.

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011
Pheo Para Alliance Patient Centered Research on Challenges for Those with Pheochromocytoma and Paraganglioma
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Background
Patients with pheochromocytoma/paraganglioma (PPGL) often face difficulties in obtaining timely and accurate diagnosis, as well as in accessing experienced specialists. However, little is known about the experiences of patients in obtaining effective care.

Methods
To address this gap and give voice to the patients, we invited potential participants, through social media, email, and the PheoPara Alliance (PPA) website, to complete a 20-min online survey. Survey of Challenges in Pheochromocytoma & Paraganglioma Experiences (SCOPPE).

Results
The respondents included 270 participants who were mostly female (80.8%), US residents (78.9%), from urban/suburban areas (57.8%), generally well-educated (75.6% with at least some university) and self-identified as white (87.7%) with a median age of 52 years (SD = 14.2). Interestingly, 77.8% of respondents had clinical genetic testing performed, and of those, 60% had a known susceptibility gene pathogenic variant, with SDHB (48.4%) and SDHD (27%) being most common. Participants reported difficulties and delays in obtaining correct diagnosis and treatment. There was a median of 29 months (IQR 6-73.5) from their first symptom to diagnosis; 48.4% saw four or more health care professionals (HCP) before being diagnosed, and 49.3% received one or more initial misdiagnoses. Many reported lack of access to an experienced medical team (28.9%) and to relevant information (25.6%), as well as poor communication among specialists (28.9%). More knowledgeable HCPs, better access to experts and medical centers, and better medical team coordination were rated as “very” / “extremely” important by at least 75% of participants. Most would prefer to make decisions about their care in partnership with their medical team (73.5%). Participants reported inability to receive several recommended treatments, including surgery, PRRT, and MIBG. Approximately 23% had to travel more than 100 miles to be treated by a specialist.

Conclusion
Overall, delays, misdiagnoses, and treatment inaccessibility present significant risks to patients’ health. It is important for HCPs to be aware of, and act to alleviate, these important difficulties identified by our participants. As such, the PPA has developed a program to recognize Clinical Centers of Excellence (CCE) and Clinical and Research Centers of Excellence (CRCE) to provide clear information for patients on where to gain valuable multi-disciplinary expert care. The program is ongoing, and to date, 12 centers (10 US, 2 UK) have been approved.

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012
An Appraisal of Findings from a Neuroendocrine Neoplasm (NEN) Tumor Board (TB): Is There Added Value or Is It Redundant?
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Background
Subspecialty tumor boards (TB) are uncommon and their benefit has not been clearly demonstrated for patients and providers alike. We tried to determine the decision patterns of a newly minted neuroendocrine neoplasm (NEN) tumor board (TB) and the factors behind those.

Methods
We retrospectively reviewed all NEN TB recommendations from 07/2018 to 12/2021 and recorded patient characteristics, TB outcomes and associations between them.

Results
A total of 652 patient entries were identified. Median age of participants was 61 years and an equal number of men and women were presented. Most patients (33.4%) had tumors originating in the small bowel with 16.8% of high grade and 25.9% of pancreatic origin. Imaging was reviewed 97.2% of the time, with most frequently reviewed modalities being PET (55.3%) and CT (44.3%). Imaging review determined that there was no disease progression 20.8% of the time and significant treatment changes were recommended in 36.1% of patients. Major pathology amendments occurred in 3.7% of cases and a clinical trial was identified 5.1% of the time. There was no association between patient or disease presentation with the tumor board outcomes. There was a slight decrease in number of patients discussed per session, from 10.0 to 8.2 (P < 0.001) when the TB transitioned to a virtual format during the COVID-19 pandemic but all other factors remained unchanged.

Conclusion
NEN TB relies heavily on image review, can impact significant treatment changes in patients with rare tumors like NENs, and was not affected by the switch to a virtual format. Finally, none of the examined factors were predictive of the tumor board recommendations.

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Trials In Progress
Phase 1a/Ib Study of BAY1895344 Plus Topoisomerase I Inhibitors with a Focus on Poorly Differentiated Neuroendocrine Carcinomas and Pancreatic Adenocarcinoma

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Background

Advanced small cell lung cancer (SCLC), extra-pulmonary neuroendocrine carcinoma (EP-NEC) and pancreatic adenocarcinoma (PDA) are rapidly progressive cancers characterized by unbridled replication stress. Patients with these malignancies possess dismal prognoses with limited options after initial first-line chemotherapy. These tumors rely on the integrity of DNA damage repair pathways to ensure genomic stability. The ataxia telangiectasia and Rad3-related (ATR) protein kinase is a potential therapeutic target in these cancers and is activated by replication stress. The ATR inhibitor BAY 1895344 has demonstrated cytotoxic potential in SCLC and gastrointestinal cancer xenografts in combination with the topoisomerase I (TopI) inhibitors topotecan and irinotecan. We developed a phase I study combining BAY 1895344 with irinotecan or topotecan.

