Endocrine Abstracts

October 2023 Volume 98
ISSN 1479-6848 (online)

North American Neuroendocrine Tumor Society 2023

NANETS
NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

published by
bioscientifica

Online version available at
www.endocrine-abstracts.org

Endocrine Abstracts

Volume 98
October 2023

Abstracts Presented at the 16th Annual Multidisciplinary NET Medical Symposium of the North American Neuroendocrine Tumor Society

October 4–6, 2023, Montreal, QC, Canada

Corresponding Author:
Kathleen Van De Loo
NANETS
136 Everett Road
Albany, NY 12205
Phone: 518-465-4549
staff@nanets.net

CONTENTS

16th Annual Multidisciplinary NET Medical Symposium NANETS 2023

Basic Science

B1

Spatial profiling of neuro-immune interactions in gastroenteropancreatic NETs

Suzann Duan[1], Travis W. Sawyer[2], Brandon L. Witten[1], Heyu Song[1] & Juanita L. Merchant[1]
[1]The University of Arizona College of Medicine, Tucson, AZ; [2]The University of Arizona Wyant College of Optical Sciences, Tucson, AZ

Background
Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are heterogeneous malignancies that arise from complex cellular interactions within the tissue microenvironment. Until recently, the absence of reliable methods to unmix tumor- and stroma-derived signals has precluded a comprehensive understanding of how GEP-NETs arise in different tissues. Here, we sought to decipher tumor-derived signals from the surrounding microenvironment by applying Nanostring Digital Spatial Profiling (DSP) to hormone-secreting and non-functional GEP-NETs. By combining this approach with *in vitro* studies in human-derived organoids, we demonstrate the convergence of cell autonomous immune and pro-inflammatory signals that suggests their role in neuroendocrine differentiation and tumorigenesis.
Methods
DSP was used to evaluate the expression of 40 neural and immune-related proteins in surgically resected duodenal and pancreatic NETs ($n = 20$) primarily comprised of gastrinomas (18/20). A total of 279 regions of interest were examined between tumors, adjacent normal and abnormal-appearing epithelium, and the surrounding stroma. The results were stratified by tissue type and Multiple Endocrine Neoplasia I (MEN1) status. Immunohistochemical (IHC) staining of the tumors ($n = 30$) confirmed neuro-immune protein expression and cellular reprogramming of preneoplastic tissues. Cell autonomous inflammatory features were further evaluated by IHC and RNAscope, while functional pro-inflammatory signaling was tested using patient-derived duodenal organoids.
Results
Duodenal gastrinomas (DGASTs) showed significant immune exclusion compared to pancreatic NETs. Compared to non-MEN1 tumors, MEN1 DGASTs and preneoplastic lesions exhibited reduced immune infiltrates coincident with neural reprogramming and a senescent phenotype. Despite a paucity of immune cells, DGASTs showed strong intratumoral expression of the pro-inflammatory and pro-neural factor IL-17B (4/6 patients), whereas expression of this cytokine was restricted to the stroma in pancreatic NETs (3/3). Treatment of human duodenal organoids with IL-17B activated NF-kB and STAT3 signaling and induced the expression of neuroendocrine markers.
Conclusions
Multiplexed spatial protein analysis identified tissue-specific neuro-immune signatures in GEP-NETs. DGASTs are characterized by an immunologically cold microenvironment that permits cellular reprogramming and neoplastic transformation of the preneoplastic epithelium. Moreover, DGASTs cell autonomously express pro-inflammatory factors consistent with a senescent phenotype, including tumor-derived IL-17B, that stimulate the neuroendocrine phenotype.
ABSTRACT ID 23313
DOI: 10.1530/endoabs.98.B1

B2

TMEM127 exerts a tumor suppressive role in pheochromocytoma by mediating RET ubiquitin-dependent degradation

Hector Gonzalez-Cantu[1], Qianjin Guo[1], Zi-Ming Cheng[1], Matthew Rotondi[1], Gabriela Huelgas-Morales[1], Jonathan Lefkowitz[1], Purushoth Ethiraj[1], Zhijun Qiu[1], Wan Song[1], Bethany N. Landry[1], Hector Lopez[1], Cynthia M. Estrada-Zuniga[1], Shivi Goyal[1], Mohammad Aasif Khan[1], Timothy J. Walker[2], Exing Wang[3], Fagian Li[4], Yanli Ding[4], Ricardo C. T. Aguiar[1,5], Lois M. Mulligan[2] & Patricia L. M. Dahia[1,5]
[1]Division of Hematology and Medical Oncology, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX; [2]Division of Cancer Biology and Genetics. Cancer Research Institute, Queen's University, Kingston, Ontario, Canada; [3]Department Cell Structure and Anatomy, UTHSCSA, San Antonio, TX; [4]Department of Pathology, UTHSCSA, San Antonio, TX; [5]Mays Cancer Center, UTHSCSA, San Antonio, TX

Background
TMEM127 encodes for a ubiquitously expressed transmembrane protein with limited knowledge into its role. TMEM127 germline loss-of-function is a driver of pheochromocytoma and paraganglioma (PPGLs), tumors derived from the adrenal medulla and extra-adrenal paraganglia, respectively. Molecularly, TMEM127 mutant PPGLs belong to the kinase cluster, characterized by kinase signaling transcriptional programs. Receptor tyrosine kinase RET, a driver of PPGLs via germline or somatic gain-of-function mutations similarly belongs to the kinase cluster. Previously, we reported that TMEM127 loss led to mTOR signaling activation, suggesting that TMEM127 loss had an impact on kinase signaling pathways associated with mTOR, such as RET. Compellingly, and in line with the shared kinase signaling pathway signatures, TMEM127 mutant PPGLs display high levels of RET at the protein level, a phenomenon which is conserved in murine and cell line models. Here we sought to mechanistically interrogate the impact of TMEM127 loss on RET in an oncogenic context.
Methods
Primary tumor samples harboring different mutations, engineered Tmem127 KO mice, and engineered TMEM127 KO cell lines were analyzed for the abundance, localization, turnover, and signaling of RET as impacted by TMEM127 loss. Additionally, we interrogated the impact of TMEM127 functional motifs in targeting RET for degradation via recruitment of an E3 ligase. Lastly, we interrogated the RET-dependent oncogenic impact of TMEM127 loss on RET by investigating viability, proliferation, and transformation features *in vitro* and *in vivo*.
Results
Compellingly, and in line with the shared kinase signaling pathway signatures, TMEM127 mutant PPGLs display high levels of RET at the protein level, a phenomenon which is conserved in murine and cell line models. Further investigation revealed that TMEM127 impacted RET degradation. Mechanistically, we showed that TMEM127 was critical for the recruitment of NEDD4, an E3 ligase, to ubiquitinate RET, targeting it for endosomal trafficking and lysosomal degradation, with TMEM127 loss impacting RET localization and abundance. Our experiments with functional TMEM127 mutants determined that its C-terminal PxxY motifs were necessary to recruit NEDD4 to target RET for degradation. Lastly, *in vitro* and *in vivo* models of TMEM127 loss were found to be sensitive to RET clinical grade inhibitors.
Conclusion
Our data supports a novel tumor suppressive role of TMEM127 in PPGLs by targeting RET for degradation via recruitment of NEDD4, establishing the RET accumulation in TMEM127 mutant PPGLs as a dysregulation of this mechanism. Translationally, our work supports the clinical benefit of RET targeted therapy in TMEM127 mutant PPGLs.
Abstract ID 23325
DOI: 10.1530/endoabs.98.B2

B3

Translational biomarkers in G2-3 NENs: Analysis from NET-001 and NET-002 trials

Jose E. Nunez[1], Jeffrey Bruce[2], Arnavaz Danesh[2], David L. Chan[3], Victor Rodriguez-Freixinos[4], Julie Hallet[1], Sten Myrehaug[1], Calvin Law[1], Trevor Pugh[2] & Simron Singh[1]
[1]Sunnybrook Health Sciences Centre, [2]University Health Network, [3]University of Sydney, [4]Debiopharm

Background
The treatment of neuroendocrine neoplasms (NENs) of higher grade remains a dilemma. In these patients the role of immunotherapy is still unclear and predictive biomarkers are an unmet need. Herein, we present a revised translational analysis of the NET001 and NET002 (NCT03278405, NCT03278379) clinical trials.
Methods
Patients with advanced WHO G2-3 NENs who had a gastroenteropancreatic (GEP) or a bronchial primary (excluding typical carcinoid) and had 0-2 prior lines of systemic therapy were given avelumab 10mg/kg/iv every 2 weeks as their treatment. NET001 explored G3 neuroendocrine carcinomas (NECs) with poor differentiation (PD), whereas NET002 investigated G2-3 well differentiated (WD) neuroendocrine tumors (NETs). We identified genetic abnormalities in pre-treatment samples by doing whole-exome sequencing and whole transcriptome RNA sequencing in order to find potential predictive biomarkers.
Results
This analysis included samples from seven patients (2 small bowel, 1 pancreas, 1 lung, and 3 others; 4 from NET-001 and 3 from NET-002). Four samples were previously discarded as a result of contamination and sample exchange problems. The median age was 72 (range: 37-80), 28% of patients had ECOG PS 1-2, and 71% had prior therapy with 1 or more lines. The median Ki-67 index was 50% (10-100). The median progression free survival (PFS) was 60 days (NET-001 median PFS = 44 days vs NET-002 median PFS = 69 days, $P = 0.19$) and the median overall survival (OS) was 85 days (NET-001 median OS = 75 days vs

NET-002 median OS = 85 days, $P = 0.78$). Exome sequencing revealed only one RB1 mutation and one MEN1 mutation in a PD NEC and a WD NET, respectively. Two PD NECs exhibited p53 mutations. In PD NECs, differential gene expression analysis revealed that stem-cell-associated genes such as E2F1/2/7/8, SOX2, and 17 HOX genes were overexpressed (fdr < 0.05). Neither the tumor mutational burden (TMB) nor PD-L1 expression differed significantly between WD NETs and PD NECs. Interestingly, TMB was approximately 10 per MB within all the samples.

