Endocrine Abstracts

October 2022 Volume 89
ISSN 1479-6848 (online)

North American Neuroendocrine Tumor Society 2022

NANETS
NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

published by
bioscientifica

Online version available at
www.endocrine-abstracts.org

Endocrine Abstracts

Volume 89
October 2022

Abstracts Presented at the 15th Annual Multidisciplinary NET Medical Symposium of the North American Neuroendocrine Tumor Society

October 27–29, 2022, Washington, DC

Corresponding Author:
Kathleen Van De Loo
NANETS
136 Everett Road
Albany, NY 12205
Phone: 650-762-6387
staff@nanets.net

CONTENTS

15th Annual Multidisciplinary NET Medical Symposium NANETS 2022

Basic Science

B1

Single-Cell ATAC and Single-Nucleus RNA Sequencing Uncovers Cellular Heterogeneity Within Pancreatic Neuroendocrine Tumors

Shreya Rajhans[1], Ethan Mondell[1], James Madigan[3], Nhi Truongvo[1], Li Wang[1], Michael Kelly[2], Samira M. Sadowski[3] & H. Efsun Arda[1]
[1]Laboratory of Receptor Biology and Gene Expression, Center for Cancer Research, National Cancer Institute; [2]Single-Cell Analysis Facility, Center for Cancer Research, National Cancer Institute; [3]Surgical Oncology Program, Center for Cancer Research, National Cancer Institute.

Background
Pancreatic neuroendocrine tumors (PNETs) are a rare, understudied form of cancer with few curative options, and their occurrence is rising. With approximately 4,000 new cases diagnosed per year in the US, and a 5-year relative survival rate of 54%, it's imperative to understand the molecular mechanisms governing PNET carcinogenesis. To date, most studies used whole-tumor sequencing to characterize PNETs, 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 transcriptomes of single cells obtained from resected tumors.
Methods
Assay 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 nuclei 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 multiomics 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 PNETs, 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 pancreas 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 of PNET progression are unknown and there is little known about intra-PNET heterogeneity. The current targeted therapy approved for metastatic PNETs is Lu177-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.
Abstract ID 21437
DOI: 10.1530/endoabs.89.B1

B2

Multiple Layers of Epigenetic Regulation Cooperate to Silence Expression of Somatostatin Receptor Type 2 in Pancreatic Neuroendocrine Tumors

James P. Madigan[1], Rupali Sharma[1], Ethan Mondell[2] & Samira M. Sadowski[1]
[1]Surgical Oncology Program, Center for Cancer Research, National Cancer Institute, NIH; [2]Laboratory of Receptor Biology and Gene Expression, Center for Cancer Research, National Cancer Institute, NIH.

Background
Pancreatic neuroendocrine tumors (P-NETs) are a rare cancer with increasing incidences worldwide. Low-grade P-NETs are unique in that they express high levels of Somatostatin Receptor Type 2 (SSTR2), which represents a target for both tumor imaging and therapeutics. P-NET grade inversely correlates with SSTR2 tumor staining, and higher tumor grade is associated with poor patient prognosis. Unfortunately, application of SSTR2-targeted treatment options is currently limited in high-grade P-NETs, due to loss of SSTR2 expression. Beyond understudied promoter CpG DNA methylation and nebulous histone deacetylation events, little is known regarding the full scale of actual epigenetic events that conspire to negatively control SSTR2 expression. The goal of our ongoing studies is to obtain a comprehensive understanding, at the molecular level, of the epigenetic events and players which control SSTR2 expression.
Methods
Two high-grade P-NET cell lines, BON1 and QGP1 (both with low SSTR2 expression), and one low-grade P-NET cell line, NT-3 (high SSTR2 expression), were employed in our studies. Both small molecule inhibitors/drugs and validated shRNA, targeting various epigenetic enzymes, were utilized in functional assays to determine their potential effects on SSTR2 expression. Western blot analysis was used to gauge potential increased expression of SSTR2, along with changes in global expression levels of selected epigenetic marks. Chromatin immunoprecipitation (ChIP) was used to measure levels of specific histone-based epigenetic marks located on the SSTR2 gene promoter. Bisulfite Next-Generation Sequencing was employed to determine, both qualitatively and quantitatively, levels of CpG methylation in SSTR2 gene regulatory elements.
Results
We have demonstrated that DNMT3B is the sole DNA methyltransferase responsible for silencing SSTR2 expression in P-NETs. Additionally, we identified Class I HDACs as the main histone deacetylases important for SSTR2 expression regulation. Furthermore, we discovered that Polycomb Repressor Complexes 1 and 2 (PRC-1 and PRC-2) are central to SSTR2 silencing. Removal of activating histone H3K4 methylation marks is an additional mechanism for silencing SSTR2 expression. Finally, we identified the chromatin remodeling enzyme, Lymphoid-Specific Helicase (LSH), likely in tandem with DNMT3B, as a negative regulator of SSTR2 expression in P-NETs.
Conclusions
Multiple inhibitory epigenetic mechanisms cooperate to silence expression of SSTR2 in P-NETs. Knowledge gained from our studies will assist in formulation of novel epigenetics-based intervention strategies, to increase expression of SSTR2, for improved imaging and therapeutic treatment of high-grade P-NETs.
Abstract ID 21438
DOI: 10.1530/endoabs.89.B2

B3

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

Eleonora Pelle[1], Mauro Cives[2], Elliot Medina[3], Charlotte C. Mason[3], Sebastian A. Snedal[4], Xiomar E. Bustos-Perez[4], Leticia Tordesillas[4], Miguel Gomez Fontela[4], Renata A. Marques Rossetti[4], Gabriele Maiorano[5], Vince Luca[3], Patrick Hwu[6], Daniel Abate-Daga[7] & Jonathan Strosberg[1]
[1]Department of GI Oncology, Moffitt Cancer Center, Tampa, Florida, USA; [2]Department of Interdisciplinary Medicine, University of Bari Aldo Moro, Bari, Italy; [3]Department of Drug Discovery, Moffitt Cancer Center, Tampa, Florida, USA; [4]Departments of Immunology, Moffitt Cancer Center, Tampa, Florida, USA; [5]Institute of Nanotechnology NANOTEC, National Research Council, Lecce, Italy; [6]Moffitt Cancer Center, Tampa, Florida, USA; [7]Departments of Immunology and Cutaneous Oncology, Moffitt Cancer Center, Tampa, Florida, USA.

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-cells 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 (pAcGP67a) designed for protein expression in insect cells using Baculovirus. Trichoplusia-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 SSTR2. CD3+ T cells isolated from the peripheral blood of healthy donors were co-incubated with 293T cells stably transduced to concurrently express SSTR2 and green fluorescent protein (GFP) in the absence or presence of the BiTE. The SSTR2- 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 synapsis.
Abstract ID 21446
DOI: 10.1530/endoabs.89.B3

B4

Simultaneous Inhibition of DNA Methylation and Histone De-acetylation for Enhanced SSTR2 Expression In Vitro

Jason Whitt[1], Hailey Houson[2], Rachael Guenter[1], Madisen Murphy[1], Suzanne Lapi[2] & Renata Jaskula-Sztul[1]
[1]Department of Breast and Endocrine Surgery, University of Alabama at Birmingham, Birmingham, AL 35233, USA; [2]Department of Radiology, University of Alabama at Birmingham, Birmingham, AL 35233, USA.

Background
Neuroendocrine tumor (NET) patients with diminished SSTR2 expre-ssion 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 his-tone de-acetylation enhanced SSTR2 expression and *in vitro* binding of [^{68}Ga]DOTATATE. Our **hypothesis** is that epigenetic modifiers with different mechanisms of action, have superior effect in upregulation of SSTR2 when comparing 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 was used to determine the IC50. After a 48h incubation with subtoxic concentrations of either single drug or a combination, mRNA expression levels of SSTR2 were measured by quantitative real-time PCR. Following a 72h incubation with VPA, Decitabine, or a combination of both, cell lysates were collected, quantified, and Western blot analysis was performed to determine the effects of treatment on the protein expression of SSTR2. For functional SSTR2 analysis, DOTATATE was radiolabeled with ^{68}Ga and incubated with cells at a concentration of 10 nM for 2 h. After washing, cells were lysed and radioactivity was assessed using a gamma counter. Activity was normalized to protein content via BCA assay and expressed as percent added dose per mg protein (%ID/mg).
Results
We have shown that com-bination 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 WI-38 or the normal thyroid cell line Htori-3 showed an increase in [^{68}Ga]DOTATATE 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}Ga]DOTATATE binding comparing to either single drug. Furthermore, treatment of non-neuroendocrine cell lines exhibited no increase in radionuclide binding. The epigenetic upregulation of SSTR2 expression could improve the efficacy and toxicity profile for targeted radionuclide therapy of NETs with [^{177}Lu]DOTATATE.
Abstract ID 21460
DOI: 10.1530/endoabs.89.B4

B5

Oncolytic Seneca Valley Virus (SVV-001) Overcomes Checkpoint Inhibitor Resistance and Demonstrates a Systemic Anti-tumor Response in a Syngeneic Tumor Model

Paul L. Hallenbeck[1], Sunil Chada[1], Neil Sankar[1] & Aman Chauhan[2]
[1]Seneca Therapeutics, Inc., Blue Bell, PA; [2]Division of Medical Oncology, Department of Internal Medicine, Markey Cancer Center, University of Kentucky, Lexington, KY.

Background
Oncolytic viruses (OV) hold potential for not only delivering durable anti-tumor responses but also converting immunologically "cold" tumors to "hot" tumors. Seneca Valley Virus (SVV-001) is a naturally occurring oncolytic picornavirus found to have selectivity for tumor cells with neuroendocrine (NE) properties. Because of the paucity of syngeneic murine NE tumor models, we evaluated the efficacy of Seneca Valley Virus (SVV), in combination with checkpoint inhibitors (CPI) using the CPI-resistant Pan02 model that is permissive for SVV replication. SVV has been tested in three clinical trials of patients having neuroendocrine neoplasms as a single intravenous dose monotherapy. The results were encouraging with patients showing evidence of clinical benefit and only one reported DLT in the 76 patients treated.
Methods
SVV was injected intra-tumorally in established Pan02 tumors along with systemic injection of anti-PD-1 and/or anti-CTLA4 (CPIs). Naïve Pan02 tumors were injected on the contralateral side of animals showing tumor growth control or regression and growth of primary treated and untreated contralateral tumors monitored. Tumors were resected to evaluate immune cell infiltration via FACS analysis.
Results
SVV reversed resistance to CPIs and enhanced efficacy over CPI(s) alone resulting in complete cures in $>83\%$ of mice with primary and abscopal tumors. SVV plus aPD1 + aCTLA4 resulted in 5 of 6 mice cured of their primary tumor. The animals were challenged on their contralateral flank with naïve Pan02 tumor cells to evaluate systemic and abscopal immune effects. All mice (5/5) that cleared the primary Pan02 tumor also eradicated the abscopal secondary tumors. Control treated Pan02 tumor-bearing mice were all sacrificed due to tumor burden by day 70 (median survival <50 days). Control animals treated with aPD1 + aCTLA4 showed transient tumor regressions but these animals all grew large tumors, requiring sacrifice. In contrast, the SVV + aPD1 + aCTLA4 primary tumors were eliminated within 44 days and these animals remain tumor-free for >160 days. Contralateral tumors were eradicated in all 5 animals that rejected the primary tumor, demonstrating potent systemic immunity. SVV treatment showed marked increases in CD3+ and CD8+ T-cell infiltration of tumors with the combination of SVV + CPIs showing the highest infiltration.
Conclusions
These data show that SVV + CPI converted immunologically "cold" tumors to "hot" tumors. These studies serve as a foundation for translating SVV oncolytic virotherapy combined with anti-PD-1 and anti-CTLA4 antibodies in patients with neuroendocrine neoplasms with a clinical trial anticipated to begin in H2, 2022.
Abstract ID 21463
DOI: 10.1530/endoabs.89.B5

B6

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

Rachael Guenter[1], Maxwell Ducharme[2], Brendon Herring[1], Odalyz Montes[2], Tyler McCaw[1], Goo Lee[3], Deepti Dhall[3], Caroline MacVicar[1], Herbert Chen[1], Suzanne E. Lapi[2], Benjamin Larimer[2] & J. Bart Rose[1]
[1]Department of Surgery, University of Alabama at Birmingham, Birmingham, AL, USA; [2]Department of Radiology, University of Alabama at Birmingham, Birmingham, AL, USA; [3]Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA.

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 radionuclide-binding chelator 'DOTA' was covalently linked to a CALR-specific peptide 'KLGFFKR'. Then, the peptide [DOTA-Bn-SCN-$_{\beta}$AD$_{\beta}$A$_{\beta}$AKLGFFKR] was labeled with ^{68}Ga. Samples were analyzed on HPLC with an average radiolabeling efficiency of 93%. For *in vitro* radiopeptide uptake studies, pNET cells were treated with dantrolene for CALR induction and then incubated with 1 μM [^{68}Ga]DOTA-Bn-SCN-$_{\beta}$AD$_{\beta}$A$_{\beta}$AKLGFFKR for 1 hour. For the *in vivo* biodistribution study, BALB/c mice ($n=4$) were injected with ~3 MBq (5 μg) of radiopeptide 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 [^{68}Ga]-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 pNETs cells, where it can then be detected by a radiopeptide 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

DOI: 10.1530/endoabs.89.B6

B7

All-Trans Retinoic Acid Radiosensitizes Neuroendocrine Tumor Cells via Peptidyl-Prolyl Cis-Trans Isomerase 1 Inhibition

Jelani K. Williams, Jason L. Schwarz, Olga Lakiza, Stephen Kron, Ralph R Weichselbaum & Xavier M. Keutgen
University of Chicago Hospitals, Chicago, IL.

Background
Peptide receptor radionuclide therapy (PRRT) is a promising radiation-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 4Gy of radiation (IR) and either 50nM or 100nM of ATRA based on dose response curves. The poly (ADP-ribose) polymerase 1 inhibitor (PARPi) Talazoparib (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 ($P=0.0001$), 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 Talazoparib 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 cells 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

DOI: 10.1530/endoabs.89.B7

B8

CDK4/6-MEK Targeted Therapy Causes Regression and Reduced Metastatic Colonization of Pancreatic Neuroendocrine Tumors

Courtney Kaemmer[1], Shaikamjad Umesalma[1], Chandra Maharjan[1], Jordan Kohlmeyer[1], Emily Wilkerson[2], Ryan Sheehy[1], Mariah Leidinger[1], David Meyerholz[1], Sarah Bell[1], Gideon Zamba[1], Patrick Breheny[1], Edmund Lattime[3], Chandrikha Chandrasekharan[1], Andrew Bellizzi[1], Laura Herring[2], Lee Graves[2], Benjamin Darbro[1], Ziqiang Yuan[3], Steven Libutti[3] & Dawn Quelle[1]
[1]University of Iowa and Holden Comprehensive Cancer Center, [2]University of North Carolina, [3]Rutgers 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 oncogenic driver of pNET pathogenesis that acts through multiple oncogenic pathways. Kinome and phosphoproteome analyses of proliferating (RABL6A-positive) pNET cells, vs arrested (RABL6A-knockdown) controls, demonstrated that druggable 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 CD8 T cell and/or natural killer cell activation. This drug combination has not yet been evaluated in pNETs.
Methods
Synergistic effects of MEK inhibitor (Mirdametinib) 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$^{fl/fl}$;Pten$^{fl/fl}$* knockout mice that develop insulinoma by 5-6 months of age.
Results
Dual CDK4/6-MEK inhibitor therapy was highly synergistic *in vitro* 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$^{fl/fl}$;Pten$^{fl/fl}$* 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$^{fl/fl}$;Pten$^{fl/fl}$* 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 21475

DOI: 10.1530/endoabs.89.B8

B9

Deletion of Notch1 Signaling in Pancreatic Neuroendocrine Tumors Reduces Metastatic Properties

Weisheng Chen, Rachael Guenter, Brendon Herring, Renata Jaskula-Sztul, J. Bart Rose & Herbert Chen
Department of Surgery, University of Alabama at Birmingham, Birmingham, AL, USA.

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.

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 *Ascl1*, a gene repressed by Notch. RNAseq results showed an increase in expression of NE differentiation markers in Notch1-knock 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

Jason L. Schwarz[1], Jelani K. Williams[1], Olga Lakiza[1], Stephen J. Kron[2], Ralph R. Weichselbaum[3] & Xavier M. Keutgen[1]
[1]Endocrine and Neuroendocrine Surgery Research Program, Department of Surgery, University of Chicago Medicine; [2]Department of Molecular Genetics and Cell Biology, University of Chicago Medicine; [3]Department of Radiation Oncology and Cellular Biology, University of Chicago Medicine.