Methods

NCT04514497 is a phase Ia/Ib study with 3 dose escalation cohorts (irinotecan IV D1 plus BAY 1895344 PO BID D1, D2 Q4 days; irinotecan IV D1,8,15 plus BAY 1895344 QD D1-D3, D8-10 and D15-17 Q21 days; topotecan IV D1-D5 plus BAY 1895344 PO QD D2, D5 Q21 days) and 3 dose expansion cohorts. Primary objectives are to assess safety and tolerability and estimate the maximum tolerated dose and recommended phase 2 dose of the combinations. Secondary objectives include estimating pharmacokinetic profiles and assessing anti-tumor activity of the combinations. In dose escalation, patients with refractory advanced solid tumors for whom TopI inhibitors are considered SOC (small cell histology mandated) or PDA. Dose escalation will utilize a 3+3 design. Biopsies for pharmacodynamic DNA damage biomarker assessment are required in dose expansion. The tissue-based correlative studies are outlined in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Phase of Study</th>
<th>Time of Collection</th>
<th>Purpose</th>
<th>Mandatory (M)/Optional (O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>γH2AX, pH2B51</td>
<td>Dose Expansion, Archival</td>
<td>D-7 to D10</td>
<td>Measure DNA damage biomarkers</td>
<td>M</td>
</tr>
<tr>
<td>Whole Exome Sequencing, RNA Sequencing</td>
<td>Dose Expansion, Archival</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>ATM</td>
<td>Dose Expansion, Archival</td>
<td></td>
<td>Identify pla with has fad responsive to ATR inhibitor</td>
<td>O</td>
</tr>
</tbody>
</table>

Results

The trial is currently enrolling patients.

Conclusion

Anti-tumor activity has been observed with the ATR inhibitor berzosertib in combination with topotecan in patients with SCLC and EP-NEC. Based upon the potential best-in-class cytoreductive capacity of BAY 1895344 preclinically compared with other ATR inhibitors, we are hopeful that TopI inhibitors plus BAY 1895344 will represent safe and meaningful treatment options for patients with SCLC and EP-NEC which can be carried forward to more definitive efficacy-assessing studies.

Abstract ID: 21375

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COMPOSE: Pivotal Phase III Trial for Well-Differentiated Aggressive Grade 2/3 Gastroenteropancreatic Neuroendocrine Tumors Comparing 177Lu-edotreotide with Best Standard of Care

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Background

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), which frequently develop metastatic disease, represent an estimated 70% of NETs. There are limited treatment options with current standard therapies for well-differentiated aggressive grade 2 and grade 3 (Ki-67 index 15–55%) GEP-NETs; however, these may include somatostatin analogues; peptide receptor radionuclide therapy (PRRT); molecular targeted therapies (everolimus or sunitinib); chemotherapy; and cytoreductive procedures. PRRT, which uses radiolabeled somatostatin analogues to selectively target somatostatin receptor expressing tumor cells, may stabilize disease and induce objective tumor responses. The radiolabeled somatostatin analogue 177Lu-edotreotide has demonstrated promising efficacy and a favorable safety profile. Retrospective data in metastatic GEP-NETs treated with two or more 177Lu-edotreotide cycles demonstrated nearly 30 months progression free survival (PFS). COMPOSE (NCT04919226), a prospective, randomized, controlled, open-label, multi-center Phase III study, aims to extend therapeutic options for patients with well-differentiated aggressive grade 2 and grade 3, SSTR +, GEP-NETs.

Methods

COMPOSE evaluates efficacy, safety, and patient-reported outcomes of first- or second-line treatment with 177Lu-edotreotide PRRT. At least 202 patients with somatostatin receptor-positive (SSTR +) disease will be randomized 1:1 to up to six cycles of 177Lu-edotreotide, given at 6- to 8-week intervals, or to an active comparator (either chemotherapy [CAPTEM or POLUMA] or everolimus, according to investigators choice). PFS, the primary endpoint, will be assessed every 12 weeks until disease progression (RECIST v1.1) or death, whichever occurs earlier. Overall survival, assessed up to 2 years after disease progression, is a secondary outcome.