Conclusion

Patients with Grade 2-3 NENs who were treated with avelumab exhibited a distinct genomic and transcriptomic profile, according to our observations. There was no discernible difference in the expression of TMB or PD-L1 between PD NECs and WD NETs. In addition to that, a high TMB was found in all the samples. The development of more accurate predictive biomarkers for NENs should be a primary focus of future translational research.

Abstract ID 23436

DOI: 10.1530/endoabs.98.B3

B4

Cardiac autonomic dysfunction in a mouse model of carcinoid disease

Sydney Kuehn, BS[1], Sofia Penrose, BS[1], Rodney F. Pommier, MD[2] & Belinda H. McCully, PhD[3]

[1]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific- Northwest, Western University of Health Sciences, Lebanon, OR; [2]Division of Surgical Oncology, Department of Surgery, Oregon Health & Science University, Portland, OR; [3]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific- Northwest, Western University of Health Sciences, Lebanon, OR

Background

Patients with metastatic carcinoid disease confer a risk for carcinoid syndrome, characterized by hemodynamic instability and syncope. While the physiologic mechanisms linking carcinoid tumor metastases to impaired blood pressure regulation are not well understood, this may be attributed to changes in autonomic function, which is a key regulator of blood pressure. We hypothesize that metastatic carcinoid disease induces autonomic dysfunction. To test this, we longitudinally assessed autonomic function during tumor development in a mouse model of carcinoid disease.

Methods

Anesthetized J:Nu nude mice (25-30g, Jackson Laboratories) received an intrasplenic injection of vehicle (VEH, $n = 5$) or 1-2x10^7 neuroendocrine tumor BON1 cells (BON1, $n = 15$). Mice were monitored for 8 weeks to develop carcinoid liver metastasis. Stable 10-minute electrocardiogram (ECG) tracings were recorded in anesthetized animals, with a baseline tracing recorded prior to injection, and every two weeks following injection. To assess autonomic function, ECG tracings were analyzed offline (Acknowledge, Goleta, CA) for indices of heart rate variability. Specifically, the low frequency and high frequency bands were assessed to provide ratios of sympathetic (SNS) and parasympathetic (PNS) tone, respectively. A rise in the SNS ratio accompanied by a decrease in the PNS ratio represents autonomic dysfunction. Data are presented as mean $\pm$ SE. $P < 0.05$ indicates significance.

Results

Prior to injection, VEH and BON1 mice had similar baseline SNS (VEH: 0.33 ± 0.09; BON1: 0.30 ± 0.07, $P = 0.57$) and PNS (VEH: 0.67 ± 0.09; BON1: 0.69 ± 0.07, $P = 0.57$) ratios. Over time, VEH-treated mice did not show changes in SNS ($P = 0.82$) or PNS ($P = 0.82$) ratios. In contrast, BON1 mice exhibited a rise in the SNS ratio over time (main effect, $P = 0.018$), with a significant increase in the SNS ratio specifically at week 6 (0.40 ± 0.04, $P = 0.009$ vs baseline). This was accompanied by a decrease in the PNS ratio over time (main effect, $P = 0.020$), with a significant decrease at week 6 (0.58 ± 0.04, $P = 0.009$ vs baseline). Postmortem gross examination and hematoxylin-eosin staining of liver samples verified the presence of metastases in BON1 mice and its absence in VEH mice.

Conclusion

In agreement with our hypothesis, our findings show that BON1 cell-induced liver metastases confers autonomic dysfunction, characterized by increased sympathetic drive and a concurrent decrease in parasympathetic tone. Future studies are needed to determine whether autonomic dysfunction is also present in patients with carcinoid disease, and if this contributes to the development of hemodynamic instability and risk for carcinoid crisis.

Abstract ID 23458

DOI: 10.1530/endoabs.98.B4

B5

Unveiling pancreatic neuroendocrine tumors through plasma-derived small extracellular vesicles

Priya Kumari Gorai[1], Simran Rastogi[2], Seema Singh[1], Shipra Agarwal[3], Sujoy Pal[4], Tapas Chandra Nag[1], Renu Dhingra[1], Mehar Chand Sharma[3], Rakesh Kumar[5], Saroj Kumar[2,6] & Neerja Rani[1]

[1]Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India; [2]Department of Biophysics, All India Institute of Medical Sciences, New Delhi, India; [3]Department of Pathology, All India Institute of Medical Sciences, New Delhi, India; [4]Department of GI Surgery, All India Institute of Medical Sciences, New Delhi, India; [5]Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India; [6]Department of Health Science, Lulea University of Technology, Sweden

Background

The global incidence of pancreatic neuroendocrine tumors (PanNETs) has witnessed a steady rise in the past three decades. Unfortunately, the survival rates remain low primarily due to late-stage diagnoses and a lack of specific and sensitive diagnostic markers. Therefore, there is an urgent need for improved and efficient early diagnostic biomarkers. Small extracellular vesicles (sEVs) have gained significant attention in the field of tumor growth and cancer metastasis, owing to their remarkable capacity to induce metastatic behavior and proliferation. This study pioneers the investigation of the relationship between sEV concentration and PanNET grades, as well as the presence of BIRC2/cIAP and the autophagy marker Beclin-1 as cargo within sEVs derived from plasma. By examining plasma-derived small extracellular vesicles, this research sheds new light on the potential role of these vesicles as diagnostic biomarkers for PanNETs, offering a promising avenue for early detection and improved patient outcomes.

Methods

sEVs were extracted from the clarified plasma samples and subjected to morphological characterization using transmission electron microscopy. Furthermore, the presence of sEVs was validated through the expression of sEV markers CD63 and TSG101, while calnexin served as the negative control. Quantification of sEVs was conducted using nanoparticle tracking analysis (NTA), providing valuable insights into their abundance and size distribution. Subsequently, the presence of BIRC2 and Beclin-1 as cargo within sEVs derived from plasma was investigated through western blot analysis. Additionally, Immunohistochemistry (IHC) was employed to evaluate the expression of BIRC2 and Beclin-1 in both PanNET tissue and healthy control samples.

Results

This study presents compelling evidence of elevated plasma secretion of sEVs in PanNETs (Grade I & II) individuals compared to healthy controls (HCs). Moreover, higher protein expression levels of BIRC2 and Beclin-1 were observed in PanNETs compared to HCs. Notably, the immunohistochemistry (IHC) analysis of PanNET tissue revealed a parallel expression pattern for both proteins.

Conclusion

The findings unveil a potential correlation between elevated plasma secretion of sEVs and PanNET pathogenesis. Heightened expression of BIRC2 and Beclin-1 proteins further highlights their potential as important PanNET biomarkers. This study provides valuable insights into PanNET biology, paving the way for new diagnostic and therapeutic approaches.

Abstract ID 23470

DOI: 10.1530/endoabs.98.B5

B6

Prevalence of cardiac arrhythmias in a mouse model of carcinoid disease

Sofia Penrose, BS[1], Sydney Kuehn, BS[1], Rodney F. Pommier, MD[2] & Belinda H. McCully, PhD[3]

[1]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific- Northwest, Western University of Health Sciences, Lebanon, OR; [2]Division of Surgical Oncology, Department of Surgery, Oregon Health & Science University, Portland, OR; [3]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific- Northwest, Western University of Health Sciences, Lebanon, OR