Background
The use of peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors (NETs) is increasing, but PRRT remains palliative at this time. Estrogen (E2) has been extensively linked to cellular proliferation and DNA repair in other cancers. Our aim is to determine whether NET cells are similarly affected by estrogen and whether inhibition of estrogen receptor alpha (ESR1) increases radiosensitivity of NET cells, which could improve PRRT response.
Methods
Proliferation assays of three NET cell lines including QGP1 (pancreatic), GOT1 (small bowel), and NCI-H727 (lung) were performed with and without E2. ESR1 expression was measured using RT-PCR and ESR1 knockdown was established with siRNA in QGP1 cells. Viability assays combining the ESR1-inhibitor, Fulvestrant, with and without radiation (IR) (4Gy) were done in QGP1 and GOT1 cells. RT-PCR was performed to measure mRNA levels of DNA repair genes including RAD51, BRCA1, and BRCA2 following ESR1 knockdown. Using a QGP1 mouse xenograft, 5 micrograms Fulvestrant was subcutaneously injected 3 times per week, followed by 20Gy of IR, and subsequent changes in tumor volumes and cumulative survival were recorded.
Results
The presence of E2 enhanced cellular proliferation, leading to significantly increased numbers of viable cells in QGP1 ($P<.001$, after 3 days of growth), GOT1 ($P<.001$, after 5 days), and NCI-H727 ($P<.001$, after 5 days) compared to those grown without E2. ESR1 mRNA levels varied across NET cell lines, with QGP1 expressing > 8-fold higher levels when compared to GOT1 and NCI-H727. Transient knockdown of ESR1 using siRNA significantly radiosensitized QGP1 cells ($P<.0001$). This effect was similarly observed in cells treated with Fulvestrant + IR compared to IR alone in QGP1 ($P<.001$) and GOT1 cells ($P<.05$). Following treatment of QGP1 with siESR1, RAD51 ($P<.001$), BRAC1 ($P<.001$), and BRCA2 ($P<.05$) mRNA levels decreased significantly, suggesting that ESR1 affects DNA repair gene transcription in NET cells. In a mouse xenograft model ($n=20$), treatment with Fulvestrant + IR resulted in slower tumor growth and significantly increased survival when compared to Fulvestrant or IR treated mice alone ($P<.001$).
Conclusions
Estrogen influences growth of multiple NET cell lines and inhibition of 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.
Abstract ID 21557

DOI: 10.1530/endoabs.89.B10

B11

Patient-Derived Organoids and Their Potential for Precision Medicine in Neuroendocrine Tumors

Briana N Cortez[1], Suresh Kumar[1], Yasuhiro Arakawa[1], Diana Varghese[1], Rosandra Kaplan[2], Karlyne Reilly[2], Brigitte Widemann[2], Jonathan M. Hernandez[3], Craig Thomas[4], Yves Pommier[1], Nitin Roper[1] & Jaydira Del Rivero[1]
[1]Developmental Therapeutics Branch, National Cancer Institute, NIH; [2]Pediatric Oncology Branch, National Cancer Institute, NIH; [3]Surgical Oncology Program, NIH; [4]National Cancer for Advancing Translational Sciences, NIH.

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 NCT05237934) aims to develop preclinical models, such as *in vitro* 3-dimentional 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), vistusertib (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 a grade 1 (Ki-67 <3%) small bowel NET. NET17 was derived from a 36-year-old female with grade 2 liver segment metastasis. NET 18 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 NETs but had a greater effect in NET16 (IC50 = 0.39 nM) than NET17 (IC50 = 43.17 nM) and NET18 (IC50 = 6.02 nM). Dovitinib and vistusertib were more potent in NET16 (dovitinib IC50 = 1.46 μM; vistusertib IC50 = 0.17 μM) than NET17 (dovitinib IC50 = 11.18 μM; vistusertib IC50 = 16.45 μM) and NET18 (dovitinib IC50 = 9.36 μM; vistusertib IC50 = 7.77 μM). Cobimetinib had modest activity in NET 17 (IC50 = 12.02 μM) and NET18 (IC50 = 13.39 μM).
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 Herring[1], Rachael Guenter[1], Deepti Dhall[2], Herbert Chen[1], Clayton Yates[3] & J. Bart Rose[1]
[1]University of Alabama at Birmingham Department of Surgery, [21]University of Alabama at Birmingham Department of Pathology, [3]Tuskegee University Department of Biology.

Background
There are known outcome disparities between Black and White patients with pancreatic neuroendocrine tumors (pNETs). Recently, Black patients were shown to have higher rates of lymph node metastasis in smaller tumors than White patients, indicating possible differences in tumor biology. Numerous prognostic gene expression differences between racial groups have been reported in other cancers, but no such analysis has been conducted in pNETs. This study evaluated pNET transcriptomes for differential expression that may be influencing racially disparate outcomes.
Methods
Quality control of formalin-fixed, paraffin-embedded pNETs specimens and demarcation of cancer cells were performed by a board-certified pathologist before laser microdissection and RNA isolation. Sequencing was performed on an Illumina NextSeq550 at 30 million reads/sample. GRCh38 transcriptome alignments were performed using Salmon and differentially expressed genes (DEG's) determined using DESeq2. Significance was determined by FDR-adjusted P-value (q-value; qv) < 0.05 and $\log_2$ fold-change ($\log_2$FC) $\geq \pm 2$. 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.
Results
RNA sequencing was conducted on 14 and 16 grade and sex-matched primary pNETs from self-identified Black and White patients, respectively. Mean age was 51 for Black and 56 for White patients. 11/16 (69%) of White and 9/14 (64%) of Black patients were female. 8 Black patients and 8 White patients had grade 1 tumors, while 6 Black patients and 8 White patients had grade 2 tumors. Metastatic disease was present in 4 Black and 5 White patients. Using White patients as the reference level, 372 genes and 179 gene sets were significantly differentially expressed. Notably, among the top 10 differentially expressed biological processes were: angiogenesis/-blood vessel and vasculature development (qv = 1.34e-07, normalized enrichment score [NES] = 1.89), positive regulation of cell migration and locomotion (qv = 1.34e-07, NES = 1.91), and humoral immune response (qv = 9.8e-07, NES = -2.06). Among the top 5 regulator effect networks identified by IPA were: angiogenesis of lesion/cell movement of monocytes (consistency score [CS] = 19.3), activation of blood cells (CS = 18.9), and activation of cells (CS = 17.9).
Conclusions
Numerous pathways related to blood vessel development and cellular migration, key elements of metastatic development, are significantly enriched in pNETs from Black patients. Additionally, pathways related to the immune response are downregulated in Black patients. These data indicate differences in tumor biology that may influence disparate outcomes reported in Black patients with pNETS. Additional samples and incorporation of genetic ancestry are necessary to validate these findings.
Abstract ID 21456

DOI: 10.1530/endoabs.89.B12

B13

Optical Genome Mapping: a Novel Approach to Identifying Structural Variants in Metastatic Neuroendocrine Tumors

Daniel M. DePietro, MD[1,2], Isabela Gatmaytan, BA[3], Stephan Hunt, MD, PhD[1,2,3], Gregory Nadolski, MD[1,2,3], Abashai Woodard[2], Michael Soulen, MD[1,2], Terence Gade, MD PhD[1,2,3] & Daniel Ackerman, PhD[2,3]
[1]Division of Interventional Radiology, Perelman School of Medicine at the University of Pennsylvania; [2]Department of Radiology, Perelman School of Medicine at the University of Pennsylvania; [3]Penn Image-Guided Intervention Lab, Perelman School of Medicine at the University of Pennsylvania.

Background
Genomic structural variants (SVs) encompass a large portion of mutations driving cancer progression, however, there is a paucity of data regarding such drivers in metastatic neuroendocrine tumor (mNET). Existing studies have focused on short-read sequencing of primary NET samples, which can detect single nucleotide variants, but are unable to identify larger SVs. Such studies have demonstrated a low rate of genetic mutations. Optical genome mapping (OGM) represents a novel method of identifying longer sequence mutations, copy number variants (CNVs), and SVs, which may be missed by short-read technologies. This proof-of-concept study evaluated the use of OGM in mNET biopsy samples.
Methods
Patients with hepatic mNET were enrolled in a prospective cohort study of the genetic profiling of NETs from June 2019 to March 2022. Image-guided biopsies were obtained from the dominant metastasis at the time of locoregional therapy. OGM was performed using the Bionano Saphyr chip (Bionano genomics, San Diego, CA, USA). SVs and CNVs were identified using Bionano statistical software. Genomic data was correlated with tumor grade and primary site and analyzed using descriptive statistics and the student's t test. The presence of chromothripsis, an inter-chromosomal translocation event accompanied by multiple CNV states, was evaluated for using shatterseek software.
Results
Sixteen mNET samples were analyzed: 10 of small bowel origin (63%), 3 of pancreatic origin (19%), 2 of rectal origin (12%), and 1 of lung origin (6%). Three were grade 3 (19%), 12 were grade 2 (75%), and 1 was grade 1 (6%). A mean of 48 $\pm$ 43 and median of 32 (range 14-186) SVs were identified per sample. On average, deletions accounted for 44% of variants, insertions for 21%, inversions for 2%, inter-chromosomal translocations for 15%, and intra-chromosomal translocations for 18%. The mean number of SVs for grade 3 tumors was 100 $\pm$ 79 compared to 38 $\pm$ 20 for grade 2 tumors ($P = 0.27$). The mean number of SVs for pancreatic mNETS was 113 $\pm$ 64 compared to 34 $\pm$ 20 for small bowel mNETs ($P = 0.13$). Potential chromothripsis events were identified in 3 of pancreatic mNETs and 2 small bowel mNETs.
Conclusions
OGM was able to identify 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.
Abstract ID 21477

DOI: 10.1530/endoabs.89.B13

B14

Pancreatic Mixed Acinar-Neuroendocrine Carcinoma: a Single Institutional Genomic Characterization Report

Manik Amin[1], Juliana Castellano[2], Donald Green[2] & Gregory Tsongalis[2]
[1]Department of Medical Oncology, Dartmouth Hitchcock Medical Center, Lebanon, NH; [2]Department of Pathology, Dartmouth Hitchcock Medical Center, Lebanon, NH.

Background
Pancreatic mixed acinar-neuroendocrine carcinomas are a rare distinctive entity with histologic and immunohistochemical features of pancreatic acinar cell carcinoma and pancreatic neuroendocrine tumor and pose diagnostic challenges. Very few cases have been described in the literature. Genomic information about these tumors remains unknown. We identified two cases of mixed acinar-neuroendocrine carcinoma from our database since January 2020 who had full genomic information available including germline and NGS assays.
Methods
Two patients were identified from the Dartmouth Pathology database since January 2020 with a biopsy proven diagnosis of pancreatic mixed acinar neuroendocrine carcinoma. Genomic characterization was done using the Illumina TruSight Tumor 170 (TST170) sequencing assay which detects gene variants across 170 gene targets in nucleic acids extracted from FFPE tissue samples. Sequencing was performed on the NexSeq 500 system which is designed to examine single nucleotide variants, small deletions, small insertions, amplifications, fusions and splice site variants across 170 genes.
Results
Two patients identified from the database had tumors in the head of the pancreas. Results are summarized in the table below.
Conclusions
Mixed acinar neuroendocrine carcinomas of the pancreas are very aggressive neoplasms. As usually seen in GEP NENs, our patient with a higher Ki 67 index had poor prognosis as compared to the patient with the G2 tumor. The NGS results of FGFR1-TACC fusion, BARd1 mutation has been documented in brain tumors and breast cancers respectively. Similarly, DDR2 mutation has been identified as one of the actionable mutations in squamous cell carcinoma of lungs. Significance of these mutations identified in this rare tumor is yet unknown. Our

Table 1 (Abstract B14). Histopathologic and NGS characteristics of pancreatic mixed acinar neuroendocrine carcinoma patients.

Age in years/-sex	Tumor site	Type of pathology	Pathology IHC identification	Ki 67	MMR	Other hereditary syndrome	Presentation	Treatment	NGS assay results	Patient status
66/M	Pancreatic head mass	EUS guided biopsy of pancreatic head	Tumor cells positive for trypsin, synaptophysin, chromogranin, INSM1 and CKAE1/3; negative for beta catenin (negative nuclear stain)	50%	Proficient	Germline Invitae did not show any actionable mutations but a variant of uncertain significance (VUS) in the DIS3L2 gene, specifically c.2605G>A (p.Glu869Lys), was detected	Metastatic to liver and regiuonal lymph nodes.	Poor ECOG PS. No treatment	FGFR1-TACC fusion, BARD1 insertion	expired
30/M	Pancreatic head mass	EUS guided biopsy of pancreatic head Whipple with Billroth II reconstruction	tumor cells positive for trypsin and synaptophysin and are negative for ISL1,	10%	proficient	Familial adenomatous polyposis (FAP)	Localized tumor. Final pathology stageing per AJCC: pT2N0	Resection and adjuvant chemotherapy with FOLFIRINOX	DDR2, APC, CSF1R, PTCH1 substitutions.	alive

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 21566

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

Luigi Scotto PhD[1,2], Maryam Safari PhD[1,2], Ping Hou[2], Tito Fojo, MD PhD[1,2] & Susan Bates MD[1,2]

[1]Columbia University, [2]James J. Peters VA Medical Center.

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 HADC 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.

Abstract ID 21574

DOI: 10.1530/endoabs.89.B15

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

Michael K. Schultz[1,2], Dijie Liu[2], Mengshi Li[2], Brianna S. Cagle[2], Zhiming Dai[2], Dongyoul Lee[2], Kelly Orcutt[2], Edwin Sagastume[2], Nicholas J. Baumhover[2], Ivy Vance[2], Amos Hedt[2], Yusuf Menda[1] & Frances L. Johnson[2]

[1]Department of Radiology, University of Iowa; [2]Viewpoint Molecular Targeting, Inc.

Background

Peptide-based targeted alpha-particle radiotherapy has emerged as a promising approach to cancer treatment. $^{203}Pb/^{212}Pb$ is the only elementally identical isotope pair for this application. Tyr^3-Octreotide (TOC) peptide ligands targeting SSTR2 have been widely investigated preclinically and clinically. [^{177}Lu]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 [$^{203/212}$Pb]PSC-PEG2-TOC in preclinical mouse model in comparison with [^{177}Lu]DOTATATE.

Methods

PSC-PEG2-TOC was radiolabeled with ^{203}Pb and ^{212}Pb by published methods[1, 2]. [^{177}Lu]DOTATATE was synthesized and radiolabeled using published methods[3]. Biodistributions were conducted in female athymic nu/nu mice bearing AR42J tumor xenografts following intravenous injection of 74 kBq of ^{203}Pb-labeled PSC-PEG2-TOC at 1, 3, 6 and 24 h post-injection (pi). Single or fractionated doses of [^{212}Pb]PSC-PEG2-TOC (total activity at 4.44 MBq) were administered to mice bearing AR42J tumors for efficacy evaluation. Administered fractionated doses of [^{177}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 ^{203}Pb at high specific activity (50-100 MBq/nmol). 24-h radiochemical purity and maintained near quantitative levels in excipients. *In vivo* biodistribution studies demonstrated high tumor uptake and rapid renal clearance for [^{203}Pb]PSC-PEG2-TOC. The administration of 4 fractionated doses of [^{212}Pb]PSC-PEG2-TOC produced 100% complete tumor responses at 100 days post therapy initiation and was well-tolerated compared to [^{177}Lu]DOTATATE, which produced improved PFS (28.5 days), but no complete responses.

Conclusions

These data demonstrate that [$^{203/212}$Pb]PSC-PEG2-TOC has the potential to produce a higher rate of objective tumor responses than beta-particle emitting therapeutics for NETs.

Abstract ID 21938

DOI: 10.1530/endoabs.89.B16

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

Simron Singh[1,2], Wieneke Buikhuisen[3], Jaume Capdevila[4], Martyn E Caplin[5], Christian Grohe[6], Dieter Hörsch[7], Markus Raderer[8], Diane Reidy-Lagunes[9], Edward M Wolin[10], Christelle Pommie[11], Xuan Mai Truong[11] & Eric Baudin[12]
[1]Division of Medical Oncology, University of Toronto; [2]Sunnybrook Odette Cancer Center, Sunnybrook HSC, Toronto, Ontario, Canada; [3]Department of Thorax Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands; [4]Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), IOB Quirón-Teknon, Barcelona, Spain; [5]Neuroendocrine Tumour Unit, Royal Free Hospital School of Medicine, London, UK; [6]Department of Respiratory Diseases, Evangelische Lungenklinik, Berlin, Germany; [7]ENETS Centre of Excellence, Zentralklinik Bad Berka GmbH, Bad Berka, Germany; [8]Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria; [9]Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical Center, New York, NY, USA; [10]Division of Hematology and Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [11]Ipsen, Boulogne-Billancourt, France; [12]Endocrine Oncology Unit, Gustave Roussy, Villejuif, France.

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. The adapted primary endpoint was centrally confirmed progression-free survival (PFS) during 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 Ishak 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 (Faivre 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 in the PBO arm (73%) who transitioned to OL-LAN. Over the DB + OL-LAN phase, median (95% CI) centrally assessed PFS based on RPSFT was 13.5 (11.0; not calculable [NC]) months for PBO and 16.6 (11.3; 21.9) months for LAN (HR [95% CI]: 0.78 [0.48; 1.52]; $P=0.601$). Data by NET subtype are shown in the table.
Median (95% CI) PFS (months)

	LAN (observed; DB + OL)	PBO (with RPSFT)	HR (95% CI)
All patients	16.6 (11.3; 21.9) [$n=50$]	13.5 (11.0; NC) [$n=26$]	0.78 (0.48; 1.52) $P=0.601$
TCs	21.9 (12.8; NC) [$n=28$]	13.9 (13.4; NC) [$n=16$]	–
ACs	13.8 (5.4; 16.6) [$n=22$]	11.0 (2.8; 16.9) [$n=10$]	–

Conclusions
The risk of disease progression or death was lower with LAN vs PBO in patients with advanced, well-differentiated bronchopulmonary NETs (HR = 0.78). However, despite adjusting for PBO crossover, the HR 95% CI included 1.00, reflecting the lack of statistical significance in this small sample. LAN may provide some clinical activity for TCs.
Abstract ID 21377

DOI: 10.1530/endoabs.89.C1

C2

Pembrolizumab for the Treatment of Recurrent High Grade Neuroendocrine Neoplasms

Lindsay A Hunter, MD[1,2], Jonathan Whisenant, MD[2] & G. Weldon Gilcrease, MD[1]
[1]Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; [2]Utah Cancer Specialists, Salt Lake City, UT.

Background
High-grade neuroendocrine neoplasms (HG-NENs) are a heterogenous and biologically aggressive rare subset of NENs. 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, Ki67 >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 NEBC had stable disease for 8.3 months. These findings are consistent with prior publications assessing pembrolizumab in metastatic grade 3 NENs.
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)

Callisia N. Clarke, MD, MS[1], Paul Cockrum, BSci, PharmD, RPh[2], Thomas J.R. Beveridge, MSc, PhD[2], Michelle Jerry, MS[3], Donna McMorrow, BS[3], Anh Thu Tran, PharmD[3] & Alexandria T. Phan, MD[4]
[1]Medical College of Wisconsin, Milwaukee, WI; [2]Ipsen Biopharmaceuticals, Basking Ridge, NJ; [3]Merative, Cambridge, MA; [4]Phan & Associates, Houston, TX.