Results

COMPOSE recruitment commenced in September 2021 and currently includes 26 open sites in Australia, France, Italy, the Netherlands, Spain, Sweden, the United Kingdom, and the United States. More sites and countries will follow.

Conclusion

COMPOSE results are expected to inform about optimal treatment options for patients with well-differentiated aggressive grade 2 and grade 3 SSTR + GEP-NETs, including for first-line therapy.

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Phase 2 Study to Evaluate the Safety, Pharmacokinetics, and Dose Response of Paltusotine Carcinoid Syndrome

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Background

Neuroendocrine tumors (NETs) are classified as functional or non-functional based on the presence of characteristic symptoms, related to tumoral secretion of biologically active peptides or amines. Carcinoid Syndrome (CS) is the commonest functional NET syndrome, seen at diagnosis in 19% of patients. It is characterized in over 80% of cases by watery diarrhea (mainly due to serotonin hypersecretion) or cutaneous flushing. Somatostatin is a neuropeptide that inhibits the secretion of many hormones, including pituitary growth hormone and serotonin from functional NETs. While long-acting somatostatin receptor ligands (SRLs) are mainstay treatments for CS, relief of the symptoms at labeled doses is inadequate for many patients. Paltusotine is a novel oral, nonpeptide, selective
somatostatin receptor type 2 (SST2) agonist. It appears to be equally effective as long acting injectable SRLs in maintaining plasma IGF-1 levels in patients with acromegaly. Paltusotine was well tolerated in Phase 2 studies, with the most common adverse events (AEs) being headache, arthralgia, diarrhea, and abdominal pain.

Methods
This randomized, open-label, parallel-group, multi-center study will examine the safety, tolerability, pharmacokinetics, and exploratory efficacy of paltusotine in patients with CS. Patients with documented well-differentiated, grade 1 or II NETs with CS, who are either naïve to therapy with SRLs or have symptomatic control (bowel movement and flushing frequency) on SRLs, will be eligible to participate. The study includes a Screening Period of 2 weeks in patients naïve to SRLs and up to 12 weeks in patients washing out of SRLs. An electronic diary will be used to capture symptom frequency. Patients washing out of SRLs will be eligible for randomization when symptomatic worsening occurs during any 7-day period. After completion of screening, subjects will be randomly assigned to the 40 mg vs 90 mg daily open-label dose groups for 8 weeks. In addition to collection of safety data and serum paltusotine levels (to generate pharmacokinetic profiles in this patient population), a full suite of biomarkers and efficacy assessments will be explored for paltusotine in NETs. Following completion of the Randomized Treatment Phase, subjects may be eligible to enter the Open-Label Extension (OLE) Phase of the study in which they will receive paltusotine for an additional 50 weeks.

Results
Currently enrolling. NCT05361668

Conclusion
Phase 2 clinical study with paltusotine, a somatostatin agonist, in progress

T5
A Phase 2 Open-Label Study of Belzutifan (a HIF-2α Inhibitor) Monotherapy in Patients with Advanced/Metastatic Pancreatic Neuroendocrine Tumors
Camilo Jimenez1, Julián Haddou2, Jaydara Del Rivero3, Satya Das4, Othon Illopolous5, Alexander Sultanbaev2, Elena Artamonova6, Eric Janson7, Karel Pắcak8, Wei Wang9, Fan Jin10, Girish S. Naik9 & Jaume Capdevila10
1The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 2Gustave Roussy, Villejuif Cedex, France; 3Developmental Therapeutics Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; 4Vanderbilt University Medical Center, Nashville, TN, USA; 5Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; 6GBUZ Republican Clinical Oncological Dispensary, Ufa, Russia; 7Federal State Budgetary Institution N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Moscow, Russia; 8National Institutes of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA; 9Merck & Co., Inc., Rahway, NJ, USA; 10Vall Hebron University Hospital and Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain.

Background
Patients with advanced neuroendocrine carcinoma (PPGL) or pancreatic neuroendocrine tumor (panNET) are in need of novel targeted therapies. Hypoxia-inducible factor 2α (HIF-2α) is one of the key oncogenic drivers in neuroendocrine tumors. Hypoxia signaling pathway alterations or other mechanisms that stabilize HIFs are common in some PPGLs and panNETs. Belzutifan (MK-6482), a HIF-2α inhibitor, has shown antitumor activity in advanced renal cell carcinoma and localized von Hippel-Lindau (VHL) disease-associated tumors, including panNETs. The current phase 2 study (NCT04924075) will evaluate the efficacy and safety of belzutifan in patients with advanced PPGLs or panNETs.