Background

Neuroendocrine tumors that release prostaglandins and biogenic amines that can impact cardiac function. In consequence, patients with carcinoid liver metastases are at risk for carcinoid heart disease. This is primarily characterized by fibrosis in the heart that leads to plaques on the valvular cusps, leaflets and walls of the atrium and ventricles leading to a thickened right heart with regurgitation. Interestingly, 50-80% of patients with carcinoid heart disease also have irregular electrocardiogram (ECG) tracings, with common abnormal findings of

non-specific ST segment changes and sinus tachycardia. What is not known is when the onset of these arrythmias occur relative to metastatic disease progression. Therefore, the purpose of our study was to longitudinally assess the occurrence of cardiac arrythmias during the course of tumor development in a mouse model of carcinoid disease.
Methods
Anesthetized (3-5% isoflurane in 100% O_2), J:Nu nude mice (25-30g) received intrasplenic injection of 1x107BON1 neuroendocrine tumor cells (BON1, $n = 12$) or vehicle (VEH, $n = 5$). Mice were monitored for 8 weeks to allow the development of liver carcinoid metastases. During this period, stable 10-minute ECG tracings were recorded in anesthetized mice every two weeks. Tracings were assessed for ECG irregularities and heart rate. ECG irregularities were identified as abnormal tracings that deviated from a normal sinus rhythm. Livers were assessed for metastases by gross examination and hematoxylin-eosin (H&E) staining.
Results
Over the duration of the study, VEH mice did not present with abnormal ECG tracings at any time point. In contrast, abnormal ECG tracings were present in 83% (10/12) of BON1 mice during at least one time point during weeks 2-8 ($P = 0.029$ vs VEH). Abnormal rhythms were predominantly characterized by irregularly irregular rhythms, and biphasic P-wave and QRS complexes. The highest presence of abnormal rhythms occurred during week 4, which were present in 58% (7/12) BON1 mice ($P = 0.044$ vs VEH). Heart rate did not change over time in either VEH ($P = 0.888$) or BON1 ($p = .390$) mice. Upon tissue collection, gross dissection and H&E staining verified evidence of metastatic tumor growth in BON1 mice, and its absence in VEH mice.
Conclusions
Our findings identify the time course of when cardiac arrythmias can develop in a mouse model of carcinoid disease. We specifically show an early presence of varied abnormal ECG rhythms, which primarily occur at four weeks following BON1 cell injection. Future studies are needed to determine the etiology of arrythmia development in this mouse model, and how it may impact cardiac function.
ABSTRACT ID 23651

DOI: 10.1530/endoabs.98.B6

B7

Genomic analyses of multifocal ileal neuroendocrine tumors

Netta Mäkinen[1,2], Meng Zhou[1,2], Zhouwei Zhang[1,2], Yosuke Kasai[3], Grace E. Kim[4], Chrissie Thirlwell[5,6], Eric Nakakura[3] & Matthew Meyerson[1,2]
[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [2]Cancer Program, Broad Institute of Harvard and MIT, Cambridge, MA; [3]Department of Surgery, University of California, San Francisco, CA; [4]Department of Pathology, University of California, San Francisco, CA; [5]University of Exeter School of Medicine and Health, RILD Building, Exeter, UK; [6]Research Department of Oncology, UCL Cancer Institute, London, UK

Background
Small intestinal neuroendocrine tumor (SI-NET) is one of the major cancer subtypes of the small bowel. Most SI-NETs locate in the terminal ileum with a high incidence of multiple synchronous primary tumors. The only essentially curative treatment of SI-NETs is complete surgical resection; however, most SI-NET patients cannot undergo surgery as they typically present with an extensive metastatic disease. Several high-throughput sequencing studies have reported low somatic mutation rates in SI-NETs. Loss of heterozygosity at chr18 is the most frequent genomic event identified, occurring in ~60% of tumors, and the only established, recurrently mutated gene is CDKN1B, altered in ~8% of tumors. A deeper understanding of the molecular mechanisms underlying SI-NETs is urgently needed for the optimal treatment of the patients.
Methods
Our sample cohort consisted of 144 well-annotated fresh-frozen tissue specimens from 23 de-identified SI-NET patients, including 85 primary tumors, 21 metastases, and 38 patient-matched normal ileum and/or whole blood specimens. Thirteen SI-NET patients had been diagnosed with multiple synchronous primary tumors. Whole-genome sequencing was used to characterize the genomic landscape of SI-NETs, and to study the potential roles of field cancerization and germline variation in their tumorigenesis.
Results
We observed lack of shared somatic variation among the synchronous primary tumors of each multifocal SI-NET patient. There was rarely any overlap between the somatic mutational profiles of unifocal SI-NETs or between uni- and multifocal SI-NETs. Our data also indicated that multiple metastases from the same patient can originate from either one or several different primary tumors. We identified altogether >250 acquired genomic alterations among the normal ileum samples of SI-NET patients when compared to their matched whole-blood specimens, all of which were also present in the patient-matched primary tumor(s). None of these alterations were recurrent among the patients. Additionally, we have identified ~100,000 recurrent germline variants with a minor allele frequency of $\geq 5\%$ among the SI-NET patients. We will next assess if these variants are enriched in our patient cohort.
Conclusion
Our results indicate major genomic diversity among uni- and multifocal SI-NETs, suggesting that SI-NETs originate independently. Different metastatic dissemination patterns highlight the need to identify and carefully remove all primary tumors. SI-NETs are unlikely to arise from normal small intestine due to field cancerization based on our current data. We are also pursuing other hypotheses that could elucidate the SI-NET tumorigenesis. Finding the cause(s) of SI-NETs is essential for decisions regarding prevention, treatment, surgery, and patient outcome.
Abstract ID 23657

DOI: 10.1530/endoabs.98.B7

B8

ATRX: a novel predictive biomarker for peptide receptor radionuclide therapy in neuroendocrine tumors

M. Hammad[1], Z. Lee[2], S.L. Asa[3], K. Aboody[1], A. Mahipal[4], D. Bajor[4], S. Chakrabarti[4], J.E. Selfridge[4], L.M. Ocuin[5], R.S. Hoehn[2], J. Winter[5], J. Ammori[5], J. Hardacre[5], S.H. Tirumani[2], L.E. Henke[6] & A. Mohamed[4]
[1]Department of Stem Cell Biology and Regenerative Medicine, City of Hope National Medical Center & Beckman Research Institute, Duarte, CA; [2]Department of Radiology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [3]Department of Pathology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [4]Department of Medicine, Division of Hematology and Medical Oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [5]Department of Surgical Oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [6]Department of Radiation Oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH. Corresponding author: Amr Mohamed, MD, amr.mohamed@uhhospitals.org

Background
Peptide receptor radionuclide therapy (PRRT) including Lutetium177 (Lu177) has changed the treatment landscape of metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). There is a subgroup of patients who are resistant or develop resistance after initial success to PRRT, indicating that accurate predictive markers are urgently needed to identify who will benefit from PRRT. We hypothesize that expression of ATRX (Alpha Thalassemia and Mental Retardation X-linked) could predict patients who might respond to PRRT.
Methods
A retrospective review at UH Seidman Cancer Center included clinical and radiological data review for patients with metastatic well-differentiated GEP-NETs who have received PRRT. We identified patients based on their response and performed bulk RNA sequencing (RNA-Seq) using RNAs extracted from formalin-fixed, paraffin-embedded tissue; candidates identified were then examined with IHC staining. We also examined the basal expression of ATRX in BON1 and QGP1 cell lines using western blot and qPCR analysis. Based on these results we then knocked out (KO) ATRX in the BON-1 cell line, exposed the KO cells to irradiation and then measured cell viability by Calcein AM viability day once daily for 3 days after irradiation. Statistical graphs were used to evaluate the hypothesis.
Results
Patient samples demonstrated that PRRT non-responders have higher ATRX expression compared to responders. BON1 cells exhibited a high basal ATRX expression; greater and more rapid cell death was seen in irradiated ATRX KO cells compared to non-irradiated KO cells and irradiated cells with normal ATRX expression. This cytotoxic effect peaked on day 3 post-irradiation, with 60% of cells in the irradiated KO group having died, which is 3 times and 1.5 times the cytotoxicity for the ATRX KO only and irradiation groups, respectively.
Conclusion
Overexpression of tissue ATRX mRNA in NETs is correlated with resistance to PRRT. Tissue ATRX mRNA and/or protein expression may be a useful biomarker for monitoring the response to PRRT. The addition of tissue ATRX expression measurement to future clinical trials as an exploratory biomarker seems warranted and may bring a novel targeted therapy to improve PRRT outcome.
Abstract ID 23662

DOI: 10.1530/endoabs.98.B8

B9

Machine learning algorithm to classify multiphoton microscopy images of pancreatic neuroendocrine tumors

Noelle Daigle[1], Suzann Duan[2], Juanita L. Merchant[2] & Travis W. Sawyer[1,2]
[1]University of Arizona Wyant College of Optical Sciences, [2]University of Arizona College of Medicine

Background
Surgery is the preferred method of treatment for most pancreatic neuroendocrine tumors (PNETs), particularly functional PNETs or those greater than 2 cm in largest dimension. Existing techniques include intraoperative ultrasound and manual palpation, both of which have inherent disadvantages such as poor resolution and low contrast against normal pancreatic tissue. This results in surgeons performing more demolitive resections, such as the Whipple procedure, when they may not be strictly necessary in order to ensure total removal of tumors. Therefore, improving surgical localization methods could greatly improve patient outcome and quality of life. Multiphoton microscopy (MPM) is an optical imaging technique capable of visualizing intrinsic biomarkers through two-photon fluorescence, and collagen through second harmonic generation (SHG), notably without the aid of exogenous labels and with increased penetration depth compared to conventional microscopy. Here we test the use of MPM as a new method of microscopic tumor localization by applying this data to novel machine learning algorithms designed to automatically classify tissue types.
Methods
Formalin-fixed paraffin-embedded PNET ($n = 36$) and normal pancreas ($n = 21$) samples were imaged with a multiphoton microscope at five excitation and emission wavelengths corresponding to four endogenous fluorophore and SHG signals. Images covered an area approximately 4 mm by 4 mm. Texture features were then extracted using Haralick's method, and a computer model trained to classify the samples as tumor or normal tissue using linear discriminant analysis. Sets of one to six features were tested, and models assessed using a leave-one-out-approach. Accuracy of classifiers was evaluated as the ratio of the number of correctly identified samples.
Results
As the number of features increases, accuracy of the classifiers increases until plateauing at $n = 5$ features.