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 Extrapulmonary Poorly Differentiated Neuroendocrine Carcinomas (PD NEC)

Nicole McLaughlin[1], Patrick McGarrah[2], Rachel Eiring[2], Konstantinos Leventakos[2], Mohamad Sonbol[3], Jason Starr[4], Timothy Hobday[2] & Thorvardur Halfdanarson[2]
[1]Internal Medicine, Mayo Clinic, Rochester, MN, USA; [2]Medical Oncology, Mayo Clinic, Rochester, MN, USA; [3]Hematology/Medical Oncology Department, Mayo Clinic Cancer Center, Phoenix, AZ, USA; [4]Oncology, Mayo Clinic, Jacksonville, FL, USA.

Background
Extrapulmonary 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-NR). The median PFS for the cisplatin group was 7.6 months (95% CI: 5.4-12.4) vs 4.1 months (95% CI: 2.8-6.6) for the carboplatin group (p value 0.04). The median OS for the cisplatin group was 17.3 months (95% CI 12.4-27.3) vs 11.6 months (95% CI: 9.1-26.5) in the carboplatin group (p value 0.17). DCR was 88% in the cisplatin group vs 63% in the carboplatin group (p value 0.0001). In univariate analysis, the differences in median OS and PFS were not statistically significant when accounting for age, creatinine, cell morphology, and male sex.

Table 1. Baseline Characteristics

	Cisplatin Group ($n=34$)	Carboplatin Group ($n=33$)	p value
Male, n (%)	21 (62%)	26 (79%)	0.13
Age, median (range)	59 (21-84)	66 (31-86)	0.01
Stage 3-4, n (%)	31 (91%)	33 (100%)	0.29
Site, n (%)	5 (15%)	2 (6%)	
Head & Neck	10 (29%)	5 (15%)	
Colorectal	6 (18%)	11 (33%)	
Other GI	4 (12%)	8 (24%)	
Unknown	4 (12%)	6 (18%)	
Pancreas	3 (9%)	1 (3%)	
Genitourinary	2 (6%)	0 (0%)	
Gynecologic			
Morphology, n (%)	7 (21%)	9 (27%)	
Large cell	12 (35%)	7 (21%)	
Small cell	15 (44%)	17 (52%)	
Nonspecified			
Ki67, median (range)	84 (30-99)	70 (35-90)	0.18
Creatinine, median (range)	0.9 (0.6-1.8)	0.9 (0.58-2.2)	0.44

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.
Abstract ID 21435

DOI: 10.1530/endoabs.89.C4

C5

c-MET Expression in MEN1-associated Neuroendocrine Tumors

Raisa Ghosh MD, Maya Lee BS, Rana Tora BS, James Welch MGC, CGC, Vaishali I, Parekh BS, Jaydira del Rivero MD, William F, Simonds MD, Lee Scott Weinstein MD, Jenny E, Blau MD, Sunita K, Agarwal Ph.D & Smita Jha MD
National Institutes of Health Bethesda, MD.

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 organ sources or different tumor types). Where available, we identified specimens from multiple source 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 ($n=3/4$), stomach ($n=1/1$), ovary ($n=1/1$), pancreas ($n=$ 1/5), and lymph nodes ($n=1/3$), 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.
Abstract ID 21443

DOI: 10.1530/endoabs.89.C5

C6

An Open-Label, Phase 1b/2 study of Surufatinib in Combination with Tislelizumab in Patients with Advanced Neuroendocrine Tumors

Jennifer R. Eads, MD[1], Satya Das, MD[2], Daneng Li, MD[3], Amr Mohamed, MD[4], Christopher Tucci, MBS, CCRP[5], Shivani Nanda, MS[5], John S. Kauh, MD, FACP[5], Marek K. Kania, MD, MBA[5] & Arvind Dasari, MD[6]
[1]Department of Medicine, University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA, USA; [2]MSCI, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; [3]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [4]Seidman Cancer Center, Case Western Reserve University, Cleveland, OH, USA; [5]HUTCHMED International Corporation, Florham Park, NJ, USA; [6]MD 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

receptor 1; and colony-stimulating factor 1 receptor. Tislelizumab is a humanized immunoglobulin G4-variant anti-programmed cell death protein-1 monoclonal antibody. Combining surufatinib and tislelizumab may have synergistic effects, where inhibition of angiogenesis and stimulation of an immune response may enhance overall antitumor activity compared to each agent alone.
Methods
This is an open-label, Phase 1b/2 dose escalation (ESC)/expansion (EXP) study (NCT04579757) to determine the recommended Phase 2 dose (RP2D) and/or the maximum tolerated dose for the combination of surufatinib and tislelizumab in patients with advanced solid tumors and to explore the preliminary antitumor activity of the combination. ESC used a 3+3 design at 2 surufatinib dose levels 250 mg and 300 mg once daily. In EXP, patients received surufatinib orally once daily at the RP2D and tislelizumab 200 mg intravenously every 3 weeks. Findings from 2 EXP cohorts of thoracic and gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are reported here.
Results
The surufatinib RP2D established in ESC was 300 mg once daily. Twenty-nine patients with NETs were enrolled in EXP (9 thoracic NET, 20 GEP NET). All patients had received prior anticancer treatment: 25 (86.2%) somatostatin analogs, 14 (48.3%) radionuclide therapy, 10 (34.5%) everolimus, and 2 (6.9%) sunitinib. No patient demonstrated a complete response. Partial responses were seen in 5 (17.2%) patients (2 small bowel and 1 each pancreas, lung, and unknown); and stable disease was seen in 10 (34.5%) patients. The objective response rate was 11.1% (95% confidence interval [CI]: 0.3, 48.2) for the thoracic NET cohort and 20.0% (95% CI: 5.7, 43.70) for the GEP NET cohort (including 1 unconfirmed partial response). All 29 (100.0%) patients reported at least 1 treatment emergent adverse event (TEAE); 20 (69.0%) patients reported TEAEs $\geq$ grade 3. The most common TEAEs of any grade were increased aspartate aminotransferase (AST) (51.7%), nausea and hypertension (44.8% each), decreased appetite and fatigue (41.4% each), and increased alanine aminotransferase (ALT) (34.5%). The most common $\geq$ grade 3 TEAEs were increased AST in 6 (20.7%) patients and increased ALT in 5 (17.2%) patients. The most common TEAEs leading to surufatinib dose reduction were increased AST and ALT in 2 (10%) patients each in the GEP NET cohort.
Conclusions
The combination of surufatinib and tislelizumab demonstrated antitumor activity in pretreated US patients with thoracic and GEP NETs with a manageable safety profile.
Abstract ID 21448

DOI: 10.1530/endoabs.89.C6

C7

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

Taymeyah Al-Toubah MPH, Eleonora Pelle MD & Jonathan Strosberg MD
H. Lee Moffitt Cancer Center and Research Institute, Department of GI Oncology.

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 NENs 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.
Abstract ID 21451

DOI: 10.1530/endoabs.89.C7

C8

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

Taymeyah Al-Toubah, MPH[1], Brian Morse, MD[2], Mintallah Haider, MD[1], Tiffany Valone, PA[1] & Jonathan Strosberg, MD[1]
[1]H. Lee Moffitt Cancer Center and Research Institute, Department of GI Oncology; [2]H. Lee Moffitt Cancer Center and Research Institute, Department of Diagnostic Imaging.

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%) (atypical 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.
Abstract ID 21453

DOI: 10.1530/endoabs.89.C8

C9

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

Patrick C Lee[1], Edik M Blais[2], Jun Gong[1], Arsen Osipov[1], Natalie Moshayedi[1], Shant Thomassian[1], Camille Ng[1], Jennifer Chuy[3], Lynn M Matrisian[4], Emanuel F Petricoin III[2], Michael J Pishvaian[5] & Andrew E Hendifar[1]
[1]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [2]Perthera, Inc, McLean, VA, USA; [3]NYU Langone Health, New York, NY; [4]The Pancreatic Cancer Action Network, Manhattan Beach, CA; [5]Johns Hopkins University, Baltimore, MD.

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 $MEN1^{mut}/DAXX^{wt}$ 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*-mutated/*DAXX*-wildtype subset; however, other PI3K/AKT/mTOR alterations were common across all *MEN1*-mutated cases.

PFS Strata ($n=25$)	Univariate Cox Significance (p)	Hazard Ratio (HR) [95% Conf. Interval]	Multivariate Cox Significance (p)	Hazard Ratio (HR) [95% Conf. Interval]
$MEN1^{mut}/DAXX^{wt}$ vs Other NGS Profiles	$P=0.0094$	HR=**0.16** [0.04-0.64]	$P=0.0097$	HR=**0.16** [0.04-0.64]
1st Line CAPTEM vs 2nd Line CAPTEM	$P=0.68$	HR=0.8 [0.27-2.34]	$P=0.86$	HR=0.91 [0.32-2.58]

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 21454

DOI: 10.1530/endoabs.89.C9

C10

ACTH-secreting Pancreatic Neuroendocrine Neoplasms: A Case-Series
Eleonora Pelle, MD[1], Taymeyah Al-Toubah, MPH[1], Julie Hallanger-Johnson, MD[2] & Jonathan Strosberg, MD[1]
[1]H. Lee Moffitt Cancer Center and Research Institute, Department of GI Oncology; [2]H. 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 NEN 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 systemic therapy were very poor. Median overall survival was 56 months from time of initial cancer diagnosis but only 18 months from diagnosis of Cushing's syndrome.
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/endoabs.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
Shir Fuchs Orenbach & Asi Haviv
Amryt Pharmaceuticals DAC.

Background
Oral octreotide capsules (OOC) are approved in the United Sates 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 C_{max}, and the AUCs after administration of 20 mg, 60 mg, and 80 mg. Power model exponents ranged from 0.73 (C_{max}) to 1.0 for $AUC_{0\text{-}inf}$. 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 treatment-emergent 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/endoabs.89.C11

C12

Financial Toxicity and Supportive Care in Neuroendocrine Tumor: A Biobank Study
Arya Mariam Roy[1], Jasmine Kaur[1], Kristopher Attwood[2] & Renuka Iyer[1]
[1]Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, New York; [2]Department of Biostatistics & Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, New York.

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 and 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

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

Cole Blanford, Donglin Yan, Ning Li, Alison Woodworth, Gaby Gabriel, Riham El Khouli, Aman Chauhan & Lowell Anthony

College of Medicine, Departments of Medicine, Pathology, Radiology, and Markey Cancer Center, University of Kentucky, Lexington, KY.

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 $r_{s/H} = 0.72$, p (2-tailed) < 0.001 ($n=19$); and $r_{s/C} = 0.61$, 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.

Abstract ID 21520

DOI: 10.1530/endoabs.89.C13

Clinical - Nuclear Medicine/ Interventional Radiology/Imaging

C14

Cardiac Neuroendocrine Tumor Metastases on 68Ga-DOTATATE PET/CT

Hwan Lee, Vandan Patel, Abhijit Bhattaru, Christopher Jean, Daniel A Pryma & Paco E Bravo
Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA.

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 ^{68}Ga-DOTATATE PET/CT.
Methods
The medical records of 406 neuroendocrine tumor patients who underwent ^{68}Ga-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 were compared to an external cohort of 11 patients with active cardiac sarcoidosis who underwent ^{68}Ga-DOTATATE 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 ^{68}Ga-DOTATATE PET/CT reports. The cardiac SUVmax in the NET cohort (mean $\pm$ SD: 18.6 $\pm$ 22.3) was significantly higher compared to the cardiac sarcoid cohort (2.4 $\pm$ 0.6) without any overlap in values ($P<0.05$). Similar results were obtained with SUVmax-to-background ratio (26.2 $\pm$ 31.4 vs. 2.6 $\pm$ 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 ^{68}Ga-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
DOI: 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

Ebrahim Delpassand[1], Soheil Mohammadi Yazdi[1], Shashank Ghantoji[2], Antonio Reis Nakasato[2], Corinne Denise Strickland[2], Rodolfo Nunez[1], Afshin Shafie[1], Susan Cork[1], Clare Byrne[3], Jackson Tang[3], Kyle Runeckles[3] & Jeetvan Patel[2]
[1]Excel Diagnostics and Nuclear Oncology Center, Houston, TX; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [3]Asclepius Analytics, New York, NY.

Background
Advanced neuroendocrine tumors (NETs) are associated with poor prognoses. A 4-dose regimen of lutetium Lu 177 (^{177}Lu)-DOTATATE has been shown to improve progression-free survival (PFS) and overall survival (OS) 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 $\leq$4 doses of ^{177}Lu-DOTATATE and who, following disease progression and a period of $\geq$6 months since the end of initial treatment, were re-treated with $\geq$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 ^{177}Lu-DOTATATE re-treatment, 19 (61%) were male and 29 (94%) were white. Overall, patients received a median of 6 doses (4 initial and 2 re-treatment doses). Mean $\pm$ sd administered activity was 41.9 $\pm$ 4.4 GBq. Two patients received additional re-treatment (1 and 2 doses, respectively) following a second period of $\geq$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 ^{177}Lu-DOTATATE after progression appeared to be well tolerated and offered disease control in patients with progressive NETs following initial ^{177}Lu-DOTATATE treatment.

Table 1. Summary of Efficacy and Safety Outcomes

Outcome	Initial Treatment ($n=31$)	Re-treatment ($n=31$)
Response, n (%)		
Complete response	0	0
Partial response	11 (35%)	7 (23%)
Stable disease	20 (65%)	14 (45%)
Progressive disease	0	3 (10%)
Unknown	0	7 (23%)
Median PFS, months (95% CI)	20.2 (13.5–25.8)	9.6 (5.5–16.2)
Median OS, months (95% CI)	42.6 (31.2–53.8)	12.6 (9.6–18.9)
Grade 3/4 hematotoxicity (Including leukopenia, neutropenia, and thrombocytopenia), n (%)	1 (3%)	3 (10%)

Abstract ID 21354
DOI: 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

Shannon Fortin Ensign, MD, PhD[1], Muskan Agarwal, MD[2], Molly Klanderman, PhD[3], Mohamed Badawy, MB, BCh[4], Thorvardur R. Halfdanarson, MD[5], Derek R. Johnson, MD[6,7], Mohamad Bassam Sonbol, MD[1] & Ayse T. Kendi, MD[6]
[1]Department of Hematology-Oncology, Mayo Clinic, Phoenix, AZ; [2]Department of Internal Medicine, Mayo Clinic, Phoenix, AZ; [3]Department of Quantitative Health Sciences, Mayo Clinic, Scottsdale, AZ; [4]Department of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center; [5]Department of Medical Oncology, Mayo Clinic, Rochester, MN; [6]Department of Radiology, Mayo Clinic, Rochester, MN; [7]Department of Neurology, Mayo Clinic, Rochester, MN.

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 between imaging modalities

($N=24$) displayed a significantly higher SUV max (median 7.9 vs. 4.0, $P=0.008$) and Krenning score (median 3.0 vs. 2.0, $P=0.005$) on Ga-68-DOTATATE PET compared to cases with a discordant prediction of meningioma ($n=24$). In cases with lower SUV max values Ga-68-DOTATATE was more likely to discordantly predict meningioma without agreement by the corresponding MRI. Prior cranial radiation or use of a somatostatin mimetic did not affect quantitative radiographic measures, and MRI-based tumor size was similar across groups.
Conclusions
Lesions with increased avidity may be more confidently predicted as meningioma in Ga-68-DOTATATE PET scans, and caution should be exercised in lesion type prediction among low SUV cases. The continued development of SSTR-based imaging biomarker signatures across incidental CNS lesion subtypes will further define the role of this imaging modality in the clinical diagnosis and management of presumed meningiomas.
Abstract ID 21355

DOI: 10.1530/endoabs.89.C16

C17

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

Michael C. Soulen[1], Ursina R. Teitelbaum[2], Rosemarie Mick[3], Jennifer Eads[2], Jeffrey I. Mondschein[1], Mandeep Dagli[1], Diana van Houten[1], Nevena Damjanov[2], Charles Schneider[2], Keith Cengel[4] & David C. Metz[5]
[1]Division of Interventional Oncology, [2]Division of Medical Oncology, [3]Department of Biostatisitics, Epidemiology and Informatics, [4]Department of Radiation Oncology, and [5]Department of Gastroenterology; Neuroendocrine Tumor Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA.

Background
Capecitabine-Temozolomide (CapTem) is an effective oral chemotherapy 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 radioembolized 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. Clinical and laboratory assessment was done monthly and imaging every 3 months. Toxicities were assessed using CTCAE v5. Resposne was evaluated by RECIST. Hepatic-PFS, PFS and overall survival (OS) were estimated using Kaplan-Meier, subgroups were compared using the log rank test.
Results
35/37 patients completed the prescribed regimen. Primary sites of disease were pancreas (16), lung (10), gut (7) and unknown (4). Mean duration of CapTem was 12 months (range, 4-32 mo). Toxocites were as expected for each therapy individually. ORR in the liver was 72% with a disease control rate of 100%. Median PFS was 36 mo (95% CI, 25-45 months). Differences in PFS among primary sites were not significant. Median overall survival was 41 months (95% CI, 24-87 months) from initiation of CapTemY90 therapy and 130 months (95% CI, 56-172 months) from initial diagnosis.
Conclusions
Combined modality CapTem with TARE provides durable control of G2 NET liver metastases for substantially longer than expectations for embolotherapy or chemotherapy alone.
Abstract ID 21371

DOI: 10.1530/endoabs.89.C17

C18

Radiosensitization for TARE: Does Duration of Chemotherapy Affect PFS?

List of participants and their roles in the submission

Michael C. Soulen[1], Ursina R. Teitelbaum[2], Rosemarie Mick[3], Jennifer Eads[2], Jeffrey I. Mondschein[1], Mandeep Dagli[1], Diana van Houten[1], Nevena Damjanov[2], Charles Schneider[2], Keith Cengel[4] & David C. Metz[5]
[1]Division of Interventional Oncology, [2]Division of Medical Oncology, [3]Department of Biostatisitics, Epidemiology and Informatics, [4]Department of Radiation Oncology, and [5]Department of Gastroenterology; Neuroendocrine Tumor Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA.

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-domianant grade 2 metastatic NETwere 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 simulation 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 bilobar disease had the other lobe was 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 chemo 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-escaltion of chemotherapy to improve quality of life without sacrificing disease control.
Abstract ID 21372

DOI: 10.1530/endoabs.89.C18

C19

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

Igryl S. Cordero-Hernandez, Alicia C. Ross, Arvind Dasari, Daniel M. Halperin, Beth Chasen & James C. Yao
The University of Texas MD Anderson Cancer Center, Houston, TX.