Methods
This open-label, multicenter, single-arm, phase 2 study is enrolling patients aged ≥12 years (body weight ≥40 kg if aged 12–17 years) with histopathologically documented, unresectable, locally advanced/metastatic PPGLs (BP ≤150/90 mmHg, ≤135/85 mmHg if adolescent)) (cohort A1) or histopathologically documented, advanced/metastatic well-differentiated G1/G2 (2017 WHO criteria) panNETs with progression on prior targeted therapy (cohort A2). Other eligibility criteria include progressive disease (PD) ≥12 months from screening, measurable disease per RECIST v1.1 by blinded independent central review (BICR), ECOG PS ≤1, and archival/new tumor sample for biomarker analysis. Approximately 140 patients (70/cohort) will be enrolled and receive belzutifan 120 mg once daily until PD or unacceptable toxicity. Tumor imaging occurs initially at week 9, then every 8 weeks through week 49, and every 12 weeks thereafter. The primary study endpoint is objective response rate per RECIST v1.1 by BICR. Secondary endpoints are duration of response, time to treatment response, disease control rate, progression-free survival, overall survival, and safety. Enrollment began in August 2021, and is ongoing at 44 international sites.

Results
N/A

Conclusion
N/A

Abstract ID 21413

DOI: 10.1530/endoabs.89.T5

T6
ACTION-1: A Randomized Phase Ib/3 trial of RYZ101 Compared with SoC in SST2+ Well-Differentiated GEP-NET with Progression Following Lu-177 SSA
Thomas Hope1, Samuel Mehr2, Michael Morris3, Daneng Li4, Daniel Halperin, MD3, Jonathan Stroberg5, Helossa Soares5, Heather Jacene5, Marianne Pavel6, Pamela L. Kunz10, Denis Ferreira11, Joanne Li11, Kimberly Ma11, Jessica Rearden11, Susan Moran11 & Simon Singh11

Background
The NEC expansion cohort will seek to enroll 10 patients. If at least one objective response is observed, and safety is confirmed, the regimen will be considered for future study.

Endocrine Abstracts (2022) Vol 89
Background

Well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are commonly characterized by overexpression of somatostatin receptor subtype 2 (SSTR2), which can be targeted by radiopharmaceutical therapy (RPT) via radiolabeled somatostatin analogs (SSAs). RYZ101 (Ac-225 DOTATATE) is a first-in-class, highly potent alpha-emitting RPT being developed for the treatment of SSTR2+ solid tumors. Alpha-particles (such as emitted by Actinium-225) have a shorter path length (40–100 μm) and higher linear energy transfer (80–100 keV/μm) than beta-particles, potentially allowing for higher cancer cell kill rates and less damage to healthy tissues. ACTION-1 is a 2-part, global, randomized, controlled, open-label, Phase Ib/II trial of RYZ101. Part 1 (Phase Ib) will determine the safety, pharmacokinetics, and recommended Phase 3 dose (RP3D) of RYZ101. Part 2 (Phase II) will compare RYZ101 at the RP3D with standard of care (SoC) in patients with advanced SSTR2+ GEP-NETs with disease progression following prior Lu-177-labeled SSAs.

Methods

Adults with grade 1–2, well-differentiated, inoperable, advanced SSTR2+ GEP-NETs that have progressed (RECIST v1.1) following 2–4 cycles of therapy with Lu-177 SSA are eligible. Patients unresponsive to prior Lu-177 SSA (disease control <3 months after last dose of Lu-177 SSA) are excluded. Patients must have an ECOG status 0–2 and adequate hematologic and renal function. Part 1 is an uncontrolled dose de-escalation study based on Bayesian optimal interval design (de-escalation will occur if DLT incidence estimated >25%). RYZ101 is administered intravenously every 4 weeks for up to 4 cycles. Dose levels (reduction in level planned): Level 0 (starting dose), 120 kBq/kg (3.2 μCi/kg); if necessary, Level –1, 90 kBq/kg (2.4 μCi/kg); Level –2, 60 kBq/kg (1.6 μCi/kg). In Part 2, ~210 patients will be randomized (1:1) to receive RYZ101 RP3D every 4 weeks for up to 4 cycles or investigator’s choice SoC (octracetate LAR 30mg intramuscular or lanreotide ATG 120mg SC, Q4W). CAM2029 self-carer administration is allowed after ≥3 successful supervised administrations. Randomization stratified by: histological grade, tumor origin, intended comparator. Primary outcome: progression-free survival (PFS); time from randomization to date of first documented disease progression (RECIST 1.1) or death, assessed by a Blinded Independent Review Committee. The study is intended to power a hazard ratio of 0.65. Key secondary outcomes: overall survival; response rate; rescue medication use; patient satisfaction; adverse events. After primary PFS analysis, patient overall survival will be followed for up to 2 years. If CAM2029 displays superiority in the primary analysis, the comparator group may switch to CAM2029 20mg Q2W. Patients in any treatment group experiencing progressive disease in the randomized part of the study may proceed to an open-label extension with intensified CAM2029 treatment, to investigate effects of higher frequency dosing. First patient randomized in Nov 2021, with readout (following 194 events) expected by 2024 end. This novel head-to-head superiority trial is anticipated to demonstrate the potential benefits of CAM2029 as a first-line therapy in patients with well-differentiated GEP-NET. Results