Number of features	Accuracy of classifier
1	78.9%
2	82.5%
3	89.5%
4	93.0%
5	93.0%

Conclusion
We have demonstrated that using $n = 4$ features, we are able to distinguish between PNETs and normal pancreatic tissue to 93.0% accuracy. By building this model, we can begin to test which imaging wavelengths and texture features are optimal for distinguishing the two tissue types, which in turn provides guidelines for the development of new surgical guidance instruments. This supports the continued investigation of MPM as a clinical imaging technique, and lays the groundwork for the integration of machine learning methods to real time imaging.
Abstract ID 23691

DOI: 10.1530/endoabs.98.B9

B10

Notch1 and Notch3 signaling interplay regulates pancreatic neuroendocrine cell proliferation

Rachael Guenter, Weisheng Chen, Yuvasri Golivi, Mario Robledo, Renata Jaskula-Sztul, Herbert Chen & Bart Rose
Department of Surgery, University of Alabama at Birmingham, Birmingham, AL

Background
The 5-year survival rate for patients with advanced pancreatic neuroendocrine tumors (pNETs) is less than 30%. Notch signaling is a transmembrane receptor pathway with four distinct isoforms, activation of which is linked to cellular differentiation, cell fate, and viability. Both Notch1 and Notch3 signaling have been shown to be dysregulated in pNETs. Notch3 activation has been shown to repress Notch1 activity in other cancers. We hypothesize that activation of Notch3 can reduce Notch1-mediated proliferation in pNETs.
Methods
Genetic deletion of Notch1 (N1-KO) in a pNET cell line (BON) was achieved using CRISPR/Cas9 to create a compound heterozygous knockout at exon 3. An inducible Notch1 overexpression cell line was generated by stably transfecting BON with a plasmid construct containing the Notch1 active form (N1ICD) under a Tet-On regulator. A constitutively on Notch3 cell line was generated by lentiviral transduction of BON with a plasmid overexpressing the Notch3 active form (N3ICD). Real-time quantitative PCR was used to measure mRNA transcript levels, and western blot was used to measure protein expression. Two-dimensional (2D) viability was measured by MTT assay, and three-dimensional (3D) proliferation was measured by spheroid size.
Results
We found that deletion of Notch1 reduced the expression of Notch3 at both the mRNA and protein levels. Increased cell density (ligand availability) or treatment with valproic acid (known Notch1 inducer) lead to increased N3ICD in wild-type (WT) BON but not in N1-KO. Overexpression of N1ICD was associated with increased expression of known downstream target Hes1, as well as Notch3. In contrast, forced overexpression of N3ICD lead to increased Notch1 expression but not Hes1 when compared to a BON cell line transfected with an empty vector. Functionally, N1-KO and N3ICD overexpression cells both had reduced proliferation in both 2D and 3D cell culture.
Conclusion
The Notch1 and Notch3 receptors produce signaling cascades that regulate growth in pNET cells through distinct mechanisms. Reduction of Notch1 signaling suppresses growth, while the same effect can be achieved with Notch3 overexpression. Thus, specifically upregulating Notch3 may be a strategy to block Notch1-mediated proliferation in pNET cells.
Abstract ID 23724

DOI: 10.1530/endoabs.98.B10

B11

The Notch1 pathway is a critical regulator of SSTR2 expression in neuroendocrine tumors

Rachael Guenter[1], Jason Whitt[1], Weisheng Chen[1], Hailey Houson[2], J. Bart Rose[1], Herbert Chen[1], Suzanne Lapi[2] & Renata Jaskula-Sztul[1]
[1]Department of Surgery, University of Alabama at Birmingham, Birmingham, AL;[2]Department of Radiology, University of Alabama at Birmingham, Birmingham, AL

Background
Patients with neuroendocrine tumors (NETs) have a 5-year survival rate of 30-60%. Surgery, and newly approved 'tar-geted radionuclide therapy (TRT)' with [^{177}Lu]DOTATATE, are the only curative options for patients with NETs. TRT is limited to pa–tients that have high levels of somatostatin receptor subtype 2 (SSTR2) and can im-prove the survival of patients with low-grade tumors, but has little effect on high-grade NETs that express low SSTR2 levels. The development and growth of neuroendocrine tumors is regulated by the Notch1 pathway. Based on our recent findings, we hypothesized that Notch1 signaling can regulate SSTR2 at both the basal level and with HDACi-induced expression in neuroendocrine tumors.
Methods
To determine if Notch1 was upstream of SSTR2, the Notch1 gene was deleted in a pancreatic NET cell line (BON) using CRISPR/Cas9. Wild-type BON and cells lacking Notch1 (BON-N1-KO) were then treated with vehicle, 1mM, or 4mM of valproic acid (VPA; HDACi) for 48h. Total protein was isolated, and a western blot was performed to measure total SSTR2 and Notch1 expression. A functional radiopeptide uptake study was performed to determine *in vitro* binding of [^{68}Ga]DOTATATE to BON and BON-N1-KO cells pretreated with vehicle, 1mM or 4mM VPA for 48h.
Results
Previously, we have shown that epigenetic modifiers, including histone deacetylase inh-ibitors (HDACi), robustly increase SSTR2 expression in NETs *in vitro* and in preclinical mouse NET models. The absence of the Notch1 gene resulted in lower induction of total SSTR2 comparing to wildtype pancreatic NET cells following HDACi treatment. Importantly, we ob-served a reduced radiopeptide [^{68}Ga]DOTATATE uptake by pancreatic NET cells lacking Notch1, even when treated with an HDACi to induce SSTR2, suggesting a decreased membrane density of SSTR2 when Notch1 was absent.
Conclusion
Our data show that Notch1 is upstream of SSTR2 and regulates its membranous expression. SSTR2 and Notch1 signaling are two critical pathways involved with the detection and progression of NETs and identifying the me-cha-nisms which allow ma-xi-mal re-ex-pre-ssion of SSTR2 may improve NET treat–ment response. Moreover, Notch-induced SSTR2 activation could enhance SSTR2 targeted NET therapy.
Abstract ID 23728

DOI: 10.1530/endoabs.98.B11

B12

Notch1 receptor-mediated metabolic flexibility promotes a survival advantage in pancreatic neuroendocrine neoplasms

Weisheng Chen, Rachael Guenter, Brendon Herring, Yuvasri Golivi, Jason Whitt, Melissa Sammy, Cole Adams, Renata Jaskula-Sztul, Herbert Chen & Bart Rose
Department of Surgery, University of Alabama at Birmingham

Background
Cancer cells utilize both oxidative phosphorylation (OXPHOS) and glycolysis to generate energy. Switching between OXPHOS and glycolysis can promote tumor progression. The mechanisms governing oncogenic metabolic flexibility are largely unknown, but recent data has suggested that Notch1 dysregulation in cancer cells can contribute to altered metabolic phenotypes. We hypothesized that Notch1 signaling supports metabolic flexibility in pancreatic neuroendocrine tumor (pNET) cells.
Methods
We established a Notch1-knockout (N1-KO) pNET cell line by deleting Notch1 at exon 3 in BON cells using CRISPR/Cas9. Seahorse Glycolytic Rate Assay and Mitochondria Stress Test were used to measure the glycolytic and mitochondrial activities of cells. A glycolysis deprivation assay was employed to determine cell viability at varying glucose concentrations. Single end RNAseq was performed using the Illumina NGS platform, to a read depth of 50M.
Results
Compared to wild-type (WT) BON, the N1-KO cells had reduced basal oxygen consumption rate (28.2 $\pm$ 1.3 vs. 40.7 $\pm$ 1.4; $P = 0.02$, ATP production (21.9 $\pm$ 1.0 vs. 29.6 $\pm$ 0.98; $P = 0.04$), and maximal respiration (39.4 $\pm$ 1.7 vs. 63.7 $\pm$ 2.1; $P = 0.004$). N1-KO cells also had a reduction in basal glycolysis, as measured by proton efflux rate, compared to WT (48.7 $\pm$ 2.6 vs. 57.7 $\pm$ 6.2; $P = 0.2$). To test metabolic flexibility, WT and N1-KO cells were starved of glucose (0mM), compared to normal glucose (17.5mM) and viability was measured over time. By day 5, the N1-KO group had a viability of 0%, whereas 13% of WT cells were alive. To determine if Notch1 loss was associated with altered expression of established metabolic genes, we performed RNAseq on WT and N1-KO cells. Differential gene expression analysis found multiple OXPHOS-related genes (UQCC2, COX15, COX20) and glycolysis-related genes (Slc1a1, Slc2a4, Hk1, Hk2) were significantly down-regulated in N1-KO cells.
Conclusion
Our study shows that Notch1 signaling facilitates metabolic reprogramming as a survival advantage in pNET cells. Targeting Notch1 signaling to mediate cellular metabolism may be a novel therapeutic strategy in pNETs.
Abstract ID 23738
DOI: 10.1530/endoabs.98.B12