Background
We observed patients with well-differentiated NETs who received PRRT with ^{177}Lu-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 ^{177}Lu-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 other/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 (7/39 [18%]; $P=0.0009$). 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

(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 of metastatic NET following PRRT. All transformation following 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/endoabs.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

Camilo Jimenez, MD[1], Nancy Stambler, DrPH[2], Vincen A. DiPippo, PhD[2] & Daniel A. Pryma, MD[3]
[1]Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas M.D. Anderson Cancer Center, Houston, Texas; [2]Progenics Pharmaceuticals, Inc., a Lantheus company; N. Billerica, Massachusetts; [3]Department of Radiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Background
High-specific activity iodine-131 metaiodobenzylguanidine (HSA I-131 MIBG; AZEDRA®) is the only FDA approved systemic treatment for locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL). We have previously described pivotal 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
Patients with iobenguane-avid PPGL 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 were 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/healthy 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 $\pm$ 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 ($+16.4$)); 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 PPGL 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/endoabs.89.C20

C21

Characterizing Bone Metastases in Patients with Well-Differentiated Neuroendocrine Neoplasms Utilizing Ga68-DOTATATE PET

Tucker W. Coston, MD[1], Himil J. Mahadevia, MBBS[2], Marie M. Plante, MD[3], Joseph M. Accurso, MD[4], Akash Sharma, MD, MBA[5], Geoffrey B. Johnson, MD, PhD[4], Jonathan B. Ashman, MD, PhD[6], Ayse Tuba Kendi, MD[7], Mohamad Bassam Sonbol, MD[8], Timothy J. Hobday, MD[9], Thorvardur R. Halfdanarson, MD[9] & Jason S. Starr, DO[1]
[1]Mayo Clinic Florida, Division of Hematology & Medical Oncology; [2]University of Missouri-Kansas City, Division of Internal Medicine; [3]Mayo Clinic Florida, Division of Internal Medicine; [4]Mayo Clinic Florida, Division of Nuclear Medicine; [5]Mayo Clinic Florida, Division of Radiology; [6]Mayo Clinic Arizona, Division of Radiation Oncology; [7]Mayo Clinic Minnesota, Division of Nuclear Medicine; [8]Mayo Clinic Arizona, Division of Hematology & Medical Oncology; [9]Mayo Clinic Minnesota, Division of Medical Oncology.

Background
Tumors of neuroendocrine origin are a rare, heterogenous 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: "Dotatate" AND "met*" or "lesion" AND "bone" or "osse*" or "skel*". The individual medical records identified from the generated report were then reviewed to include only patients with 1) well-differentiated NETs of GI and pancreatic origin, lung carcinoid, paraganglioma/pheochromocytoma, 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/pheochromocytoma, 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/pheochromocytomas (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

DOI: 10.1530/endoabs.89.C21

C22

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

Orjola Prela MD, Brennen Caveney BS & Darren R Carpizo MD, PhD
University of Rochester Medical Center.

Background
Despite the superiority of ^{68}Ga-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 ^{68}Ga-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 ^{68}Ga-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 ^{68}Ga-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 with a median age of 65 had a diagnosis of GI or pancreatic neuroendocrine tumor and underwent a ^{68}Ga-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 histologically moderately/well differentiated. Following ^{68}Ga-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 sandostatin and 1 patient being down-staged and taken off sandostatin, 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 ^{68}Ga-DOTATATE PET/CT.
Conclusions
Our retrospective study demonstrates that ^{68}Ga-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.
Abstract ID 21450
DOI: 10.1530/endoabs.89.C22

C23

Somatostatin receptor expression in lung neuroendocrine tumors: an analysis of Dotatate PET scans

Taymeyah Al-Toubah, MPH[1], Eleonora Pelle, MD[1], Ghassan El-Haddad, MD[2] & Jonathan Strosberg, MD[1]
[1]H. Lee Moffitt Cancer Center and Research Institute, Department of GI Oncology; [2]H. Lee Moffitt Cancer Center and Research Institute, Department of Interventional Radiology.

Background
Somatostatin receptor (SSTR) expression in metastatic lung neuroendocrine (carcinoid) tumors has not been well-characterized using modern positron emission tomography (PET) imaging. Understanding degree and uniformity of SSTR expression is important to establish the role of SSTR targeted treatments, including peptide receptor radiotherapy (PRRT), in lung NETs.
Methods
Retrospective review of medical records and imaging studies of patients with metastatic lung NETs who underwent Dotatate PET imaging (^{68}Ga or ^{64}Cu) at Moffitt Cancer Center since introduction of Dotatate PET CTs in 3/2017 through 2/2022.
Results
A total of 22 patients were identified with metastatic lung NETs (3 typical, 19 atypical) who underwent either ^{68}Ga or ^{64}Cu Dotatate PET imaging. 3 patients had complete absence of SSTR expression and 1 patient very weak expression (less than normal liver). Among the remaining 18 patients, only 8 had uniformly positive Dotatate PET scans whereas 10 patients had heterogenous expression (mix of SSTR positive and negative tumors). 2 of the typical (low-grade) NETs had positive uniform SSTR expression and the 3rd (with low mitotic rate but ki67 of 10%) had heterogeneous expression. In total, only 8/22 patients (36%) had uniformly positive receptor expression which would render them candidates for treatment with PRRT.
Conclusions
The majority of metastatic lung NETs are either SSTR negative or express heterogenous patterns of SSTR expression and are thus suboptimal candidates for SSTR targeted therapy, particularly with PRRT. SSTR imaging in lung NETs should be evaluated carefully for uniformity of expression.
Abstract ID 21452
DOI: 10.1530/endoabs.89.C23

C24

MIBG and DOTATATE Therapy for Pheochromocytoma and Paraganglioma: A Single Institution Experience

Erik Mittra, Nadine Mallak, Guillaume Pegna, Emerson Chen, James Lim & Rodney Pommier
Oregon Health & Science University, Portland, OR, USA.

Background
Since the FDA-approval of Lu177-DOTATATE and I131-MIBG radiopharmaceutical 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.
Abstract ID 21473
DOI: 10.1530/endoabs.89.C24

C25

Evaluation of 68Ga-DOTATATE PET After Two Cycles of Peptide Receptor Radionuclide Therapy (PRRT) in Neuroendocrine Tumors (NET)

Duan Heying[1], Song Hong[1], Ferri Valentina[1], Fisher George[2], Shaheen Shagufta[2], Sha Jagruti[1], Nguyen Judy[1], Moradi Farshad[1], Franc Ben[1], Davidzon Guido[1], Iagaru Andrei[1] & Mari Aparici Carina[1]
[1]Department of Radiology, Division of Nuclear Medicine and Molecular Imaging, Stanford University, Stanford, CA; [2]Department of Medicine, Division of Oncology, Stanford University, Stanford, CA.

Background
We aimed to evaluate the added information provided by ^{68}Ga-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 ^{177}Lu-DOTATATE were included. All patients had ^{68}Ga-DOTATATE PET (PET/CT or PET/MRI) at baseline, after two cycles, and upon completion of PRRT. RECIST 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 ^{68}Ga-DOTATATE PET contributing to their quality of life as it provided important peace of mind. After two PRRT cycles, 0/105

(0%) patients showed complete response (CR), 54/105 (51%) partial response (PR), and 40/105 (38%) had stable disease (SD) with agreement between RECIST and SSTR-density. In 11/105 (11%) patients RECIST and SSTR-density were discordant: progressive disease (PD) according to RECIST was seen in 11/11 patients, while evaluation of SSTR-density showed true progression in 4/11 and pseudo-progression in 7/11 patients. Follow-up imaging after completion of PRRT verified results from interim imaging: 4/11 had true progression while the other 7/11 patients showed PR. The pattern of pseudo-progression consisted in an up to 2 mm increase in size of known NET lesions, with or without central necrosis or new stranding, but no new lesions. The SSTR-density in these patients was stable or decreased when related to the liver. Chromogranin A was available in 37/105 patients. The change in chromogranin A did not positively correlate with response to treatment.

Conclusions

Our data show that a ^{68}Ga-DOTATATE PET after two cycles of PRRT provides important reassurance for the patient about the status of the disease and response to treatment. No patient showed CR after two cycles of PRRT, clearing concerns about possible overtreatment. ^{68}Ga-DOTATATE PET is more accurate in assessing treatment response after two cycles than RECIST, allowing continuation of treatment in patients with pseudo-progression. Change in tumor marker did not correlate well with response to treatment after two treatment cycles.

Abstract ID 21480

DOI: 10.1530/endoabs.89.C25

C26

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

Oregon Health & Science University, Portland, OR.

Background

Since their FDA-approval in 2018, both Lu177-DOTATATE and I131-MIBG radiopharmaceutical therapies 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 therapy at our institution since 2018. At our institution, the choice of treatment is first guided by the degree of uptake on functional imaging, followed by the FDA-label for the therapy. Parameters evaluated here include the uptake on pre-therapy DOTATATE and MIBG scans, and the tumor genotype.

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.
  2. MIBG: Positive, DOTATATE: Positive
  3. MIBG: Negative, DOTATATE not performed.
- No mutation detected ($n=1$): MIBG: Positive, 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 I-131 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.
- No mutation detected ($n=1$): MIBG: Positive, DOTATATE: not performed.

In summary, DOTATATE PET was positive in all patients, with the exception of one case that showed heterogeneous somatostatin receptor expression (93.3%, $n=14/15$). MIBG scan was positive in 50% (8/16) of patients, and heterogeneous in another 18.9% (3/16).

Conclusions

Our data is consistent with literature supporting DOTATATE PET as a first line imaging agent for PPGLs across all genetic mutations. However, in our experience, pre-therapy functional imaging with both agents should be performed and used to guide the therapeutic choice as tumors positive with both agents are preferentially treated with I131-MIBG given the FDA label. Additional data is needed for confirmation of these findings.

Abstract ID 21573

DOI: 10.1530/endoabs.89.C26

C27

Performance of 68Ga-DOTATATE PET/CT, 18F-FDG PET/CT, CT, and MRI Spine in the Detection of Spinal Bone Metastases in Metastatic Pheochromocytoma/Paraganglioma

Abhishek Jha[1], Mayank Patel[1], Babak Saboury[2], Corina Millo[3], Alexander Ling[4], Ritu Shah[4], Clara C. Chen[2], Leah Meuter[1], Sara Talvacchio[1], Marianne Knue[1], Frank I. Lin[5], Geraldine O'Sullivan Coyne[6], Alice P. Chen[6], Naris Nilubol[7], Peter Herscovitch[3], David Taïeb[8], Ali Cahid Civelek[9], Jorge A. Carrasquillo[10] & Karel Pacak[1]

[1]Section on Medical Neuroendocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 10 Center Dr., Bldg. 10, Room 1E-3140, Bethesda, MD, 20892, USA; [2]Nuclear Medicine Division, Radiology and Imaging Sciences, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [3]Positron Emission Tomography Department, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [4]Radiology and Imaging Sciences, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [5]Molecular Imaging Program, National Cancer Institute, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [6]Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA; [7]Surgical Oncology Program, Center for Cancer Research, National Cancer Institute, 10 Center Dr., Bldg. 10, Room 4-5952, Bethesda, MD, 20892, USA; [8]Department of Nuclear Medicine, La Timone University Hospital, CERIMED, Aix-Marseille University, Marseille, France; [9]Nuclear Medicine, Radiology and Radiological Science, Johns Hopkins Medicine, Baltimore, MD, USA; [10]Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, MD, 10065, USA.

Background

To evaluate and compare the diagnostic performance of ^{68}Ga-DOTATATE PET/CT to ^{18}F-FDG PET/CT, CT of neck, chest, abdomen and pelvis (CT), and MRI of cervical, thoracic, and lumbar spine (MRI spine), for the detection of spinal bone metastases in metastatic pheochromocytoma and/or paraganglioma (PPGL).

Methods

Between 2014 and 2019, 41 consecutive metastatic PPGL patients (19 females; mean age, 43 years) underwent ^{68}Ga-DOTATATE PET/CT, ^{18}F-FDG PET/CT, and MRI (sagittal T1w, sagittal STIR, axial T1w, and axial T2w) for evaluation of spinal bone metastases. Thirty patients also underwent CT (iv and oral contrast). The mean ($\pm$standard deviation) duration between ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT was 21 ± 46 days, between ^{68}Ga-DOTATATE PET/CT and CT 18 ± 40 days, and between ^{68}Ga-DOTATATE PET/CT and MRI spine 27 ± 40 days. Per patient and per lesion detection rates of ^{68}Ga-DOTATATE PET/CT, ^{118}F-FDG PET/CT, CT, and MRI spine was calculated. Counting of spinal bone metastases was limited to a maximum of one lesion per vertebrae. A composite of all the scans served as an imaging comparator. McNemar test was used to compare detection rates between the scans. Two-sided p values <0.05 were considered statistically significant.

Results

All patients were positive for spinal bone metastases, with 484 lesions on the imaging comparator. ^{68}Ga-DOTATATE PET/CT demonstrated a per lesion detection rate of 401/484 [82.9%, 95% confidence interval (CI): 79.2-86.1%]. ^{18}F-FDG PET/CT, MRI spine, and CT showed significantly lower per lesion detection rates of 262/484 (54.1%, 95% CI: 49.6-58.6%; $P<0.0001$), 350/484 (72.3%, 95% CI: 68.1-76.3%; $P=0.001$), and 117/327 (35.8%, 95% CI: 30.6-41.2%; $P<0.0001$), respectively. The per patient detection rates of ^{68}Ga-DOTATATE PET/CT was 41/41 (100%, 95% CI: 91.4-100%), and that of ^{18}F-FDG PET/CT, MRI spine, and CT was 36/41 (87.8%, 73.8-95.9%), 39/41 (95.1%, 83.5-99.4%), and 25/30 (83.3%, 65.3-94.3%), respectively. Further, ^{68}Ga-DOTATATE PET/CT was found to detect greater or equal lesions compared to ^{18}F-FDG PET/CT, MRI spine, and CT in 38/41 (92.7%), 30/41 (73.2%), and 27/30 (90.0%) patients, respectively.

Conclusions

^{68}Ga-DOTATATE PET/CT showed a significantly superior detection rate of spinal bone metastases compared to ^{18}F-FDG PET/CT, CT, and MRI spine. Besides

providing a whole-body analysis, it maybe the modality of choice to evaluate metastatic spine disease especially in the treatment planning and response assessment of the targeted radionuclide therapy (^{223}Ra, ^{177}Lu/^{90}Y, ^{131}I).
Abstract ID 21579
DOI: 10.1530/endoabs.89.C27

C28

Diagnostic Performance of PET or PET/CT Utilizing 18F-DOPA, 68Ga-DOTATATE, 18F-FDG, 18F-FDA, and CT and MRI in the Detection of MEN2A-related-pheochromocytoma

Abhishek Jha[1], Mayank Patel[1], Alexander Ling[2], Clara C. Chen[3], Corina Millo[4], Kailah Charles[1], Sara Talvacchio[1], Josephine Ezemobi[1], Peter Herscovitch[4], Frank I. Lin[5], Naris Nilubol[6], David Taïeb[7], Ali Cahid Civelek[8], Jorge Carrasquillo[5,9] & Karel Pacak[1]
[1]Section on Medical Neuroendocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 10 Center Dr., Bldg. 10, Room 1E-3140, Bethesda, MD, 20892, USA; [2]Radiology and Imaging Sciences, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [3]Nuclear Medicine Division, Radiology and Imaging Sciences, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [4]Positron Emission Tomography Department, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [5]Molecular Imaging Program, National Cancer Institute, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [6]Endocrine Oncology Branch, Center for Cancer Research, National Cancer Institute, 10 Center Dr., Bldg. 10, Room 4-5952, Bethesda, MD, 20892, USA; [7]Department of Nuclear Medicine, La Timone University Hospital, CERIMED, Aix-Marseille University, Marseille, France; [8]Nuclear Medicine, Radiology and Radiological Science, Johns Hopkins Medicine, Baltimore, MD, USA; [9]Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, MD, 10065, USA.