Patient enrollment began Nov 2021; readout expected by end of 2024.

Conclusion


Abstract ID 21419

DOI: 10.1530/endoabs.89.T7

T8

Phase II Trial Evaluating [177Lu]Lu-DOTA-TATE in Adolescents with Somatostatin Receptor (SSTR)-positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs), Pheochromocytomas and Paragangliomas (PGLs)

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Background

GEP-NETs and PGLs in pediatric patients are rare; however, recognition of these diseases has increased recently. 10–20% of pediatric patients with GEP-NETs and up to 47% of pediatric patients with PGLs present with metastatic disease at diagnosis. The disease is often unresectable with poor prognosis, and very few non-surgical therapies are approved for these patients. Due to paucity of data surrounding treatments for pediatric patients with advanced GEP-NETs and PGLs, there are high unmet needs in this population. SSTR subtype-2 is overexpressed by GEP-NET and PGL tumors; therefore, it is a relevant target for radioligand therapy with [177Lu]Lu-DOTA-TATE. [177Lu]Lu-DOTA-TATE is approved in the United States for adult patients with SSTR-positive GEP-NETs. It has demonstrated efficacy and an acceptable safety profile in several studies evaluating adult patients, but clinical data for use in pediatric GEP-NETs and PGLs are limited. The need for additional treatment options for adolescents with GEP-NETs and PGLs provides a strong rationale to evaluate [177Lu]Lu-DOTA-TATE in these patients.
Eligible patients will receive 4 cycles of [177Lu]Lu-DOTA-TATE (7.4 differentiates) in the primary cohort and PPGLs in the exploratory cohort. Patients aged 18 years old with advanced, inoperable, SSTR-positive GEP-NETs (grade 1/2, well-differentiated) in the primary cohort and PPGLs in the exploratory cohort. Safety assessments will be performed regularly after each cycle and during follow-up. Primary endpoints are target organ absorbed radiation dose and incidence of adverse events (AEs) after the first cycle. Secondary endpoints are AE incidence within 6 months (short-term follow-up) and 5 years (long-term follow-up) after last dose, PK and dosimetry vs 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 (NCT04711135) will enroll ≥58 patients with GEP-NETs and as many patients with PPGLs as possible across sites in the United States (Iowa, Kentucky, Ohio, Pennsylvania, and Texas), Canada, and Europe. Due to the rarity of these diseases, patient referrals will be highly important.

Results
Study recruiting.

Conclusion
Study recruiting.

Abstract ID 21423
DOI: 10.1530/endoabs.89.T8

T9
PRecedeNET Trial: Phase III Randomised Controlled Trial of PRRT with Lutetium – 177 DOTATATE Plus Chemotherapy vs PRRT Alone in FDG-avid, Well-Differentiated Gastro-Entero-Pancreatic Neuroendocrine Tumors

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Background
Well-differentiated GEP NETs show positive uptake on Ga-68-DOTATOC PET/CT, a somatostatin-receptor (SSTR)-specific imaging tracer. 18F-FDG PET/CT is preferred for aggressive, high-grade NETs as GLUT (glucose-transporter) receptor expression entails poorer prognosis. Grade 2 NET may demonstrate heterogeneous uptake of both tracers; suggestive of tumor heterogeneity. PRRT is widely available at reasonable cost since Lu-177-DOTATATE is manufactured indigenously, and is recommended in all International Guidelines. CAPTEM (Capetibinic-Temozolamide) regimen is equally cost-effective; hence combination treatment would be reasonable. We propose to prospectively study combination of PRRT and chemotherapy vs PRRT alone in FDG-avid well-differentiated NETs, to generate robust evidence to address tumor heterogeneity.