B13

Dissecting the role of neuronal mimicry in pancreatic neuroendocrine tumours

Zoey Wang[1,2], Areeba Qureshi[1], Nilakshi Kulathunga[1], Carol Schuurmans[1,3], Housheng Hansen He[2,4] & Iacovos Michael[1,2]
[1]Sunnybrook Research Institute, Toronto, ON; [2]Department of Medical Biophysics, University of Toronto; Department of Laboratory Medicine and Pathobiology, University of Toronto; [4]Princess Margaret Cancer Centre, University Health Network

Background
Pancreatic neuroendocrine tumours (PanNETs) are an understudied cancer type characterised by frequent metastasis, clinical recurrence, and high mortality rate. PanNETs originate from pancreatic islets, primarily β cells, and comprise two molecular subtypes: poorly invasive, relatively benign islet tumour (IT) and highly aggressive metastasis-like primary (MLP) tumour. The MLP subtype arises from IT through a switch in cell fate involving the acquisition of neuronal-like features, a process termed 'neuronal mimicry'. However, the precise role of this in PanNET progression and its underlying molecular mechanisms remain elusive. Here, we hypothesise that neuronal mimicry contributes to PanNET aggressiveness both through cancer cell-autonomous mechanisms and by promoting heterotypic interactions with tumour-infiltrating neurons.
Methods
Bulk RNA sequencing data of tumours derived from PanNET patients and transgenic mouse models were analysed. Samples were scored for the enrichment of gene signatures associated with neuronal programs, proliferation, and invasion, and the correlation between these were determined. To examine heterotypic cancer-neuron interactions, multiplex immunofluorescence imaging with markers for cancer cells and neurons was performed on mouse model-derived tumours, in addition to *in vitro* co-culturing of PanNET cells with murine dorsal root ganglia (DRG).
Results
Transcriptomic analyses of primary IT, primary MLP, and metastatic tumours revealed an upregulation of neuronal gene signatures during PanNET progression, coinciding with increased proliferative and invasive capacities. Quantitative immunofluorescence showed increased sympathetic innervation of the tumour core in advanced MLP lesions compared to IT. Finally, IT-like cancer cells undergo morphological changes resembling neurons, particularly development of neurites, when co-cultured with DRG. Interestingly, the neurites formed are more prominent with a higher DRG-to-cancer cell ratio in the co-culture, suggesting a dose-dependent effect.
Conclusion
Our results implicate neuronal mimicry as a potential driver of PanNET progression through both cancer cell-intrinsic and cell-extrinsic mechanisms. At the cell-extrinsic level, acquisition of neuronal-like features by cancer cells may potentiate crosstalk with neurons in the tumour microenvironment, in turn promoting tumour progression to more aggressive phenotypes. Future experiments examining tumour innervation by different types of neurons at varying stages of disease progression will provide further mechanistic insight. At the cell-intrinsic level, activation of neuronal genes may directly confer cancer cells a growth advantage; this will be investigated further by genetic approaches, such as gain- and loss-of-function assays. The effect of pharmacologically disrupting cancer-neuron interactions will also be assessed, for instance using inhibitors of β-adrenergic receptors. Results from these studies may illuminate novel therapeutic avenues for PanNET by targeting neuronal gene programs and tumour innervation.
Abstract ID 23764
DOI: 10.1530/endoabs.98.B13

B14

Scandium-43-DOTATATE, a Novel Positron Emission Tomography (PET) Tracer for Neuroendocrine Tumor Imaging

Hannah J. Zhang[1], Antonino J. Pusateri[1], Jason P. Meier[1], Olga Lakiza[1], Mohammed Bhuiyan[1], Hsiu-Ming Tsai[1], Lara Leoni[1], Kaustab Ghosh[1], Richard Freifelder[1], Chih-Yi Andy Liao[1], Yonglin Pu[1], Daniel Appelbaum[1], Ralph Weichselbaum[1], Jerry Nolen[2], Chien-Min Kao[1], David Rotsch[2,3], Chin-Tu Chen[1] & Xavier M. Keutgen[1]
[1]The University of Chicago, Chicago, IL; [2]Argonne National Laboratory, Lemont, IL; [3]Oak Ridge National Laboratory, Oak Ridge, TN

Background
Neuroendocrine tumors (NETs) represent a heterogenous group of neoplasms and their diagnosis can be challenging. In 2019, FDA approved ^{68}Gallium labeled DOTATATE PET tracer for SSTR2 overexpressing NETs, which has been widely adopted since. However, limitations of ^{68}Ga-DOTATATE have led to the development of additional radiotracers for the diagnosis of NETs. Herein we report on a novel PET tracer using ^{43}Sc for DOTATATE labeling. ^{43}Sc provides a longer half-life when compared against ^{68}Ga and its lower positron energy provides better quality of PET imaging and less deposit of radiation into non-tumoral tissues.
Methods
^{43}Sc production was achieved at the University of Chicago Cyclotron Facility through the ^{42}Ca(d,n)^{43}Sc reaction. The radiolabeling was done on a thermomixer at 450 rpm for 30 min at 95°C. The crude was passed through a conditioned C18 SPE cartridge where ^{43}Sc-DOTATATE was trapped and eluted in EtOH. Cellular uptake and internalization studies were conducted using the SSTR2 over-expressing pancreatic NET cells, QGP1-SSTR2 and the parental QGP1 cells served as a negative control. *in vivo* PET/CT imaging was conducted on male nude mice bearing QGP1 and QGP1-SSTR2 tumor xenograft on the right and left forelimbs respectively. Dynamic PET acquisition started right before the injection of ^{43}Sc-DOTATATE via a tail vein catheter, and followed by CT imaging for anatomy and attenuation correction. Select tissues were collected post-imaging for biodistribution.
Results
Radiolabeling efficiencies were routinely $>97\%$. Specific activity as high as 660 μCi/nmole was achieved with $>99\%$ radiochemical purity. The highest SSTR2-QGP1 uptake of $>60\%$AA/10^5cells was observed at pM level of ^{43}Sc-DOTATATE and ~70% of this activity was internalized. QGP1 cells showed baseline levels of ^{43}Sc-DOTATATE uptake while unlabeled DOTATATE diminished radiotracer uptake in the QGP1-SSTR2 cells. PET imaging revealed that specific uptake of ^{43}Sc-DOTATATE in QGP1-SSTR2 xenografts peaked at 1 hr after IV injection. No signal was observed in QGP1 tumors. The time-activity curve showed a clear separation between surrounding tissues and tumors starting at~30 min post-injection. Biodistribution analyses post-injection confirmed strong tracer localization, ~30 %ID/g, in QGP1-SSTR2 tumors, with substantially

lower uptake seen in both the kidneys and QGP1 tumors, 10 and 4 %ID/g, respectively.
Conclusion
Cellular uptake and internalization in SSTR2 overexpressing pNET cells are higher than those in SSTR2-deficient cells, demonstrating ^{43}Sc-DOTATATE labeling was successful with high purity and specific activity. High uptake in QGP1-SSTR2 xenografts indicates that this radiotracer is a promising novel diagnostic agent for the clinical diagnosis of NET malignancies.
Abstract ID 23766
DOI: 10.1530/endoabs.98.B14

B15

Investigating serotonin metabolism in neuroendocrine cancers

Dane H. Tow[1], Maclain Ridder[1], Catherine G. Tran[1], Luis C. Borbon[1], Guiying Li[1], Courtney A. Kaemmer[2,7], Ellen Abusada[3], Aswanth Harish Mahalingam[4], Anguraj Sadanandam[4], Chandrikha Chandrasekharan[5,7], Joseph Dillon[5,7], Douglas R. Spitz[6,7], Dawn E. Quelle[2,3,7], Carlos H.F. Chan[1,7], Andrew Bellizzi[3,7], James R. Howe[1,7] & and Po Hien Ear[1,7]
[1]Department of Surgery, University of Iowa Carver College of Medicine, Iowa City, IA; [2]Department of Neuroscience and Pharmacology, University of Iowa Carver College of Medicine, Iowa City, IA; [3]Department of Pathology, University of Iowa Carver College of Medicine, Iowa City, IA; [4]Centre for Translational Immunoncology, Division of Molecular Pathology, The Institute of Cancer Research, London, UK; [5]Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA; [6]Department of Radiation Oncology, Division of Free Radical and Radiation Biology, The University of Iowa Hospitals and Clinics, Iowa City, IA; [7]Holden Comprehensive Cancer Center, University of Iowa Carver College of Medicine, Iowa City, IA. Corresponding author: Po Hien Ear