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 2019 guidelines for radionuclide imaging of PHEO and paraganglioma, ^{18}F-fluoro-L-dihydroxyphenylalanine (^{18}F-FDOPA) is recommended as a positron emission tomography (PET) radiotracer of choice followed by ^{68}Ga-DOTA(0)-Tyr(3)-octreotate (^{68}Ga-DOTATATE) and ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG), respectively in the detection of PHEO associated with multiple endocrine neoplasia 2A (MEN2A), caused by germline mutation in *rearranged during transfection (RET)* gene. No study has compared the diagnostic performance of these radiotracers in patients with MEN2A-related PHEO. The purpose of this prospective study was to evaluate and compare the detection rates of ^{18}F-FDOPA, ^{68}Ga-DOTATATE, ^{18}F-FDG, and ^{18}F-fluorodopamine (^{18}F-FDA) PET or positron emission tomography/computed tomography (PET/CT), contrast-enhanced computed tomography (CT), and contrast-enhanced magnetic resonance imaging (MRI) in the detection of MEN2A-related PHEO.
Methods
Between 2008 and 2021, 19 patients (females:males, 10:9; mean age, 36.3 ± 9.9 years) prospectively underwent 18F-FDOPA PET ($n=3$) or PET/CT ($n=11$), 68Ga-DOTATATE PET/CT ($n=12$), 18F-FDG PET/CT ($n=18$), and 18F-FDA PET ($n=4$) or PET/CT ($n=4$), CT ($n=20$) and MRI ($n=18$). The mean duration between scans was less than a month. The scans were evaluated by a nuclear medicine physician or radiologist. The histopathologic diagnosis served as the reference standard. The McNemar test was used to compare PHEO detection rates between the imaging modalities. Two-sided p values <0.05 were considered significant.
Results
Nineteen patients had 26 PHEOs [12 unilateral (7 right, 5 left) and 7 bilateral] on histopathology. 18F-FDOPA PET or PET/CT demonstrated a PHEO detection rate of 15/18 [83.3%, 95% confidence interval (CI): 58.6-96.4%]. 68Ga-DOTATATE PET/CT, 18F-FDG PET/CT, 18F-FDA PET or PET/CT, CT, and MRI showed PHEO detection rates of 12/15 (80.0%, 95% CI: 51.9-95.7%), 7/23 (30.4%, 95% CI: 13.2-52.9%), 6/12 (50.0%, 95% CI: 21.1-78.9%), 24/26 (92.3%, 95% CI: 74.9-99.1%), and 22/24 (91.7%, 95% CI: 73.0-99.0%), respectively. The difference in detection rates between 18F-FDG and other scans was significant ($P<0.05$).
Conclusions
The study was performed in a small cohort of MEN2A-related PHEO patients demonstrating CT, an anatomic imaging modality with the highest detection rate whereas in functional imaging, ^{18}F-FDOPA PET/CT showed the highest detection rate followed by ^{68}Ga-DOTATATE, ^{18}F-FDA, and ^{18}F-FDG in supporting the 2019 EANM/SNMMI guidelines. A difference in detection rates between various imaging modalities and ^{18}F-FDG was found.
Abstract ID 21580
DOI: 10.1530/endoabs.89.C28

C29

Diagnostic Performance of PET or PET/CT Utilizing 18F-DOPA, 68Ga-DOTATATE, 18F-FDG, 18F-FDA, and CT and MRI the Detection of VHL-related Pheochromocytoma

Abhishek Jha[1], Mayank Patel[1], Alexander Ling[2], Clara C. Chen[3], Corina Millo[4], Kailah Charles[1], Sara Talvacchio[1], Josephine Ezemobi[1], Peter Herscovitch[4], Frank I. Lin[5], Naris Nilubol[6], David Taïeb[7], Ali Cahid Civelek[8], Jorge Carrasquillo[5,9] & Karel Pacak[1]
[1]Section on Medical Neuroendocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 10 Center Dr., Bldg. 10, Room 1E-3140, Bethesda, MD, 20892, USA; [2]Radiology and Imaging Sciences, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [3]Nuclear Medicine Division, Radiology and Imaging Sciences, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [4]Positron Emission Tomography Department, Warren Grant Magnuson Clinical Center, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [5]Molecular Imaging Program, National Cancer Institute, National Institutes of Health, 10 Center Dr., Bldg. 10, Bethesda, MD, 20892, USA; [6]Endocrine Oncology Branch, Center for Cancer Research, National Cancer Institute, 10 Center Dr., Bldg. 10, Room 4-5952, Bethesda, MD, 20892, USA; [7]Department of Nuclear Medicine, La Timone University Hospital, CERIMED, Aix-Marseille University, Marseille, France; [8]Nuclear Medicine, Radiology and Radiological Science, Johns Hopkins Medicine, Baltimore, MD, USA; [9]Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, MD, 10065, USA.

Background
The purpose of this prospective study was to evaluate and compare the detection rates of ^{18}F-L-dihydroxyphenylalanine (^{18}F-FDOPA), ^{68}Ga-DOTATATE, ^{18}F-FDG, and ^{18}F-fluorodopamine (^{18}F-FDA) PET or positron emission tomography/computed tomography (PET/CT), computed tomography (CT), and magnetic resonance imaging (MRI) in the detection of *VHL*-related pheochromocytoma (PHEO).
Methods
Between October 2007 and October 2021, twelve patients (females: males, 5:7; mean age, 27.9 ± 13.6 years) prospectively underwent ^{18}F-DOPA PET ($n=2$) or PET/CT ($n=7$), ^{68}Ga-DOTATATE PET/CT ($n=6$), ^{18}F-FDG PET/CT ($n=11$), and ^{18}F-FDA PET ($n=2$) or PET/CT ($n=2$) with VHL-related PHEOs. Additionally, these patients also underwent CT ($n=12$) and MRI ($n=11$). The mean duration between CT and ^{18}F-FDOPA was 10 ± 15 days, between CT and ^{68}Ga-DOTATATE 7 ± 10 days, between CT and ^{18}F-FDG 5 ± 10 days, between CT and ^{18}F-FDA 3 ± 2 days, and between CT and MRI 2 ± 4 days. The PET or PET/CT and CT and MRI 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. PHEO detection rates were compared for all of the imaging modalities. For statistical analysis, the McNemar test was used to compare detection rates between the imaging modalities. Two-sided p values <0.05 were considered significant.
Results
Twelve patients had 19 PHEOs [3 unilateral (2, right) and 6 bilateral). 18/19 tumors underwent surgical resections and were proved to be PHEOs on histopathologic examination and 1 PHEO is awaiting surgery in whom a clinical diagnosis of PHEO was made. ^{18}F-FDOPA PET or PET/CT demonstrated a PHEO detection rate of 12/14 [85.7%, 95% confidence interval (CI): 57.2-98.2%]. ^{18}F-FDG PET/CT, ^{68}Ga-DOTATATE PET/CT, ^{18}F-FDA PET or PET/CT, and CT, and MRI showed PHEO detection rates of 16/17 (94.1%, 95% CI: 71.3-99.6%), 5/9 (55.6%, 95% CI: 21.2-86.3%), 4/6 (66.7%, 95% CI: 22.3-95.7%), 17/19 (89.5%, 95% CI: 66.9-98.7%), and 17/17 (100%, 95% CI: 80.5-100%), respectively. The difference in detection rates between none of the imaging modalities achieved a statistical significance ($P<0.05$).
Conclusions
The study was performed in a small cohort of in *VHL*-related PHEO demonstrating MRI, an anatomic imaging modality with the highest detection rate whereas amongst functional PET or PET/CT imaging, ^{18}F-FDG showed the highest detection rate followed by ^{18}F-FDOPA, ^{18}F-FDA, and ^{68}Ga-DOTATATE. However, no difference in detection rates by various imaging modalities was found and hence, multicentric clinical trials needs to be conducted to support the statistical relevance as it was not seen in this study.
Abstract ID 21581
DOI: 10.1530/endoabs.89.C29

Clinical - Surgery/Applied Pathology

C30

Liver-Directed Therapy of Neuroendocrine Liver Metastases

Léamarie Meloche-Dumas[1], Frédéric Mercier[1], Victoria Barabash[2], Calvin Law[3], Natalie Coburn[2,3], Simron Singh[2,3], Sten Myrehaug[2,3], Wing Chan[4] & Julie Hallet[2,3]
[1]Centre hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada; [2]Sunnybrook Research Institute, Toronto, Ontario, Canada; [3]Odette Cancer Centre/Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [4]Cancer Research Program, Institute of Clinical Evaluative Sciences (ICES), Toronto, Ontario, Canada.

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 0.93, 95%CI 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
DOI: 10.1530/endoabs.89.C30

C31

Goblet Cell Adenocarcinoma (GCA) of the Appendix: Interrogating Proteomics to Identify Potential Actionable Targets

Krutika Patel, MBBS, MD[1], Liping Du, PhD[2], Frank Revetta, PhD[1], Mary Kay Washington, MD, PhD[1], Jordan Berlin, MD[3] & Satya Das, MD, MSCI[3]
[1]Department of Pathology, Immunology and Microbiology, Vanderbilt University Medical Center; [2]Department of Biostatistics, Vanderbilt University Medical Center; [3]Department of Medicine, Vanderbilt University Medical Center.

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 over-expression by immunohistochemistry (3+ membranous staining, > 10% of tumor cells in 4 patients and 2+ 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-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 $P = .2$). 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 $P = .09$).
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.
Abstract ID 21374
DOI: 10.1530/endoabs.89.C31

C32

Surgical Management of G3 Gastroenteropancreatic Neuroendocrine Neoplasms: A Systematic Review and Meta-Analysis

Ioannis A. Ziogas, MD, MPH[1,2], Panagiotis T. Tasoudis, MD[2], Luis C. Borbon, MD[3], Scott K. Sherman, MD, FACS[3], Patrick J. Breheny, MS, PhD[4], Chandrikha Chandrasekharan, MBBS[5], Joseph S. Dillon, MD[5], Andrew M. Bellizzi, MD[6] & James R. Howe, MD, FACS[3]
[1]Department of Surgery, University of Colorado, Anschutz Medical Campus, Aurora, CO 80045, USA; [2]Surgery Working Group, Society of Junior Doctors, Athens 15123, Greece; [3]Department of Surgery, Division of Surgical Oncology and Endocrine Surgery, University of Iowa Carver College of Medicine, Iowa City, IA 52242, USA; [4]Department of Biostatistics, University of Iowa College of Public Health, Iowa City, IA 52242, USA; [5]Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA 52242, USA; [6]Department of Pathology, University of Iowa Carver College of Medicine, Iowa City, IA 52242, USA.

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 gastrointestinal primary tumor sites 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).

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

Classification	Studies, n	Patients, n (surgery vs non-surgery)	Hazard Ratio (<1 favors surgery)	95% Confidence Interval
G3 GEP NEN (NET & NEC)	12	1,788 vs 857	0.40	0.31-0.53
G3 Pancreatic NEN (NET & NEC)	8	451 vs 370	0.31	0.24-0.40
G3 Gastrointestinal NEN (NET & NEC)	3	1,207 vs 379	0.42	0.34-0.52
G3 GEP NET (not NEC)	3	62 vs 25	0.26	0.11-0.61

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.
Abstract ID 21402

DOI: 10.1530/endoabs.89.C32

C33

High-Grade Pancreatic Neuroendocrine Neoplasms: Interobserver Diagnostic Accuracy and Relationship with Clinicopathological and Molecular Characteristics

Mehran Taherian, MD, Rebecca Waters, MD, Wai Chin Foo, MD, Dipen Maru, MD, Susan C. Abraham, MD, Asif Rashid, MBBS, PhD, Huamin Wang, MD, PhD, Dongguang Wei, MD, Melissa W. Taggart, MD & Deyali Chatterjee, MD
Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX.

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 (κ)= 0.334). There was a majority agreement of $\geq$ 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 (2071+/- 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=0.01). 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

DOI: 10.1530/endoabs.89.C33

C34

Grade Creep and the Importance of Tissue Sampling: Changes in Ki-67 and Grade in Serial Neuroendocrine Tumor Samples

Suzie Byun[1], Daniel M. DePietro[2], Daniel Ackerman[3], Terence P. Gade[2] & Michael C. Soulen[2]
[1]Perelman School of Medicine at the University of Pennsylvania; [2]Division of Interventional Radiology, Department of Radiology, University of Pennsylvania; [3]Department of Radiology, University of Pennsylvania.

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$\pm$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

Kristen E. Limbach, MD, Kelly M. Mahuron, MD, Philip H. G. Ituarte, PhD, Jonathan Kessler, MD, Daneng Li, MD & Gagandeep Singh, MD
City of Hope National Medical Center, Duarte, CA.

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.

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. Eighteen 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%, $P=0.008$). Median OS from time of initial diagnosis was significantly longer in patients that received LDT compared to those who did not (29.9 vs 13.5 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?

Luis C. Borbon, MD[1], Catherine G. Tran, MD[1], Scott K. Sherman, MD[1], Po Hien Ear, PhD[1], Chandrikha Chandrasekharan, MD[2], Andrew M. Bellizzi, MD[3], Joseph S. Dillon, MD[2], Thomas M. O'Dorisio, MD[2] & James R. Howe, MD[1]
[1]Department of Surgery, University of Iowa Carver College of Medicine, Iowa City, IA; [2]Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA; [3]Department of Pathology, University of Iowa Carver College of Medicine, Iowa City, IA.

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 included well-differentiated neuroendocrine tumors (G3NET) and poorly-differentiated neuroendocrine carcinomas (G3NEC). 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).

Table. Overall Survival in 463 Surgically Resected GEP-NEN Patients and 31 Non-resected G3 Patients

WHO Classification (n)	Median OS (months)	HR (95% CI)	*P*-value*
G1NET ($n=211$)	268.1	Reference	-
G2NET ($n=208$)	129.9	1.89 (1.27 to 2.81)	0.002
G3NET ($n=39$)	50.5	4.70 (2.42 to 9.11)	<0.001
G3NEC ($n=5$)	28.5	7.99 (2.42 to 26.4)	<0.001
G3NET- No resection ($n=12$)	19.0	15.2 (6.93 to 33.5)	<0.001
G3NEC- No resection ($n=19$)	12.4	21.8 (12.0 to 39.4)	<0.001

WHO = World Health Organization; OS = Overall Survival; HR = Hazard Ratio; CI = Confidence Interval;
* Using multivariable cox proportional hazards model adjusting for grade and T, N, M-stage

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 G3NENs 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 G3NEN series (mOS 11-19 months), suggesting surgery should be considered in carefully selected patients with G3NENs, especially those with well-differentiated G3NETs.
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

Seth J Concors, MD, Ching-Wei D Tzeng, MD, Naruhiko Ikoma MD, Michael Kim MD, Hop Tran Cao, MD, Jeffery E Lee, MD, Matthew HG Katz, MD & Jessica E Maxwell, MD, MBA
Department of Surgical Oncology, Division of Surgery, MD Anderson Cancer Center at the University of Texas.

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 0.96, $P<0.001$), 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

C39

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

Katherine E McElroy, MD[1], Ahmer Irfan, MD[1], Sushanth Reddy, MD[1], Clayton Yates, PhD[2], Herbert Chen, MD, FACS[1] & J. Bart Rose, MD[1]
[1]The University of Alabama at Birmingham; [2]Tuskegee University.

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 LMN as well as patient racial group and incidence of LMN. A logistic regression model was utilized to determine correlation between LMN, 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 LMN 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 appears to be similar in Asian patients. Though overall risk of LMN was shown to increase with size, Asian pNET patients did not exhibit increased risk of LMN until PTS >3cm. Our findings suggest current size-based guidelines are accurate for Asians, but more research is 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

Nancy Joseph[1], Alan Paciorek[2], Bryan Khuong Le[3], Farhana Moon[3], Li Zhang[2] & Emily Bergsland[4]
[1]Department of Pathology, University of California San Francisco, San Francisco, CA, USA; [2]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA; [3]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [4]Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA, USA.

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 metastatic and 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 NENs. The median age was 61 and 41% were female, with no differences in NEC vs G3NET 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 CDKN2A (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 (53%), 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 G3NET. 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.
Abstract ID 21470
DOI: 10.1530/endoabs.89.C40

C41

SSTR-2 Expression in Solid Tumors: An Immunohistochemistry Analysis

Aman Chauhan[1,4], Susanne Arnold[1,4], Therese Bocklage[2,4], Donglin Yan[3,4], Ning Li[3,4], Lowell Anthony[1,4] & Derek Allison[2,4]
[1]Division of Medical Oncology, University of Kentucky; [2]Department of Pathology, University of Kentucky; [3]Department of Biostatistics, University of Kentucky; [4]Markey Cancer Center, University of Kentucky.

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 SSTR-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 cancer (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, $n=10$), paraganglioma and pheochromocytoma (Code 6, $n=20$), poorly differentiated neuroendocrine carcinoma (Code 7, $n=9$), and p16 negative squamous cell cancer (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
As expected, well-differentiated NET expressed very high SSTR-2 positivity with high intensity. However, a subset of small cell carcinoma and head and neck p16 positive squamous cell carcinoma were observed to express SSTR-2. Targeting SSTR-2 in small cell carcinoma and head and neck cancer with the help of radiolabeled somatostatin analog could be a promising therapeutic approach.

Based on our SSTR-2 IHC data, a prospective study of SSTR-2 assessment with the help of gallium 68 dotatate PET imaging in small cell lung cancer patients is currently underway at Markey Cancer Center.
Abstract ID 21481

DOI: 10.1530/endoabs.89.C41

C42

Small Intestinal NET Recurrence – When Why and How?

Priya K. Pai, Hallbera Gudmundsdottir, Sean P. Cleary & Thorvardur R. Halfdanarson
Mayo Clinic Rochester.

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 Gl 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.
Abstract ID 21565

DOI: 10.1530/endoabs.89.C42

C43

Post-Operative Biochemical Surveillance Thresholds Can be Used to Monitor for Sympathetic Pheochromocytoma/Paraganglioma Recurrence and Metastasis

Michael S Lui[1], Sarah B Fisher[1], Elizabeth G Grubbs[1], Nancy D Perrier[1], Steven G Waguespack[2], Jeena Varghese [2], Mouhammed A Habra[2], Camilo Jimenez[2] & Paul H Graham[1]

[1]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA; [2]Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, USA.

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-susceptibilty 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.
Abstract ID 21577

DOI: 10.1530/endoabs.89.C43

Population Science

P1

Cervical Neuroendocrine Carcinomas: A Population-Based Analysis of Clinicopathologic Characteristics and Survival Outcomes in Comparison with Conventional Cervical Malignancies

Leonidas N. Diamantopoulos[1], Dimitrios Korentzelos[2], Dimitrios Makrakis[3] & Rohit Bhargava[4]
[1]Department of Medicine, University of Pittsburgh Medical Center, 3459 Fifth Ave, Pittsburgh, PA 15213, USA; [2]Department of Pathology, University of Pittsburgh Medical Center, 3459 Fifth Ave, Pittsburgh, PA 15213, USA; [3]Division of Medical Oncology, Department of Medicine, University of Washington, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, 1144 Eastlake Ave E, LG-465, Seattle, WA, 98103; [4]Department of Pathology, University of Pittsburgh Medical Center Magee-Women's Hospital, Pittsburgh, PA, 15213, USA.

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 adenocarcinoma (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 – LNEC, NEC not-otherwise specified - NEC NOS), 8052, 8070-76 and 8084 for SCC, 8140, 8144, 8145, 8147, 8260, 8310, 8480-82 for AC. Demographic/clinicopathologic/treatment/survival data were extracted. SEER summary 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.
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, 10,738 patients (20%) with AC. SCNEC, LCNEC, and NEC NOS were associated with a significantly higher proportion of distant-stage disease (42%, 48%, and 41% respectively), in comparison to cervical SCC (13%) and AC (12%), all $P<0.001$. Median OS was 18 months (95% CI: 15.4 – 20.6) for SCNEC, and 15 months for LCNEC (95% CI: 12.2 – 17.8) and NEC NOS (95% CI: 12.8 – 17.2) respectively, and was significantly inferior to SCC (194 mos, 95% CI; NR, NR) and AC (NR, 95% CI; NR, NR), all $P<0.001$. The presence of SCNEC, LCNEC, or NEC NOS was independently associated with shorter OS in the multivariate analysis, when adjusted for other significant clinicopathologic factors, including stage, age, ethnicity, and completion of hysterectomy. Hysterectomy (regardless of type), was significantly associated with prolonged OS in the CNECs cohort (HR 0.48, 95%CI; 0.39 – 0.60).
Conclusion
CNECs were associated with advanced stage of disease and shorter OS compared to SCC and AC, conferring dismal prognosis in patients with cervical neoplasms. Despite their rarity, their aggressive behavior warrants a high index of clinical suspicion, accurate pathologic diagnosis, and early definitive intervention. Further studies are needed to better understand the biological underpinnings behind this aggressive behavior and the role of novel systemic treatments.
Abstract ID 21336
DOI: 10.1530/endoabs.89.P1

P2

Factors Impacting Survival Outcomes of Islet Cell Carcinoma

Tiffany Chu, Robert W. Hu & Peter T. Silberstein
Creighton University School of Medicine, Omaha NE.