Methods
This is a 2-arm, parallel design, open label, superiority, phase 3 randomized controlled trial, with 1:1 randomisation. Arm A being PRRT with Lu-177-DOTATATE, 180-200 mCi administered intravenously for 4 cycles, at interval duration of 6-8 weeks and Arm B being PRRT with Lu-177-DOTATATE, 180-200 mCi administered intravenously for 4 cycles, at interval duration of 6-8 weeks plus CAP-TEM Protocol: Day 1: Oral Capetibine 1500 mg/m2, per oral, twice daily within 15 min of food for 14 days, followed by 2 week rest period. One week before every cycle - Hematological, liver function, renal function and quality of life parameters shall be assessed. Immediately after PRRT and on day 15, hematological, liver function parameters will be assessed. At each visit history, physical examination and adverse events (CTCAE version 4.03) would be noted. Primary End-points of the study are Progression-free survival and Objective Response Rate on RECIST 1.1 and EORTC criteria. Secondary End-points being Quality of Life parameters and Overall Survival.

Results
Based on the NETTER-1 trial, we assumed that PRRT will give a 2 year PFS of 60%, the experimental arm will improve the 2 year PFS by an absolute value of 15%. With a type 1 error (one-sided) of 5% and Type 2 error of 20 %, with 10% lost to follow up, with study duration of 8 years, sample size of 162 patients, with 95 events required for analysis. For any statistical test performed, significance level will be set to 5%. The study period is 6 years and follow-up period is 2 years.

Conclusion
Based on the hypothesis, that combination therapy is more efficacious than PRRT alone, this study shall provide a reliable conclusion with regards to the superiority between both the arms.

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T10
Pilot Study of TQ Formula in Combination with Nivolumab and Ipilimumab in Metastatic Gastroenteropancreatic Neuroendocrine Carcinomas (GEP-NECAs)

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Background
TQ Formula (TQ, C10H12O2), is an oral formulation, derived from the black seed (Nigella sativa, Ranunculaceae family), and has anti-oxidant, anti-angiogenic effects. TQ Formula has been shown to induce significant immune modulatory effects in a recently published Covid-19 study. Previous studies reported blackseed’s apoptotic and anti-proliferative effects of its components on multiple cancer types, including colon, breast and ovarian adenocarcinoma. Our preliminary results in high grades neuroendocrine carcinoma (NEC) cell lines (NEC-T2) indicate that TQ Formula plus Immune checkpoint inhibitors (ICIs) can suppress cell growth and induce apoptosis through suppression of commons driver pathways. Additionally, TQ Formula synergized with ICIs leading to significantly enhanced cell kill in NEC cellular models. Clinically, in a case report of three subjects with NEC of GEP origin administered TQ Formula derived black seed capsules with dual ICIs (nivolumab plus ipilimumab) showed improved response rate of 100%, with two years median progression free survival without additional toxicities. Based on our preliminary data, this pilot study is in progress to evaluate the anti-tumor efficacy of this novel combined regimen (TQ plus nivolumab and ipilimumab) in the second line setting for metastatic GEP-NEC.

Methods
The study is a single-arm clinical trial to investigate the synergistic anti-angiogenic and apoptotic effect of combined TQ Formula plus dual ICPIs in a small pilot study of 10 patients with metastatic high grade GEP-NECs refractory to first-line chemotherapy. All patients will receive TQ Formula (oral capsules), three 500mg tabs (1500mg) BID daily, plus triweekly ICPIs (intravenous nivolumab 240 mg and Ipilimumab 1 mg/kg) for 4 cycles then resume TQ Formula with the same daily dose with maintenance biweekly nivolumab to complete a total of 6 months treatment. Primary end point of the study is to determine the antitumor activity of TQ Formula plus nivolumab and ipilimumab in subjects with metastatic GEP-NECs who progressed on first line therapy. Secondary endpoints include time to progression (TTP) and safety profile using this combined regimen. Predictive biomarkers include MMR status, and TMB level, PDL-1 expression, and angiogenesis profile (VEGFR1, VEGFR2, CD34, POF and microvascular density) for association with clinical benefit. The final analysis will be performed to assess efficacy after 10 patients become evaluable.

Clinicaltrials.gov: NCT05262556.

Results
NA

Conclusion
NA

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