Background
Small bowel neuroendocrine tumors (SBNETs) originate from enterochromaffin cells in the intestine which synthesize and secrete serotonin. Other NETs and other cancers may also produce serotonin but do not store them in vesicles. The rate limiting enzyme of serotonin biosynthesis is tryptophan hydroxylase 1 (Tph1). Patients with high serotonin level could develop carcinoid syndrome, which can be treated with somatostatin analogues and the Tph1 inhibitor telotristat ethyl (TE) in severe cases. Little is known about the effect of serotonin on tumor cells during the dynamic process of neuroendocrine cancer growth. Here, we determined the effect of serotonin inhibition on tumor growth *in vitro* and *in vivo* using genetic and pharmacologic approaches. We identified improved tumor inhibition by combining TE with sunitinib, a tyrosine kinase inhibitor (TKI). In addition, we engineered a serotonin biosensor to track changes in serotonin levels in real-time.
Methods
The levels of Tph1 in various cancer cell lines were determined. The biological effects of Tph1 inhibition using shRNAs targeting TPH1 stable knockdown and TE +/- sunitinib treatment were tested. Control and knockdown lines were assessed for their growth rates, angiogenesis potential, serotonin levels, endothelial cell tube formation, tumor weight, and tumor vascularity. To create a biosensor to detect endogenous serotonin levels in live cells, we fused the serotonin binding domain and Renilla luciferase reporter. Mass spectroscopy, immunofluorescence, and western blotting were used to study serotonin metabolism under different conditions.
Results
TPH1 is highly expressed in SBNETs and several other cancer types. TPH1 knockdown cells and TE treated cells showed similar growth rates as control cells in vitro. However, TPH1 knockdown cells formed smaller tumors in vivoand tumors were less vascularized. The combination of TE and sunitinib led to a further decrease in tumor growth and lower serotonin levels in both tumor and blood samples. Moreover, we detected the dynamic changes in serotonin levels in tumor cells undergoing anchorage-independent growth and during serum starvation.
Conclusion
Although Tph1 inhibition with TE showed no effect on tumor cell growth in vitro, Tph1 inhibition reduced tumor formation *in vivo* and is potentiated in the presence of a TKI. Our serotonin biosensor enables real-time detection of alterations in serotonin synthesis in living cells under various growth conditions and has the potential to provide greater insight into serotonin metabolism in different stages of tumor progression and to identify therapeutic strategies to target cancer metastases and carcinoid crisis.
Abstract ID 23778
DOI: 10.1530/endoabs.98.B15

B16

Chemotherapy-mediated upregulation of SSTR2 in NET tumors in mice and in tumor biopsies from lung- and gastroenteropancreatic-NET patients

Marine A. Merlin[1,5,6,7], Isabelle Deshaies[2], Philippe Joubert[3,6,7], Jean-Mathieu Beauregard[1,4,5,7] & Girish M. Shah[1,6,7]
[1]Research Center CHU de Québec-Université Laval, Québec, QC, Canada; [2]Department of Surgical oncology, CHU de Québec-Université Laval, Québec, QC, Canada; [3]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, QC, Canada; [4]Department of Medical Imaging, CHU de Québec-Université Laval, Québec, QC, Canada; [5]Department of Radiology and Nuclear Medecine, Université Laval, Québec, QC, Canada; [6]Department of Molecular Biology, Medical Biochemistry and Pathology, Université Laval, Québec, QC, Canada; [7]Université Laval Cancer Research Center, Québec, QC, Canada

Background
The peptide receptor radionuclide therapy (PRRT) is recommended for somatostatin receptors (SSTR) positive neuroendocrine tumors (NET). However, complete remissions with PRRT remain anecdotal and NET patients with low SSTR-positivity are excluded from this treatment. Hence, any approach to increase SSTR2 expression can improve therapeutic efficacy of PRRT. Based on previous *in vitro* studies with NET cell lines, we **hypothesize** that a treatment with chemotherapeutic agents, such as temozolomide (TMZ) will upregulate SSTR2 expression in NET leading to a combination strategy to improve the efficacy of subsequent PRRT.
Methods
For ***in vivo*** study, we used BON-1 NET cell line-derived subcutaneous tumors in immunodeficient mice (n =4-5), treated them five days with 25 mg/kg TMZ or mock, and examined the biodistribution by γ-counter of ^{68}Ga-DOTA-octreotate at day 7, as well as SSTR expression in harvested tumors by RT-PCR. To validate this concept from clinical perspective, we treated ***ex vivo*** fresh tumor biopsies from above mouse model (n =6, 3 mice) and from lung- (n =6) and gastroenteropancreatic-NET (n =2) patients, with 100 μM TMZ for 5 days, followed by analyses of SSTR expression by immunoblotting and RT-PCR.
Results
In mouse model of BON-1-derived NET, the biodistribution study of ^{68}Ga-DOTA-octreotate revealed a significantly higher uptake of radioactivity at day-7 in BON-1 tumors compared to healthy tissues, which was confirmed by a 2-fold and 1.7-fold upregulation of mRNA for SSTR2 and 5 respectively. The fresh tumors from mice treated ex vivo with TMZ for five days resulted in a specific and significant upregulation of SSTR2 mRNA (and not other SSTR) from 5-11 days ($p < 0.01$-0.001). Having confirmed the validity of ex vivo approach, we began screening lung- and gastroenteropancreatic-NET patients' biopsies for their SSTR-expression response to the ex vivo TMZ treatment. Our initial results reveal a trend for the upregulation of SSTR2 mRNA between 7 to 9 days after start of chemotherapy treatment for lung- and GEP-NET.
Conclusion
Our preliminary observations suggest that a short course of chemotherapy to upregulate SSTR2 is a promising approach to increase the efficacy of subsequent PRRT. Our results could lead to clinical trials to examine which NET patients could selectively benefit from this approach during their PRRT treatment, and could also allow NET patients with low SSTR-positivity to become eligible to receive PRRT. This work is supported by NET research grant from Canadian Neuroendocrine Tumor Society (ID, PJ, JMB and GS) and by FRQS doctoral training scholarship (MM).
Abstract ID 23787
DOI: 10.1530/endoabs.98.B16

B17

YAP and TEAD form a transcriptional complex regulating neuroendocrine differentiation and tumorigenesis through a modular mechanism

Jina Nanayakkara[1], Tashifa Imtiaz[1], Xiaojing Yang[1], Markus Hafner[2], Xiaolong Yang[3] & Neil Renwick[1]
[1]Laboratory of Translational RNA Biology, Department of Pathology and Molecular Medicine, Queen's University, 88 Stuart St, Kingston, ON, Canada; [2]Laboratory of Muscle Stem Cells and Gene Regulation, NIAMS, 50 South Drive, Bethesda, MD; [3]Cancer Research Laboratory, Department of Pathology and Molecular Medicine, Queen's University, 88 Stuart St, Kingston, ON, Canada

Background
Neuroendocrine tumors (NETs) are unusual tumors with neural and secretory morphology and loss of Yes-associated protein (YAP). YAP is a transcriptional

co-activator of the Hippo pathway and canonical oncogene in numerous cancers, except NETs. Although YAP typically binds TEAD transcription factors to drive gene expression, we demonstrate that YAP-TEAD complex formation represses NET differentiation and tumorigenesis through targeted gene dysregulation.
Methods
Using lung (H727) and pancreatic (BON1) NET cells, we compared neuroendocrine markers (chromogranin A, INSM1), cell proliferation, and anchorage-independent cell growth after overexpressing constitutively active YAP (YAP-S127A) or mutant YAP (YAP-S127A/S94A) that disrupts YAP-TEAD binding. Subsequently, we mapped YAP-TEAD DNA-binding sites using ChIP-sequencing and evaluated gene expression using RNA-sequencing.
Results
Neuroendocrine marker expression, cell proliferation and anchorage-independent cell growth diminished with active YAP, but recovered with mutant YAP. ChIP-seq revealed 34,924 YAP-TEAD DNA-binding sites predominantly within distal enhancers. Following active YAP overexpression, RNA-seq uncovered 206 upregulated genes including known Hippo targets (CTGF, CYR61), and 137 downregulated genes comprising neural and secretory functions. Interestingly, ChIP-seq clusters correspond with modular roles for YAP/TEAD activation or repression of gene expression, including targeting histone components (cluster 1), classical signalling pathways like TGFβ and Notch (cluster 2 and 3), neuroendocrine differentiation (cluster 4) and general cell functions (cluster 5 and 6). In cluster 4, YAP/TEAD binds to distal enhancers regulating master neuroendocrine transcription factors (ASCL1, INSM1, NEUROD1, NKX2-2) and represses gene expression.
Conclusion
YAP/TEAD complex formation represses NET differentiation and tumorigenesis through activation or repression of multiple transcriptional groups with differing functions, indicating a modular regulatory role. Specifically, YAP/TEAD regulates NETs through potential mechanisms including upregulation of TGF-beta and Notch signalling and downregulation of master neuroendocrine transcription factors.
Abstract ID 23797
DOI: 10.1530/endoabs.98.B17

B18

Identifying the relationship between neuroendocrine tumors (NET) and glutamic acid decarboxylase 65 (GAD65) antibody