Background
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
The mean age of diagnosis was 59 years, with older individuals having worse average survival outcomes (84 months) than their younger counterparts (126 months). Male participants on average also had worse survival outcomes (109 months) than females (121 months). The average Charlson-Deyo score was 0.38 ± 0.70. Pearson's chi-squared analysis demonstrated that those with Medicaid were less likely to be White ($P<0.001$). Furthermore, those with Medicaid were more likely to receive care at community cancer centers ($P<0.001$). Most of the cohort was treated at academic/research facilities (50.5%), followed by community centers (21.6%) and integrated network programs (16.6%). Academic/research facilities had the highest overall mean survival (123 months) compared to the other two programs (79 and 105 months, respectively). Patients who lived in metropolitan counties (defined by population size) had better mean survival outcomes (115 months), though patients who traveled further for care had consistently better survival outcomes ($P<0.001$). Patients who received PC for symptom management had worse survival outcomes than those who did not ($P<0.001$). After adjusting for all other variables, Cox proportional hazard ratios remained significant for age ($P<0.001$), race ($P=0.013$), and PC utilization ($P<0.001$).
Conclusion
Factors associated with increased survival include younger age, female sex, higher income, private insurance, receiving care at an academic/research facility, and not utilizing PC. These findings contribute to a developing understanding of disparities that impact survival outcomes of islet cell carcinoma.

Table 1: Multivariate Analysis of Survival Outcomes

Variable		Hazard Ratio (95% CI)	*P*-value
Age	Youth (14-47 years)	1 (Reference)	
	Middle-Aged (48-64)	1.35 (1.04-1.76)	0.024
	Elderly (>65)	2.67 (1.96-3.63)	<0.001
Race	White	1 (Reference)	
	Black	0.84 (0.62-1.15)	0.278
	Asian	2.94 (1.31-6.60)	0.009
Palliative Care Utilization	None	1 (Reference)	
	Chemotherapy, Hormone Therapy, or Other Systemic Drug	3.97 (1.29-12.27)	0.017

Abstract ID 21380
DOI: 10.1530/endoabs.89.P2

P3

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

Robert W. Hu, Tiffany Chu & Peter T. Silberstein
Creighton University School of Medicine, Omaha NE.

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.
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,

and treatment modality contributed to survival outcomes in patients with islet cell carcinoma.

Table 1: Multivariate Analysis of Survival Outcomes

Variable		Hazard Ratio (95% CI)	*P*-value
Age	Youth (14-47 years)	1 (Reference)	
	Elderly (>65)	2.51 (1.93-3.27)	<0.001
Insurance Status	Not Insured	1 (Reference)	
	Private Insurance	0.54 (0.32-0.89)	0.015
Percent No High School Degree	≥17.6%	1 (Reference)	
	<6.3%	0.80 (0.65-0.97)	0.026
Treatment Modality	No Treatment	1 (Reference)	
	Surgery Only	0.22 (0.19-0.26)	<0.001
	Systemic Treatment Only	1.546 (1.28-1.88)	<0.001

Conclusion

For patients with islet cell carcinoma, various socioeconomic factors impacted the treatment modality received. Demographic and socioeconomic factors, including age, insurance status, and HSD led to greater overall survival. Surgery as a category was the treatment modality that resulted in greatest overall survival. Further studies should be conducted to analyze how certain variables may affect treatment and outcomes so that we may better understand how healthcare disparities impact patients with islet cell carcinoma.

Abstract ID 21386

DOI: 10.1530/endoabs.89.P3

P4

Carcinoid Heart Disease in Patients Diagnosed with Small Bowel and Lung Neuroendocrine Tumors

Julie Hallet MD, MSc[1,2], Katrina Duncan MD, MPH[1], Simron Singh MD, MPH[2,3], Victoria Barabash MSc[4], Shaheeda Ahmed MD[2,3], Sten Myrehaug MD[2,5], Natalie Coburn MD, MPH[1,2] & Calvin Law MD, MPH[1,2]

[1]Department of Surgery, University of Toronto, Toronto, ON, Canada; [2]Susan Leslie Clinic for Neuroendocrine Tumors, Toronto, ON, Canada; [3]Department of Medicine, University of Toronto, Toronto, ON, Canada; [4]Sunnybrook Research Institute, Toronto, ON, Canada; [5]Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada.

Background

Carcinoid heart disease (CHD) is a complication of neuroendocrine tumors (NETs). While its pathophysiology and manifestations are described, little is known about its occurrence in all patients diagnosed with NETs. We examined the occurrence of CHD and explored the use of echocardiography after diagnosis of NET.

Methods

We conducted a population-based retrospective cohort study of adults diagnosed with small bowel and lung NETs (2000-2019). CHD was defined as new congestive heart failure or valvular disease. Cumulative incidence functions (CIF with 95%CI) of CHD and use of echocardiography were computed accounting for the competing risk of death. Fine-Gray models examined factors associated with CHD (reported as sub-hazard ratios – sHR with 95%CI).

Results

Of 5,735 patients with NETs, 54.1% had small bowel primaries and 48.8% metastatic disease. Median follow-up was 52 months (inter-quartile range 20-99). The CIF of CHD in all patients were 7.8% (7.0-8.4%) at 5 years and 10.7% (9.8-11.7%) at 10 years. CHD was more frequent for small bowel (10-year CIF 12.7% [11.2-14.2%]) than lung (10-year CIF 9.1% [8.0-10.3%]) NETs. No difference was observed by metastatic status. Of 1,864 patients with available urinary 5HIAA data, 64.0% had elevated results. CHD was more frequent with elevated serotonin (10-year CIF 13.5% [11.3-15.9%]) than without (10-year CIF 9.0% [95%CI 6.4-12.2%]). Higher comorbidity burden (sHR 1.3 [1.1-1.6]), small bowel primary (sHR 1.4 [1.2-1.6]), and serotonin secretion (sHR 1.5 [1.1-2.1]) were associated with increased incidence of CHD. CIF for use of echocardiography in all patients was 64.7% (63.3-66.1%) at 10 years. Use of echocardiography reached >50% in all sub-groups. Patterns of echocardiography CIF mirrored those of CHD across sub-groups.

Conclusion

CHD occurred in 10 out of 100 patients in the 10 years after small bowel and lung NETs diagnosis. Patterns of echocardiography use suggest that testing is not influenced by NET disease characteristics, with risks of under-detection in at-risk individuals. Knowledge of factors associated with CHD can be used to target future screening efforts for early diagnosis of CHD.

Abstract ID 21400

DOI: 10.1530/endoabs.89.P4

P5

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

Bahar Laderian[1], Nicole Farha[2], Alok Khorana[1], Smitha Krishnamurthi[1], Wei (Auston) Wei[3], Bassam Estfan[1], Emre Gorgun[4], Eren Berber[5], Amanjit Gill[6] & Tito Fojo[7]

[1]Cleveland Clinic Lerner College of Medicine, Taussig Cancer Institute; [2]Cleveland Clinic Lerner College of Medicine, Department of Internal Medicine; [3]Cleveland Clinic Lerner College of Medicine, Department of Quantitative Health Sciences; [4]Cleveland Clinic Lerner College of Medicine, Department of Colorectal Surgery; [5]Cleveland Clinic Lerner College of Medicine, Center for Endocrine Surgery; [6]Cleveland Clinic Lerner College of Medicine, Imaging Institute; [7]Columbia University Herbert Irving Comprehensive Cancer Center.

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 NECs. 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 19.1%; $P<0.0001$ for YO-NET and 19.0% 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

	Number	5-year survival	*P*-value
NET			
YO-No Surgery vs LO-No Surgery	2,921 vs 17,330	75% vs 54%	<0.0001
YO-Surgery vs LO-Surgery	20,631 vs 69,494	94% vs 81%	<0.0001
NEC			
YO-No Surgery vs LO-No Surgery	3,018 vs 18,873	31% vs 20%	<0.0001
YO-Surgery vs LO-Surgery	5,490 vs 21,357	83% vs 66%	<0.0001

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

P6

Evaluating the Impact of Education on Clinician Integration of Guidelines, Real-World Data, and Patient Perspectives on Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

Tariqa Ackbarali, PhD[1] & Cindy Lovelace[2]

[1]PlatformQ Health, LLC, Needham, MA; [2]Healing NET Foundation.

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 heterogeneous 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/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.
Abstract ID 21418

DOI: 10.1530/endoabs.89.P6

P7

Feasibility of e-NET: A Web-Based Health Platform to Investigate Quality of Life in Patients with Neuroendocrine Tumors

Claire K. Mulvey[1,2], Paige Steiding[1,2], Farhana Moon[1,2], Alan Paciorek[1,3], Li Zhang[1,3] & Emily K. Bergsland[1,2]
[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco CA; [2]Department of Medicine, Division of Hematology/Oncology, University of California, San Francisco San Francisco, CA; [3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA. .

Background
Patients with neuroendocrine neoplasms (NENs) have chronic symptoms from hormone overproduction, tumor growth and metastasis, and side effects from prolonged treatment. We assessed the feasibility of using a digital health platform to recruit patients with NENs to evaluate symptoms and quality of life.
Methods
eNET is a prospective, web-based, cohort study for patients with advanced NENs of any primary site, histologic grade, differentiation, and functional status. Validated surveys (baseline and every 6-12 months for 3 years) are completed online using the Eureka digital health platform, developed at the University of California, San Francisco. Survey topics include medical history, symptoms, lifestyle, and quality of life. Consented participants provide study feedback in a separate Redcap survey.
Results
The eNET study launched in April 2021. As of July 2022, 196 participants of the $n=200$ pilot cohort have enrolled. Of these, 113 (58%) have completed all surveys in the baseline study visit, with another 20 (10%) study visits still in progress. Demographic characteristics of study participants are shown in the **Table.** A majority (90%) of participants live in the United States, 10% reside in 8 other countries. Most participants (73%) are married or partnered, and 68% have bachelors or higher degree. In terms of NEN history, median time since diagnosis is 4 years (range: <1 to 45). Primary site: gastrointestinal (50%), pancreas (28%), lung (8%), other (5%), unknown (7%), or multiple (2%). Tumors grade: low (42%), intermediate (29%), high (9%), or unknown (20%). At least one feedback survey question was answered by 115 (59%) of participants; 81% were satisfied with participating in the study and 64% felt the surveys effectively captured their experience living with a NEN. Eighteen percent felt too much time was required; 13% suggested removing the fertility survey and 16% the sexual health survey. Participants expressed interest in future research on side effects from NEN treatments.

Table. Participant Demographics

Variable	n (%)
Age ($n=196$), median [range]	65 years [28, 83]
Biological sex ($n=169$)	
Female	115 (68%)
Male	54 (32%)
Race ($n=170$)	
White	156 (92%)
Asian	6 (4%)
Other	3 (2%)
Multiple races	5 (3%)
Hispanic ethnicity ($n=170$)	6 (4%)

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

DOI: 10.1530/endoabs.89.P7

P8

Multivisceral Surgical Resection of Locally Advanced Pancreatic Neuroendocrine Tumor is Associated with a Survival Benefit

Matthew C. Hernandez, MD, Kevin M. Sullivan, MD, Laleh G. Melstrom, MD, Yuman Fong, MD & Gagandeep Singh MD
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 multivisceral resection for locally advanced PNET compared to pancreatectomy alone. This study investigated the association of surgical resection on overall survival comparing pancreas 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 pancreas specific surgery (PSS) and 578 (6.7%) underwent multivisceral surgery. In the multivisceral surgery group, median overall survival was similar to PSS 41 months [95% CI 37-47] vus 45 months [95% CI 44-48] ($P=0.9$, Figure). Distant disease (HR 1.4 [95%CI 1.3-1.5]) and no receipt of surgery (HR 1.4 [95%CI 1.3-1.6]) were independent predictors of poor overall survival ($P<0.0001$).
Conclusion
Overall survival was similar in patients who underwent multivisceral and pancreas specific surgery for PNETs. When feasible, multivisceral surgery should be considered for selected patients within the confines of multidisciplinary strategies.
Abstract ID 21439

DOI: 10.1530/endoabs.89.P8

P9

Lifestyle and Neuro-endocrine Tumor (NET) Development Within the European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort

Marit Bogaards, BSc[1], Anne.M. May, PhD[2], N. Charlotte Onland-Moret, PhD[2], Amanda J. Cross, PhD[3], Linda Eriksson, PhD[4], Gerlof D. Valk, MD, PhD[1], Nicolas Girard, MD[5], Marc Gunter, PhD[3], Thomas Walter, MD PhD[6], Sylvie Lantuejoul, MD, PhD[7] & Rachel S. S. van Leeuwaarde, MD, PhD[1]
[1]Department of Endocrine Oncology, University Medical Centre Utrecht, Utrecht (NL); [2]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht/Utrecht University, Utrecht (NL); [3]Department of Epidemiology and Biostatistics, School of Public Health, Faculty of Medicine Imperial College, Londen (UK); [4]Institution of Odontology, Umeå University, Umeå (SE); [5]Département de Oncologie médicale, Pneumologie, Institut Curie, Paris (FR); [6]Département de Gastro-enterologie et Hépatologie, Hôpital Édouard-Herriot, Hospices civils de Lyon, Lyon (FR); [7]Département de Biopathologie, Centre de Lutte Contre le Cancer UNICANCER Léon Bérard, Lyon (FR).

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/endoabs.89.P9

P10

Environmental Pollution and GEP-NENS – Is There an Association?

Philip H. G. Ituarte, PhD, Nora Ruel MA, Daneng Li MD & Gagandeep Singh MD
City of Hope National Medical Center, Duarte CA.

Background
Incidence of gastroenteropancreatic neuroendocrine neoplasms (GEP-NEMs) is increasing, but etiology of sporadic, non-familial disease remains obscure. Behavioral risk factors like smoking and alcohol consumption may be associated with GEP-NENs, 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 and1,491 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. For GI-NENs the R-squared (R^2) estimate from regressing incidence rate on pollution burden score was 0.06, indicating this variable explained 6% of the variation in GI-NEN county level incidence rate. For GI-NEN incidence the R^2 measure for air pollution categories were the highest observed (diesel $R^2 = 0.07$; traffic exposure $R^2 = 0.08$). These positive correlations contrasted with results from regression of GI-NEN incidence on scores for drinking water, ozone, or groundwater which yielded R^2s close to zero. Similarly, PI-NEN incidence regressed on air pollutants yielded low R^2s (diesel PM $R^2 = 0.02$; traffic exposure $R^2 = 0.02$) but a nearly zero R^2 for pollution burden score ($R^2 = 0.0004$) 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/endoabs.89.P10

Other

O1

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, MSCI[1], Sharon Phillips, MSPH[2], Cody M Lebeck Lee, MD[1], Rajiv Agarwal, MD, MSCI[1], Emily Bergsland, MD[3], Jonathan Strosberg, MD[4], Jennifer A. Chan, MD, MPH[5], Heather LaFerriere, MLIS[6], Robert A. Ramirez, DO[1], Jordan Berlin, MD[1] & and Arvind Dasari, MD, MS[7]
[1]Division of Hematology and Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; [2]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN; [3]Department of Medicine, University of California San Francisco, San Francisco, CA; [4]Department of Gastrointestinal Oncology, H. Lee Moffit Cancer Center, Tampa, FL; [5]Dana Farber Cancer Center, Boston, MA; [6]Biomedical Library, Vanderbilt University, Nashville, TN; [7]Divison of Cancer Medicine, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center.

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 of 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 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 ($x1^2 = 8.47$, $P < .01$). 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 ($x1^2 = .32$, $P = .57$). 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 bleeding, 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 trial 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/endoabs.89.O1

O2

The Association Between Patient-Reported Symptom Burden and Urgent Healthcare Use in Patients Diagnosed with Neuroendocrine Tumors

Katrina Duncan, MD, MPH[1], Antoine Eskander, MD, ScM[2,3], Rinku Sutradhar, PhD[4], Christopher Noel, MD, PhD[2], Victoria Barabash, MSC[5], Natalie Coburn, MD, MPH[1], Calvin Law, MD, MPH[1,6], Simron Singh, MD, MPH[6,7], Sten Myrehaug, MD[6,8], Wing Chan, MPH[4] & Julie Hallet, MD, MSc[1,6]
[1]Department of Surgery, University of Toronto, Toronto, ON, Canada; [2]Department of Otolaryngology, University of Toronto, Toronto, ON, Canada; [3]Department of head and neck surgery, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [4]ICES, Toronto, ON, Canada; [5]Sunnybrook Research Institute, Toronto, ON, Canada; [6]Susan Leslie Neuroendocrine Tumors Clinic - Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [7]Department of Medicine, University of Toronto, Toronto, ON, Canada; [8]Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada.

Background
Patients with neuroendocrine tumors (NETs) have high burden of symptoms that persists over years after diagnosis. Patient-reported outcomes (PROs) are routinely screened for in oncology practice but seldomly used to trigger interventions. Further information about how PROs are linked to outcomes is necessary to improve their use for symptom management for NETs. We examined the association between PROs symptom burden and urgent healthcare use after NET diagnosis.
Methods
We conducted a population-based study of adults with NETs (2010-2019). Symptom burden was captured using routine Edmonton Symptom Assessment System (ESAS) scores within 2 years of diagnosis. Logistic regression models determined the association between ESAS scores and subsequent 14-day urgent healthcare use (emergency department visit and/or urgent hospital admission), with generalized estimating equations to account for patient-level clustering.
Results
4,278 patients completed 19,612 ESAS assessments. Each 1-point increment in drowsiness (OR 1.03, 95%CI 1.00-1.07), lack of appetite (OR 1.09, 95%CI 1.06-1.12), pain (OR 1.08, 95%CI 1.05-1.11), and poor wellbeing (OR 1.05, 95%CI 1.01-1.09) individual symptom scores were associated with higher urgent healthcare use, after adjusting for relevant covariates. We computed a global ESAS score using the highest individual symptom score (high-ESAS) for each assessment. Each 1-point increase in high-ESAS was associated with 21% increase in the odds of urgent healthcare use (OR 1.21, 95%CI 1.18-1.24). When used as categorical variable, patients with moderate (score 4-6) and severe score 7-10) high-ESAS had increased odds of urgent healthcare use compared to those with mild high-ESAS, with OR 1.78 (95%CI 1.48-2.13) and 3.33 (95%CI 2.80-4.00), respectively.
Conclusion
ESAS scores are associated with subsequent short-term urgent healthcare use after a NET diagnosis. This indicates a potential gap in managing outpatient patient-reported symptoms. Routine monitoring of ESAS scores should be leveraged to identify patients at high-risk of urgent healthcare use in need for better symptom management.
Abstract ID 21401

DOI: 10.1530/endoabs.89.O2

O3

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

Farhana Moon[1], Bryan Khuong Le[1], Alan Paciorek[2], Amie Blanco[3], Adrienne Wakeling[3], Claire K. Mulvey[4], Li Zhang[2], Nancy M. Joseph[5] & Emily Bergsland[4]
[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [2]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA; [3]Cancer Genetics and Prevention Program, University of California San Francisco, San Francisco, CA, USA; [4]Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA, USA; [5]Department of Pathology, University of California San Francisco, San Francisco, CA, US.

Background
The incidence of germline pathogenic/likely pathogenic variants (P/LPV) is relatively well described in low grade well differentiated neuroendocrine tumors (NETs). 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 gastro enteropancreatic (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 G3NETs, NECs or ambiguous G3NEN. Data were collected from germline and tumor molecular sequencing reports. In patients harboring a germline P/LPV, somatic P/LPV were evaluated.
Results
Among 88 UCSF patients with G3NEN, 15 (17%) had germline P/LPV (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

($n=30$), colorectum (CR) ($n=23$), other gastrointestinal (GI) ($n=14$), and unknown ($n=21$). Histologic subtypes: 34 NEC, 24 G3NET, and 30 ambiguous G3NEN. Fifteen of 16 total germline P/LPV were also evaluable on somatic panels and 10 (67%) were present in the tumor with high mutant allele frequency (maf), suggesting a role in tumorigenesis. Five of 15 germline P/LPV (33%, 2 MUTYH, 1 BRCA1, 1 APC, and 1 PALB2) were not present or had significantly decreased maf in the tumor, arguing against a role in tumorigenesis.

Table: Germline P/LPV in G3NENs [Note: ** not sequenced in tumor]

Gene	Mutated in germline (n)	Mutated in tumor (n)	Differentiation	Site
MUTYH	4	2	1 NEC 3 Ambiguous	2 Pancreas 2 Unknown
BRCA1	2	1	1 NEC 1 ambiguous	1 Pancreas 1 GI
APC	2	1	NEC	1 CR 1 GI
BRCA2	1	1	Ambiguous	CR
MLH1	1	1	NEC	CR
MSH6	1	1	Ambiguous	CR
NTHL1**	1	**	Ambiguous	Pancreas
PALB2	1	0	NET	CR
ATM	1	1	NEC	GI
CHEK2 and MEN1	1	1 (CHEK2 & MEN1)	NET	Pancreas

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/endoabs.89.O3

O4

Immune Cell Molecular Pharmacodynamics of Lanreotide in Relation to Treatment Response

Sabah Alaklabi[1], Orla Maguire[2], Yali Zhang[3], Jacky Chow[4], Jiamin Wang[3], Hans Minderman[2] & Renuka Iyer[1]

[1]Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [2]Flow & Image Cytometry, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [3]Biostatistics & Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [4]Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA.

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+ T 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 interferon signaling (in CD8+ 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.

	Responders ($n=9$)	Non responders ($n=8$)
Age Median (range), y	69 (34-79)	66 (50-81)
pNET	5	4
Intestinal NET	4	3
Unknown	0	1
Metastatic sites N (%)		
Liver	6	6
Nodes	1	2
Lung	0	1
Skin	0	1
Peritoneum	1	0
Ki 67		
Not specified	1	2
< %3	5	0
3% - 20%	3	4
>20%	0	2
Differentiation		
Not specified	1	0
Well differentiated	8	7
Moderately differentiated	0	1

Abstract ID 21431

DOI: 10.1530/endoabs.89.O4

O5

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

Florence Bénard[1], Frédéric Mercier[1], Sandrine Huez[2] & Marie-Pascale Pomey[3]

[1]Surgical Oncology, Department of Surgery, Centre Hospitalier de l'Université de Montréal (CHUM), 1051 Sanguinet Street, Montreal, QC, H2X 3E4, Canada; [2]Centre d'Excellence pour le Partenariat avec les Patients et le Public, 900 Saint-Denis Street, Montréal, Québec, H2X 0A9, Canada; [3]Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), 900 Saint-Denis Street, Montréal, Québec, H2X 0A9, Canada. Department of Public Health, Université de Montréal, 7101 Parc Avenue, Montréal, Québec, H3N 1X9, Canada.

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 accompaniment 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 evaluate the feasibility and concrete impacts of such a program on NET patients' trajectory of care.
Abstract ID 21433

DOI: 10.1530/endoabs.89.O5

O6

Frequency of Pulmonary Carcinoid Tumor Research Presented at Major International Neuroendocrine and Lung Cancer Scientific Meetings

Robert A. Ramirez[1], Tatsuki Koyama[2] & Satya Das[1]
[1]Vanderbilt University Medical Center, Department of Internal Medicine, Division of Hematology/Oncology, Nashville, TN, USA; [2]Vanderbilt University Medical Center, Department of Biostatistics, Nashville, TN, USA.

Background
Pulmonary carcinoid (PC) tumors represent approximately 25% of neuroendocrine tumors (NETs) and about 2% of all lung cancers. Despite the relative prevalence of PCs compared to all NETs, there is only one FDA indicated therapy (everolimus). Since regulatory approvals stem from publications that are often initially presented at scientific meetings, we sought to determine the frequency of presentations including PCs at two major international NET and lung cancer meetings.
Methods
The North American Neuroendocrine Tumor Society (NANETS) annual meeting and the International Association for the Study of Lung Cancer World Conference on Lung Cancer (WCLC) were identified as high impact scientific meetings and used as the data repository for the analysis. NANETS (2010-2021) and WCLC (2013-2021) were searched for abstracts pertaining to PCs. Abstracts were divided into the following categories: preclinical, clinical trial, clinical landscape (institutional reviews, case series, database-analyses, guidelines or similar), or trials in progress. We also recorded whether PC was included or the primary focus of the abstract. WCLC was also searched for trials related to ROS-1 positive lung cancer which represents approximately 2% of all lung cancers.
Results
A total of 18,671 abstracts were presented at both meetings and included 252 PC (1.3%). NANETS had 958 abstracts identified with 165 (17.2%) including PCs. WCLC had 17,713 abstracts with 87 (0.5%) including PCs. There were 136 (0.77%) abstracts including ROS-1 positive lung cancers at WCLC. Of abstracts which included PC, preclinical studies comprised 29 (18%) and 15 (17%) at NANETS and WCLC, respectively. Of abstracts which included PC, clinical landscape studies made up 77 (47%) at NANETS and 68 (78%) at WCLC, respectively. The total number of clinical trials/trials in progress that included PCs was 47/12 at NANETS and 3/1 at WCLC. The total number of primary PC clinical trials was 6 (3 NANETS/3 WCLC).
Conclusion
PC abstracts were underrepresented in proportion to the incidence of PC at both NANETS and WCLC. However, PC studies more likely to be presented at NANETS (20% vs 0.5%). Most abstracts that included PCs were not primarily PC-focused. The number of primary PC clinical trials were low at each meeting. ROS-1 lung cancer abstracts were better represented at WCLC compared to PC abstracts; this may account for the higher number of approved treatments for ROS-1 positive lung cancer despite similar incidence to PCs. PC patients would benefit from dedicated clinical trials to increase treatment options.
Abstract ID 21462

DOI: 10.1530/endoabs.89.O6

O7

Circulating Tumor DNA Detection Using a Personalized, Tumor-Informed Assay in Metastatic Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumor Patients

Lindsay A Hunter, MD & Heloisa P. Soares, MD, PhD
Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT.

Background
Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a clinically heterogenous group. Determining the appropriate selection of therapy and optimal monitoring can be difficult due to their diverse behavior. Furthermore, monitoring or surveillance typically consist of frequent imaging, potentially over decades. Circulating tumor DNA (ctDNA) has shown promise as a minimally 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 complied 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 MTM/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.
Abstract ID 21465

DOI: 10.1530/endoabs.89.O7

O8

Variants of Uncertain Significance (VUS) are More Common in Non-Caucasian Patients with Neuroendocrine Neoplasms (NENs)

Farhana Moon[1], Bryan Khuong Le[1], Alan Paciorek[2], Amie Blanco[3], Adrienne Wakeling[3], Claire K. Mulvey[4], Eric Nakakura[5], Li Zhang[2], Nancy M. Joseph[6] & Emily Bergsland[4]
[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [2]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA; [3]Cancer Genetics and Prevention Program, University of California San Francisco, San Francisco, CA, USA; [4]Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA, USA; [5]Department of Surgery, Division of Surgical Oncology, University of California San Francisco, San Francisco, CA, USA; [6]Department of Pathology, University of California San Francisco, San Francisco, CA, USA.

Background
Germline pathogenic or likely pathogenic (P/LP) 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; 86% ($n=239$) 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% ($n=173$), 8.3% ($n=20$) poorly differentiated neuroendocrine carcinoma (NEC), 5.4% unknown differentiation ($n=13$), plus 13.8% PPGL ($n=33$). Overall, 20% ($n=48$) 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,

95% CI: 1.74-14.84, *P*-value < 0.001]. Also, VUS detection was significantly higher in non-white population (63.4%, *n* = 40/63) compared to 40.2% of white population (*n* = 70/174) [OR = 2.58, 95% CI: 1.42-4.68, *P*-value < 0.001]. VUS prevalence did not vary by tumor differentiation- 48% of NETs (*n* = 84) and 60% of NECs (*n* = 12) (*P* = 0.25). Germline testing panel size increased over the study period and ranged from 1 to 155 genes panels. Median number of genes was 84, with increased detection of VUS in larger panels (*P* < 0.001).

Conclusion

VUS detection is common in NEN patients undergoing large panel germline testing and is more frequent in non-white and Hispanic populations. This represents current disparities in clinical genetic testing and genomic research. Larger cohorts of non-white and Hispanic populations are needed to support reclassification of VUS over time. Ongoing work is focused on assessing the downstream consequences of both germline mutations and VUS in NEN patients.

Abstract ID 21471

DOI: 10.1530/endoabs.89.O8

O9

Leveraging Transcriptomics to Grade Pancreatic Neuroendocrine Neoplasms(NENs) and Assess Molecular Alterations Associated with Somatostatin Receptor(SSTR) Subtype Expression

Emil Lou[1], Nishant Gandhi[2], Alex Farrell[2], Joanne Xiu[2], Andreas Seeber[3], Muhammad Shaalan Beg[4], Sourat Darabi[5], Michael J. Demeure[5], Jim Abraham[2], Matthew Oberley[2], John Marshall[6] & Heloisa Soares[7]
[1]Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA; [2]Caris Life Sciences, Phoenix, AZ, USA; [3]Comprehensive Cancer Center Innsbruck, Medical University of Innsbruck, Innsbruck, Austria; [4]University of Texas Southwestern, Dallas, TX, USA; [5]Hoag Memorial Hospital Presbyterian, Newport Beach, CA, USA; [6]Georgetown University, Washington, DC, USA; [7]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA.

Background

SSTR substypes are collectively expressed in the majority of NENs. However, SSTR subtype expression is not routinely assessed for clinical decision-making, including patients eligible for targeted radionucleotide therapy. Elucidating the landscape of SSTR subtypes in context of molecular profiles for low-grade (LG-) and high-grade NENs (HG-NENs) provides an opportunity to better tailor targeted therapy. Here, we leverage the ability of transcriptomics to predict NEN grade, while identifying molecular landscapes associated with SSTR subtype expression in Pancreatic NENs (PanNENs).

Methods

1768 cases of NENs were analyzed using Next Generation Sequencing(NextSeq), Whole Exome or Whole Transcriptome Sequencing(WTS, NovaSeq) at Caris Life Sciences(Phoenix, AZ). Significance was determined using chi-square, Fisher-Exact or Mann-Whitney U and p-adjusted for multiple comparisons ($q < 0.05$).

Results

Using Receiver-Operating Characteristic analysis on 318 cases with histological grade annotation (hga), we identified a threshold of *MKI67* expression which differentiated LG- from HG-NENs, with a true positive rate of 86.84% and false positive rate of 11.9%(AUC = 95%). This threshold was applied to the entire cohort to infer HG/LG. The differences between the mutational landscapes of HG- and LG-NENs were faithfully recapitulated in hga- and *MKI67*-based cohorts, including *TP53*(delta = 58.2%, 42.8%), *RB1* (delta = 46.6%, 35.2%), *KRAS* (delta = 14.8%, 10%), and *MEN1* (delta = -18.4%, -10.8%). Further, the expression of *SSTR-1*, *-2* and *-3* were lower, while *-4* was higher in HG- vs LG-PanNENs with a similar trend in *TP53*, *RB1*, *KRAS* and *MEN1 alterations* (all $q < 0.05$) as mentioned above. For each SSTR subtype, we established high and low cohorts based on their median mRNA expression. Among SSTR-1,-2-high vs low HG-PanNENs, the mutational prevalence of *MEN1* (delta = 29.5%, 34.4%), *ATRX* (delta = 16.5%, 30.4%), and *TSC2* (delta = 16.5%, 30.4%) were increased, while *KRAS* (delta = -35%, -37%) and *RB1* (delta = -35%, -41%), were decreased (all at least $P < 0.05$). Similar, but less pronounced differences were observed in LG-PanNENs. Gene Set Enrichment Analysis revealed increased adipogenesis, hedgehog and IL-2/STAT5 signaling in HG-PanNENs and increased DNA damage repair and PI3K/AKT/mTOR pathways in LG-PanNENs in the SSTR-1,-2-high cohorts. Finally, only patients with SSTR-5-high LG-PanNENs had significantly better prognosis (HR = 0.248, *P* = 0.01).

Conclusion

Here, we provide evidence that WTS can be effectively leveraged to predict NEN grade and lay the foundation for defining characteristic differences in the molecular landscapes associated with specific SSTR subtypes in HG- and LG-PanNENs. Incorporating molecular profiling in this manner can assist in tailoring treatment for patients with PanNENs.

Abstract ID 21474

DOI: 10.1530/endoabs.89.O9

O10

Germline Cancer Testing in Unselected Patients with Neuroendocrine Neoplasms: A Multi-center Prospective Study

Mohamad Bassam Sonbol[1], Samee Zane Alheraki[1], Michael Golafshar[2], Katie Kunz[3], Margaret Klint[2], Edward Esplin[4], Robert L. Nussbaum[4], Timothy Hobday[5], Jason Starr[6], Daniel Ahn[1], Tanios Bekaii-Saab[1], Niloy Jewel Samadder[1] & Thorvardur Halfdanarson[5]
[1]Mayo Clinic Cancer Center, Arizona; [2]Department of Health Services Research, Mayo Clinic, Phoenix, Arizona; [3]Department of Quantitative Health Sciences, Mayo Clinic, Scottsdale, Arizona; [4]Invitae, San Francisco, California; [5]Mayo Clinic Cancer Center, Minnesota; [6]Mayo Clinic Cancer Center, Florida.

Background

Neuroendocrine neoplasms (NEN) are known to be associated with specific familial syndromes. However, the incidence of pathogenic germline variants (PGVs) in unselected NEN patients is unknown. In this study, we aim to determine the prevalence and clinical utility of PGVs in unselected NEN patients using universal a genetic testing approach.

Methods

We undertook a prospective study of germline genetic testing using a > 80 gene next-generation sequencing panel among NEN 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. Family cascade testing was offered at no charge. Data were analyzed using descriptive statistics to look for trends across patient characteristics and results of the germline genetic testing.

Results

A total of 55 patients with NEN 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 NEN was reported in 8% (4/50) patients. PGVs were detected in 14.5% (*n* = 8) of patients. The prevalence of PGVs was 15.7% (6/38) in pancreatic primary, 11.7% (2/17) in non-pancreatic primary. PGVs detected were the following: *APC* (1), *ATM* (1), *CHEK2* (1), *MEN1* (1), *MITF* (1), *MLH1* (1), and *MUTYH* (2). VUS results are summarized in the table. Overall, a VUS was found in 38% (21/55) of the patients. Five patients had findings in mismatch repair genes (MMR): one patient had a PGV in *MLH*1, 3 patients with VUS in *MSH6*, and one patient with a VUS in *MSH2*. MMR protein testing was done in 3/4 VUS patients, and was MMR deficient in 2 of them.

	VUS (*n* = 34)
ALK	2
APC	1
ATM	1
BRIP1	2
CASR	2
CDH1	1
CHEK2	0
CTNNA1	1
DICER1	1
EGFR	1
FLCN	1
MEN1	1
MITF	0
MLH1	0
MSH2	1
MSH6	3
MUTYH	1
NBN	1
NTHL1	1
PALB2	1
PDGFRA	1
POLD1	1
RAD50	1
RECQL4	3
RET	1
SMARCA4	1
STK11	1
TERC	1
WRN	2

Conclusion

Universal multi-gene panel testing in NEN was associated with detection of heritable mutations in 15% of patients. Alterations in MMR genes were found in

9% of patients which highlights the importance of germline testing for familial counseling and treatment selection.
Abstract ID 21476
DOI: 10.1530/endoabs.89.O10

O11

Pheo Para Alliance Patient Centered Research on Challenges for Those with Pheochromocytoma and Paraganglioma

Linda Rose-Krasnor[1,2], Stephanie Alband[2], Jacques W. M. Lenders[3,4] & Lauren Fishbein[4,5].
[1]Psychology Department, Brock University, St. Catharines, ON, Canada; [2]Pheo Para Alliance; [3]Department of Internal Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany and Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands; [4]Pheo Para Alliance Medical Advisory Board; [5]Department of Medicine, Division of Endocrinology, Metabolism and Diabetes, and Department of Biomedical Informatics, University of Colorado School of Medicine, Aurora, CO.