Claudia Watkins[1], Tanner James[1] & Katharine Thomas MD[1,2]
[1]Reno School of Medicine, University of Nevada; [2]Renown Regional Medical Center

Background
Glutamic acid decarboxylase 65-kilodalton isoform (GAD65) antibody is a known to be present in inhibitory interneurons and pancreatic islet β-cells. Arino *et al* suggests that high levels of GAD65 present with neurological symptoms should prompt physicians to screen patients for occult cancer. The literature also suggests high GAD65 antibodies have been associated with various malignancies; although large studies are lacking. This research focuses on identifying a relationship, if any, between GAD65 antibody and NETs.
Methods
The Renown Enterprise Data and Analytics Department at Renown Health identified the number of patients with positive lab results for GAD65 antibody, number of patients diagnosed with a NET, number of patients with positive GAD65 antibody lab results and diagnosed with a NET, and number of patients with negative GAD65 antibody lab results and diagnosed with a NET from 2010 to present. Patients diagnosed with a NET were identified through ICD-10 (C25.4, C7A) and ICD9 (157) codes corresponding to NETs. Positive and negative lab results were identified through GAD65 antibody lab results with a positive value of >5.0 IU/ml.
Results
From 2010 to present, 1,157 patients were diagnosed with a NET. There were a total of 749 patients who had positive lab results for GAD65 antibody. Only 44 patients had both a diagnosis of NET and a GAD65 antibody level tested. One patient had both a neuroendocrine tumor diagnosis and a positive GAD65 antibody lab result and 43 neuroendocrine patients had a negative GAD65 lab result.
Conclusion
Our analysis does not support a relationship between the GAD65 antibody and a NET diagnosis. Only one patient of the 44 NET patients included in the study was found to have a NET diagnosis and test positive for the GAD65 antibody. However, of the 1,157 patients diagnosed with a NET only 44 were tested for the GAD65 antibody. A major limitation of the study is a lack of site specific data analysis. This limitation and lack of published data warrant further study into this relationship, including site specific data.
Abstract ID 23388
DOI: 10.1530/endoabs.98.B18

B19

Label-free phenotyping of duodenal neuroendocrine tumors using tissue autofluorescence microscopy and digital spatial profiling

Thomas Knapp[1], Suzann Duan[2], Juanita Merchant[2] & Travis Sawyer[3]
[1]Biomedical Engineering, University of Arizona; [2]College of Medicine, University of Arizona; [3]College of Optical Sciences, University of Arizona

Background
Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are an extremely heterogenous group of diseases with complicated treatment and management decisions. For example, patients with Multiple Endocrine Neoplasia Type 1 (MEN1)-associated gastrinomas present with more aggressive tumors and poorer outcomes. Recent work has shown that sequencing (transcriptomic, proteomic) can phenotype GEP-NETs to accurately reflect important clinical parameters such as tumor aggressiveness and metastatic potential. Unfortunately, technologies to acquire -omic signatures are technically complex, destructive to the sample, and expensive. These barriers impose severe limitations on the clinical utility of these technologies. A method to phenotype tumors at the point of care that is label-free, reproducible, and non-destructive could significantly impact our ability to treat and manage GEP-NETs. Optical imaging, for example autofluorescence microscopy, represents a promising avenue that has many ideal characteristics for point-of-care applications – it is minimally-invasive, nondestructive, spatially-resolved, sensitive to many endogenous biomarkers, and rapid. We aimed to assess the potential of autofluorescence microscopy for label-free tumor phenotyping.
Methods
We conducted Nanostring Digital Spatial Profiling (DSP) to evaluate the expression of 40 neural and immune-related proteins in surgically resected duodenal gastrinomas ($n=12$). We then performed tissue autofluorescence microscopy on serial tissue sections using a tunable multiphoton microscope with five excitation and emission wavelength bands to target fluorophores that are commonly differentially regulated in cancer including lipofuscin, collagen, NADH, FAD and Porphyrin. A total of 183 regions of interest were examined between tumors, adjacent normal and abnormal-appearing epithelium, and the surrounding stroma. Results for both DSP and imaging signatures were stratified by tissue type and MEN1 status. The two datasets were then co-registered and a correlation analysis was conducted between the imaging and proteomic markers.
Results
Analysis of the co-registered imaging and proteomic datasets demonstrates high correlation between our imaging markers, proteomic markers, and patient MEN1 status, suggesting that the technology could be used for point-of-care phenotyping. Our results show that our tissue autofluorescence markers, specifically NADH and Lipofuscin, are highly correlated with MEN1 status, suggesting metabolic alteration and a potential impact on senescence. Differences were also observed in the imaging marker for collagen, which could be related to the activation of cancer associated fibroblasts.
Conclusion
Tissue autofluorescence could be a valuable tool for point-of-care tumor phenotyping and for augmenting pathological analysis. Ultimately, this technology could be broadened to other types of NETs, with long-ranging potential for giving rise to a new class of "optical phenotyping" technologies.
Abstract ID 23395
DOI: 10.1530/endoabs.98.B19

B20

Establishment of novel PDXovo models for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs)

Nilakshi Kulathunga[1], Sara Mar[1,2], Zoey Wang[1,2], Areeba Qureshi[1], Hubert Tsui[1,3], Julie Hallet[4,5], Calvin Law[4,5], Hon S. Leong[1,2] & Iacovos P. Michael[1,2]
[1]Biological Sciences, Sunnybrook Research Institute, Toronto, ON; [2]Department of Medical Biophysics, University of Toronto, Toronto, ON; [3]Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, Toronto, ON; [4]Evaluative Sciences, Sunnybrook Research Institute, Toronto, ON; [5]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON

Background
Neuroendocrine cancers arise in the endocrine cells localized throughout the body. Most are found in the Gastroenteropancreatic (GEP) system pancreas, stomach, and small and large intestines. They are heterogenous in their etiology, morphology, and phenotypes. Due to late diagnosis and low prevalence, clinical specimens are limited for research. Thus, preclinical models are pivotal for the understanding of this disease. This study focuses on establishing a novel patient-

derived xenograft (PDX) model for GEP neuroendocrine neoplasm (GEP-NEN) known as PDXovo. Our group has already shown that the PDXovo model can be utilized in disease modeling and drug screening of numerous other cancers. Thus, we hypothesize that the PDXovo system is an alternative approach to recapitulate the disease phenotype of GEP-NEN.
Methods
For this study, patients were enrolled with informed consent, and fresh tissue samples (blood, tumor (primary and metastasis)) were collected by medical oncologists and surgical oncologists at the Susan Leslie Clinic for Neuroendocrine Tumors at the Odette Cancer Centre (OCC) at Sunnybrook Hospital. Part of the obtained tissue samples was stored in the OCC biobank, and the rest were diverted to the PDXcore facility at our institution.
Results
Using fragments from freshly resected human small intestinal NEN specimens (primary and metastases), we were able to establish NEN PDXovos with a take-rate of >90%. Ultrasound images revealed successful tumor formation and increased vascularity. Fragments of the PDXovos were fixed for histological or cryopreserved for subsequent RNA and protein analysis. The PDXovos are characterized by immunostaining for tumor-specific neuroendocrine (chromogranin and the somatostatin receptor SSTR2) and other microenvironment makers. We plan to examine the response of the PDXovos to various treatments, such as the antiangiogenic inhibitor sunitinib, the mTOR inhibitor everolimus, and the immune checkpoint inhibitor anti-PD-1 antibody, and combinations thereof.
Conclusion
The significance of the findings of this study by far is the establishment of the PDXovo model for GEP-NEN for the first time. PDXovos is more cost-effective, fast, convenient, and widely available than conventional mice experiments. Upon further validation, this will guide successful future clinical trials in GEP-NEN patients.
Abstract ID 23477

DOI: 10.1530/endoabs.98.B20

B21

Transcriptomic profiling of the BCL-2 pathway in Neuroendocrine Neoplasms (NENs)

Vineeth Sukrithan[1], Uzair Ahmed[1], Harris Krause[2], Nishant Gandhi[2], Phillip Walker[2], Emil Lou[3], Heloisa Soares[4], Ari Vanderwalde[2] & Bhavana Konda[1]
[1]The Ohio State University, [2]Caris Life Sciences, [3]University of Minnesota, [4]University of Utah Huntsman Cancer Institutes