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.
Abstract ID 21562
DOI: 10.1530/endoabs.89.O11

O12

An Appraisal of Findings from a Neuroendocrine Neoplasm (NEN) Tumor Board (TB): Is There Added Value or Is It Redundant?

Nikolaos A Trikalinos[1], Chet Hammill[2], Jingxia Liu[3], Pooja Navale[4], Kyle Winter[1], Deyali Chatterjee[5], Amir Iravani[6], Manik Amin[7] & Malak Itani[8]
[1]Department of Medicine, Division of Oncology, Washington University Medical School, St. Louis, MO, USA and Siteman Cancer Center, St Louis, MO, USA; [2]Department of Surgery, Washington University in St. Louis, St Louis, MO, USA; [3]Division of Public Health Sciences, Washington University Medical School, St. Louis, MO, USA; [4]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis MO; [5]Department of Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Department of Radiology, Fred Hutchinson Cancer Center, University of Washington, Seattle, WA; [7]Department of Medical Oncology, Dartmouth Hitchcock Medical Center, NH, 03766, USA; [8]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO.

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 in 2.6%. 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.
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.
Abstract ID 21582
DOI: 10.1530/endoabs.89.O12

Trials In Progress

T1

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

Shannon Stockton[1], G. Dan Ayers[1], Michael Cecchini[2], Raid Ajumaily[3], Jennifer Whisenant[1], Steven Gore[4], Percy Ivy[4], Patricia LoRusso[2], Jordan Berlin[1] & Satya Das[1]
[1]Vanderbilt University Medical Center, Ingram Cancer Center, Nashville, TN; [2]Yale University Cancer Center, New Haven, CT; [3]Oklahoma University Health Stephenson Cancer Center, Oklahoma City, OK; [4]National Cancer Institute, Cancer Therapeutics Evaluation Program, Bethesda, MD.

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 Q14 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 are eligible. In dose expansion, patients must have SCLC, EP-NEC (large cell or 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.
Results
The trial is currently enrolling patients.

Biomarker	Phase of Study	Time of Collection	Purpose	Mandatory (M)/Optional (O)
γH2AX, pNBS1	Dose Expansion	D-7 C1D3	Measure DNA damage biomarkers	M
Whole Exome Sequencing, RNA Sequencing	Dose Expansion, Escalation	Archival	Determine if certain mutations or expression of DNA damage repair genes predict treatment sensitivity	O
ATM	Dose Expansion, Escalation	Archival	Identify pts with tumors responsive to ATR inhibition	O

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 inhbitors 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
DOI: 10.1530/endoabs.89.T1

T2

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

Thorvardur R Halfdanarson[1], Daniel M Halperin[2], Diane Reidy-Lagunes[3], Grace Kong[4], Jaume Capdevila[5], Josh Mailman[6], Ken Herrmann[7], Rajaventhan Srirajaskanthan[8], Simone Leyden[9], Thomas Thevenet[10] & Philip Harris[10]
[1]Mayo Clinic, Rochester, MN USA; [2]MD Anderson Cancer Center, Houston, Texas, USA; [3]Memorial Sloan Kettering Cancer Center, New York, USA; [4]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [5]Vall dHebron University Hospital, Vall dHebron Institute of Oncology, Barcelona, Spain; [6]NorCal CarciNET Community, Oakland, CA; [7]University Hospital Essen, Germany; [8]Kings College Hospital, London, UK; [9]NeuroEndocrine Cancer Australia, Victoria, Australia; [10]ITM Oncologics GmbH, Garching/Munich, Germany.

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 ^{177}Lu-edotreotide has demonstrated promising efficacy and a favorable safety profile. Retrospective data in metastatic GEP-NETs treated with two or more ^{177}Lu-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 ^{177}Lu-edotreotide PRRT. At least 202 patients with somatostatin receptor-positive (SSTR+) disease will be randomized 1:1 to up to six cycles of ^{177}Lu-edotreotide, given at 6- to 8-week intervals, or to an active comparator (either chemotherapy [CAPTEM or FOLFOX] or everolimus, according to investigatoŕs 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 29 open sites in Australia, France, India, 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.
Abstract ID 21387
DOI: 10.1530/endoabs.89.T2

T3

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

Aman Chauhan, MD[1], Shagufta Shaheen, MD[2], Keith Usiskin, MD[3], Ade Odueyungbo, PhD[3], Cosina Mui, BSc[3] & Joseph Dillon, MD[4]
[1]University of Kentucky Healthcare, [2]Stanford Medicine, [3]Crinetics Pharmaceuticals, [4]University of Iowa Carver College of Medicine.

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 I 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 over any 7-day period. After completion of screening, subjects will be randomly assigned to the 40 mg vs 80 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

Abstract ID 21388

DOI: 10.1530/endoabs.89.T3

T4

Phase 1-2 Trial of Vesicular Stomatitis Virus Expressing Human Interferon-β and NIS (VSV-IFNβ-NIS), with Pembrolizumab, in Patients with Neuroendocrine Carcinoma

Patrick W. McGarrah[1], Shruthi Naik[2], Thorvardur R. Halfdanarson[1], Konstantinos Leventakos[1], Kah Whye Peng[2], Stephen J. Russell[2], Alex A. Adjei[1] & Julian R. Molina[1]

[1]Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA; [2]Vyriad, Rochester, MN, USA.

Background

Poorly differentiated neuroendocrine carcinoma (NEC) is an aggressive malignancy comprising both pulmonary and extrapulmonary primary sites. NEC includes both small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC), as well as other neuroendocrine carcinomas arising from any primary organ. The optimal systemic therapy beyond first line platinum and etoposide is not established. There is a critical need to improve upon the median survival in the second line, as most patients do not survive more than 6 months. The efficacy of single agent immune checkpoint inhibitors (ICIs) in NEC has been disappointing. One possible explanation for this is that the tumor microenvironment in NEC is non-inflamed. VSV-IFNβ-NIS is a vesicular stomatitis virus (VSV)-based oncolytic virus being tested in multiple early phase clinical trials. Preliminary studies of immune responses in patients receiving VSV-IFNβ-NIS therapy suggest some patients develop T cell responses to viral antigens and known tumor antigens. We hypothesize that VSV-IFNβ-NIS therapy may convert a non-inflamed or immune-excluded phenotype in NEC to a highly inflamed phenotype that sensitizes the tumor to the PD-1 inhibitor pembrolizumab.

Methods

This is a phase 1-2 safety run-in study designed to determine the safety of VSV-IFNβ-NIS in combination with pembrolizumab, followed by dose expansion in patients with refractory non-small cell lung cancer (NSCLC) or NEC. The safety run-in portion of this study has been completed, and we are presently testing the recommended phase 2 dose (RP2D) of VSV-IFNβ-NIS in an expansion cohort of patients with SCLC or NEC of any primary site. Patients must have previously progressed on at least one line of systemic therapy. Prior treatment with checkpoint inhibitors is permitted. Patients are treated with the RP2D of 1.0x10^11 TCID50 VSV-IFNβ-NIS on day 1, followed by pembrolizumab on day 8 and then pembrolizumab every 21 days until progression, up to 2 years. The primary objective is to estimate the response rate by RECIST 1.1. Secondary objectives include estimation of disease-control rate, duration or response, progression-free survival, overall survival, and safety signals.

Results

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.

Conclusion

Trial is currently enrolling patients. NCT03647163

Abstract ID 21395

DOI: 10.1530/endoabs.89.T4

T5

A Phase 2 Open-Label Study of Belzutifan (a HIF-2α Inhibitor) Monotherapy in Patients with Advanced/Metastatic Pheochromocytoma/Paraganglioma or Pancreatic Neuroendocrine Tumors

Camilo Jimenez[1], Julien Hadoux[2], Jaydira Del Rivero[3], Satya Das[4], Othon Iliopoulos[5], Alexander Sultanbaev[6], Elena Artamonova[7], Eric Jonasch[1], Karel Pacak[8], Wei Wang[9], Fan Jin[9], Girish S. Naik[9] & Jaume Capdevila[10]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Gustave Roussy, Villejuif Cedex, France; [3]Developmental Therapeutics Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [4]Vanderbilt University Medical Center, Nashville, TN, USA; [5]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [6]GBUZ Republican Clinical Oncological Dispensary, Ufa, Russia; [7]Federal State Budgetary Institution N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Moscow, Russia; [8]National Institutes of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA; [9]Merck & Co., Inc., Rahway, NJ, USA; [10]Vall Hebron University Hospital and Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain.

Background

Patients with advanced pheochromocytoma/paraganglioma (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 $\geq$12 years (body weight $\geq$40 kg if aged 12–17 years) with histopathologically documented, unresectable, locally advanced/metastatic PPGLs (BP $\leq$150/90 mmHg [$\leq$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) $\leq$12 months from screening, measurable disease per RECIST v1.1 by blinded independent central review (BICR), ECOG PS $\leq$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 SSTR2 + Well-Differentiated GEP-NET with Progression Following Lu-177 SSA

Thomas Hope[1], Samuel Mehr[2], Michael Morris[3], Daneng Li[4], Daniel Halperin, MD[5], Jonathan Strosberg[6], Heloisa Soares[7], Heather Jacene[8], Marianne Pavel[9], Pamela L. Kunz[10], Denis Ferreira[11], Joanne Li[11], Kimberly Ma[11], Jessica Rearden[11], Susan Moran[11] & Simron Singh[12]

[1]University of California San Francisco, CA; [2]Nebraska Cancer Specialists, Omaha, NE; [3]Advanced Molecular Imaging and Therapy, Glen Burnie, MD; [4]City of Hope Comprehensive Cancer Center, Duarte, CA; [5]Anderson Cancer Center, Houston, TX; [6]Moffitt Cancer Center, Tampa, FL; [7]Huntsman Cancer Hospital, University of Utah, Salt Lake City, UT; [8]Dana Farber Cancer Institute, Boston, MA; [9]Friedrich-Alexander University, Erlangen, Germany; [10]Yale University, New Haven, CT; [11]RayzeBio, San Diego, CA; [12]University of Toronto, Odette Cancer Center at Sunnybrook Health Sciences Center, Toronto, ON, Canada.

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 analogues (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 1b/3 trial of RYZ101. Part 1 (Phase 1b) will determine the safety, pharmacokinetics, and recommended Phase 3 dose (RP3D) of RYZ101. Part 2 (Phase 3) 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 8 weeks for up to 4 cycles. Dose levels (n=6/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 8 weeks for up to 4 cycles or investigator's choice SoC (everolimus, sunitinib, or high-dose long-acting SSA); crossover to RYZ101 is permitted. Primary endpoint: progression-free survival (PFS) by blinded independent central review (BICR) using RECIST v1.1. Secondary endpoints: overall survival; objective response rate and best overall response (BICR and investigator assessment); duration of response; disease control rate; PFS (investigator assessment); safety. Exploratory endpoints: PFS after first subsequent anticancer therapy; biomarkers; health-related quality of life. Pharmacokinetic / electrocardiogram (n=30) and dosimetry (n~8) sub-studies will be performed at select sites.
Results
ACTION-1 Part 1 is currently enrolling patients at ~10 US sites. Part 2 will commence after Part 1 at ~60 sites in North America, South America, Europe, and Asia.
Conclusion
No conclusions; TiP abstract.
Abstract ID 21414
DOI: 10.1530/endoabs.89.T6

T7

Methodology of the SORENTO Clinical Trial: Assessing Efficacy and Safety of High Exposure Octreotide Subcutaneous Depot in Patients with GEP-NET

Simron Singh, MD[1], Jaume Capdevila, MD, PhD[2], Jennifer Ang Chan, MD[3], Wouter de Herder, MD[4], Diego Ferone, MD, PhD[5], Daniel Halperin, MD[6], Josh Mailman, MBA[7], Lisa Hellström, MSc[8], Agneta Svedberg, MSc, MBA[8] & Fredrik Tiberg, PhD[8]
[1]Sunnybrook Health Sciences Center, Toronto, Canada; [2]Vall d'Hebron University Hospital, Barcelona, Spain; [3]Dana-Farber Cancer Institute, Boston, MA, United States; [4]Erasmus MC, Rotterdam, The Netherlands; [5]Endocrinology, Department of Internal Medicine & Medical Specialties, IRCCS Ospedale Policlinico San Martino, University of Genova, Italy; [6]The University of Texas MD Anderson Cancer Center, Houston, TX, United States; [7]Northern California CarciNET Community, Oakland, CA, United States; [8]Camurus AB, Lund, Sweden.

Background
Somatostatin analogues (SSAs) are first-line standard of care therapies for gastroenteropancreatic neuroendocrine tumors (GEP-NET), showing efficacy in tumor/symptom control with an established safety profile. Yet, disease progression may occur despite standard-dose SSA treatment, requiring more aggressive and toxic therapies. Retrospective/non-randomized data suggest higher-dose SSAs may benefit patients with GEP-NET who do not respond to standard-dose treatment and provide improved disease control. Octreotide depot (CAM2029) is a novel high-exposure, subcutaneous (SC) formulation. Clinical trials showed ~500% higher CAM2029 bioavailability vs octreotide long-acting release (LAR), and maintenance/reduction of NET symptoms. Prospective, randomized data are needed to confirm the efficacy/safety of novel SSAs with higher bioavailability such as CAM2029, vs standard-dose SSAs including octreotide LAR and lanreotide Autogel (ATG).
Methods
SORENTO is a randomized, multi-center, open-label, active-controlled Phase 3 trial, aiming to enroll 302 adults with GEP-NET. Key eligibility criteria: advanced, well-differentiated NET of GEP/presumed GEP origin; ≥1 measurable SR positive (by nuclear imaging) lesion according to RECIST 1.1; no or <6 months consecutive treatment with long-acting SSAs. Notably, patients with Grade 3 GEP-NET (excluded by CLARINET/PROMID trials) are eligible. Patients will be randomized 1:1 to CAM2029 20mg Q2W, or active comparator (octreotide 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 powered to detect 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
Trial in progress. ClinicalTrials.gov: NCT05050942.
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 (PPGLs)

Aman Chauhan[1], M. Sue O'Dorisio[2], Mark Gaze[3], Constantino Sábado[4], Fazia Brouri[5] & Lingfei Xu[6]
[1]Medical Oncology, University of Kentucky Markey Cancer Center, Lexington, KY, USA; [2]Pediatrics, University of Iowa Carver College of Medicine, Pediatrics, IA, USA; [3]Oncology, University College London Hospitals NHS Foundation Trust, London, United Kingdom; [4]Paediatric Oncohaematology, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [5]Clinical Trial Operations, Advanced Accelerator Applications, a Novartis company, Geneva, Switzerland; [6]Global Drug Development, Novartis Pharmaceuticals, East Hanover, NJ, USA.

Background
GEP-NETS and PPGLs 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 PPGLs 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 PPGLs, there are high unmet needs in this population. SSTR subtype-2 is overexpressed by GEP-NET and PPGL tumors; therefore, it is a relevant target for radioligand therapy with [^{177}Lu]Lu-DOTA-TATE. [^{177}Lu]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 supporting use in pediatric GEP-NETs and PPGLs are limited. The need for additional treatment options for adolescents with GEP-NETs and PPGLs provides a strong rationale to evaluate [^{177}Lu]Lu-DOTA-TATE in these patients.

Methods
This multicenter, phase II, open-label, single-arm study will evaluate the safety and dosimetry of [^{177}Lu]Lu-DOTA-TATE in adolescent patients (12 to $<$18 years old) with advanced, inoperable, SSTR-positive GEP-NETs (grade 1/2, well differentiated) in the primary cohort and PPGLs in the exploratory cohort. Eligible patients will receive 4 cycles of [^{177}Lu]Lu-DOTA-TATE (7.4 GBq/cycle), administered every 8 weeks. After the last dose, patients will be followed for 5 years. Radiation dosimetry and pharmacokinetic (PK) assessments will be done after the first [^{177}Lu]Lu-DOTA-TATE administration. Safety assessments will be performed regularly after each cycle 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 $\geq$8 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

PReCedeNT 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 Neuro-endocrine Tumors

Ameya D Puranik[1], Venkatesh Rangarajan[1], Anant Ramaswamy[2], Vikas Ostwal[2], Shailesh V Shrikhande[3], Manish Bhandare[3], Vikram Chaudhari[3], Munita M Bal[4], Archi Agrawal[1], Nilendu C Purandare[1] & Sneha Shah[1]
[1]Nuclear Medicine, Tata Memorial Hospital, India; [2]Medical Oncology, Tata Memorial Hospital, India; [3]Gastro-intestinal (HPB) Surgery, Tata Memorial Hospital, India; [4]Pathology, Tata Memorial Hospital, India.

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 heterogenous uptake of both tracers; suggestive of tumor heterogeneity. PRRT is widely available at reasonable cost since Lu-177-DOTATATE is manufactured indegenously, and is recommended in all International Guidelines. CAPTEM (Capecitabine-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-positive 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 8-12 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 Capecitabine 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.
Abstract ID 21441
DOI: 10.1530/endoabs.89.T9

T10

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

A Mohamed[1], SL Asa[3], A Azmi[5], D Bajor[1], SH Tirumani[4], JE Selfridge[1], A Mahipal[1], LM Ocuin[2], J Winter[2], J Ammori[2], J Hardacre[2], R Hoehn[2], S Chakrabarti[1], K Rostocil[1] & A Kaseb[6]
[1]Department of Medicine, Division of Hematology and Medical Oncology, UH Seidman Cancer Center; [2]Department of Surgery, Division of Surgical Oncology, UH Seidman Cancer Center; [3]Department of Pathology, UH Seidman Cancer Center; [4]Department of Radiology, UH Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH; [5]Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI; [6]Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas.

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-angiogenesis 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, PGF 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
Abstract ID 21559
DOI: 10.1530/endoabs.89.T10

Author Index