Background
BCL-2 is an anti-apoptotic protein associated with resistance to tumor cell death and is a histopathologic marker of neuroendocrine differentiation. We characterized the transcriptomic profile of BCL2 expression in NENs and its association with site, immune infiltration, and overall survival (OS).
Methods
Next-generation sequencing of both DNA (592-gene panel or whole exome) and RNA (whole transcriptome) was performed on NENs of pancreatic (P-NENs, n = 230), small bowel (SB-NENs, n =149), colorectal (CR-NENs, n =136), and lung (L-NENs; n =121) origin at Caris Life Sciences (Phoenix, AZ). Comparisons were perfomed against non-NENs; Colorectal Carcinoma (n = 15,422), Non-small cell lung cancer (n =21,565), Pancreatic cancer (n = 5,484) and Small Bowel Cancer (n =470). BCL2- or MKI67 -High (H) and -Low (L) cohorts were defined based on the top and bottom quartile expression (transcripts/million [TPM]) of these genes, respectively. Gene expression profiles were analyzed for a transcriptomic signature predictive of response to immunotherapy (T-cell inflamed score). Mann-Whitney U and χ^2 tests were applied with p-values adjusted for multiple comparisons ($p < 0.05$). OS data was obtained from insurance claims, and Kaplan-Meier estimates were calculated.
Results
NENs had significantly higher expression of BCL2 (TPM) compared to non-NEN counterparts (CR-NENs 4.22 vs 1.55; L-NEN 4.14 vs 1.90 P-NEN 1.90 vs 1.52; $p < 0.01$ all) except for SB-NENs (1.82 vs 1.53, P =0.07). BCL2 expression (TPM) was significantly higher in MKI67-H vs -L tumors (CR-NEN 5.7 vs 1.9; L-NENs: 6.9 vs 2.2; P-NENs: 2.7 vs 1.4 all $p < 0.05$), except in SB-NENs (2.5 vs 1.6, P =0.074). In P-NENs, there was a higher prevalence of RB1 mutations in BCL2-H vs -L (40 vs 4.9%, $p < 0.005$). BCL2-H tumors were more frequently T-cell inflamed across all investigated NENs (CR-NENs: 29 vs 8%, L-NENs: 37 vs 3%, P-NENs: 31 vs 3%, SB-NEN: 32 vs 5%, all $p < 0.05$). BCL2-H was associated with decreased OS as compared to BCL2-L in all tumor types (CR-NENs: HR 1.58, P =0.14; L-NENs: HR 1.75, P =0.188; P-NENs: HR 1.94, P = 0.047; SB-NENs: HR 1.059, P =0.902).
Conclusion
NENs have increased expression of BCL2 vs. non-NENs of the same site. BCL2-H co-related with high MKI67 expression. BCL2-H tumors were more inflamed/immunogenic and there was a trend towards worsening OS compared to BCL2-L within each type of NEN. The BCL-2 pathway is of interest for therapeutic investigation in aggressive NENs
Abstract ID 23650

DOI: 10.1530/endoabs.98.B21

B22

Germline whole-exome sequencing of patients with neuroendocrine neoplasms (NENs) reveals pathogenic or likely pathogenic variants in a large subset of patients

Vineeth Sukrithan, Isaiah Boateng, Sandya Liyanarachchi, Prachi Jain, Jill Buss, Anil Parwani, Manisha H. Shah, Komal Das, Martha Yearsely, Bhavana Konda, Pamela Brock & Ann-Kathrin Eisfeld
The Ohio State University

Background
We conducted whole-exome sequencing (WES) of germline(g) and somatic(s) DNA from a prospective cohort of patients with NENs (n =151) to study the genetic predisposition to NENs.
Methods
Variants obtained from gWES were filtered using a standard bio-informatics pipeline. Variant Effect Predictor (Release 107) was applied to obtain population allele frequencies. Variants were restricted to those among 974 genes obtained by combining publicly available gene lists. Fisher's exact tests were used to compare the frequencies of pathogenic/likely pathogenic germline variants with a reference population (n =74,023) from gnomad V3.1 Non-Cancer. Analysis of gene ontology was performed using the DAVID algorithm. Multiplex immunofluorescence (mIF) of samples with gMUTYH was performed.
Results
The primary site of NEN was pancreas/duodenum (47%), small intestine/unknown (38%) and lung (9%). The stage at diagnosis was limited in 56% and metastatic in 44%. Well-differentiated NETs constituted 90% of the sample and poorly-differentiated carcinomas were 10%. After excluding 7 samples for insufficient data, a total of 144 germline samples were sequenced and 3,400 variants were identified; 75 pathogenic and 99 likely pathogenic. Pathogenic/Likely Pathogenic variants were present in 78% of patients (112/144), among 127 genes. Pathogenic variants were present in 45% of patients (65/144), with 15% (22/144) patients having at least one pathogenic variant in a gene included on current clinical cancer genetics testing panels. Recurrent alterations were found in 37 genes (frequency, false discovery rate): MEN1 (5%, 1.22E-17), MUTYH (5%, 0.003), PKD1 (5%, 0.003), ATP4A (4%,0.04), PAH (4%,0.003). The three most commonly involved pathways were DNA repair (26%), cellular calcium signaling (14%) and epigenetic regulation (7%). Germline MUTYH alterations were associated with a high somatic tumor mutation burden in three out of six patients. Two out of five of these subjects with gMUTYH showed a high degree of CD3+ and CD11c+ immune infiltration on mIF.
Conclusion
We identified that around 45% of patients with neuroendocrine neoplasms have pathogenic variants in the germline whole-exome. A subset of patients with gMUTYH alterations have a high TMB and robust immune infiltration with important implications for treatment with immunotherapy.
Abstract ID 23685

DOI: 10.1530/endoabs.98.B22

B23

Calreticulin is associated with clinical characteristics in pancreatic neuroendocrine tumors

Brendon Herring[1], Caroline Macvicar[1], Rachael Guenter[1], Weisheng Chen[2], Isra Elhussin[2], Clayton Yates[2], Deepti Dhall[3], Herbert Chen[2], Goo Lee[2] & J. Bart Rose[1]
[1]Department of Surgery, University of Alabama at Birmingham, Birmingham, AL; [2]Department of Pathology, University of Alabama at Birmingham, Birmingham, AL; [3]Department of Biology, Tuskegee University, Tuskegee, AL

Background
Following IHC of CALR, H-scoring was performed by a pathologist. H-scoring was validated by MIF of the same tissue, wherein random-forest machine learning (ML) classifiers were employed to classify cells. ML classifiers were trained to distinguish between pNET cells and tumor stroma using approximately 30% of cells for the respective cell population of interest in each TMA core. Pearson's

correlations were used to evaluate the relationship between H-scoring and mean fluorescent intensity in tumor cells. H-scoring was then evaluated for a relationship with clinical variables, including tumor grade and metastatic status (both lymphatic and distant). 111 resected pNET samples were analyzed.
Methods
CALR MIF was performed for 40/89 patients. CALR H-scoring and IF were highly correlated (r= 71 [95% CI 50-83]; p < 0.0001). CALR expression was significantly higher in pNETs compared to normal pancreatic islets (p < 0.0001), as well as in primary pNETs compared to distant metastatic pNETs (P =0.02). There was however no difference in CALR expression based on tumor grade (0.82) or N stage (0.58).
Results
CALR MIF was performed for 40/111 patients. CALR H-scoring and IF were highly correlated (r= 71 [95% CI 50-83]; p < 0.0001). CALR expression differed significantly between pNETs and normal pancreatic islets (p < 0.0001), approached significance by N stage (P =0.07), but did not differ by M stage (P =0.72) or tumor grade (P =0.78).

CALR H Score (mean ± sd)				p value
Tumor/Islet	Tumor (n =111) 217±95	Islet (n =17) 53±51		< 0.0001*
Grade	G1 (n =51) 213±101	G2 (n =52) 218±92	G3 (n =6) 241±73	0.82
M Stage	M0 (n =63) 232±86	M1 (n =38) 186±105	*Mx* (n =10)	0.02*
N Stage	N0 (n =62) 219±96	N1 (n =26) 232±85	*Nx* (n =23)	0.58

Conclusion
CALR expression is increased in pNETs compared to normal islets and may be decreased in cases of distant metastatic disease. Future studies will aim to examine these relationships in a larger cohort with more diverse clinical outcome to better define this relationship.
Abstract ID 23717
DOI: 10.1530/endoabs.98.B23

B24

PARP inhibitors potentiate chemotherapy of NET cells and tumors and PAPR1-knockdown suppresses growth of NET tumors in mice#

Alicia Montoni[1], Rashmi G. Shah[1], Marc Décobert[1], Jyotika Rajawat[1,2], Véronique Richard[1], Marine A. Merlin[1] & and Girish M. Shah[1,3]
[1]CHU de Quebec Laval University Research Centre, Quebec City, QC, Canada; [2]University of Lucknow, Lucknow, India; [3]Faculty of Medicine, Université Laval, Quebec City, QC, Canada

Background
In mammalian cells, poly(ADP-ribose) polymerase-1 (PARP1) is among the earliest proteins to reach the site of DNA damage and play key roles in different cellular responses ranging from DNA repair to cell death. PARP-inhibitors are recommended in mono or combination therapy for a subset of breast and ovarian cancers with BRCAness type of DNA repair deficiency. In addition, current clinical trials are examining whether PARP-inhibitors can potentiate the efficacy of chemotherapy or peptide receptor radionuclide therapy. Here, using *in vitro* and mouse models of human-derived NET cells we examined the mechanism by which targeting PARP1-targeting could influence the growth of NET tumors and their response to chemotherapy.
Methods
We used orthotopic liver tumor model in BALB/c nude mice using human pancreatic carcinoid-derived BON-1 cells that stably express luciferase gene that facilitates bioluminescence imaging of tumors. To examine the role of PARP1 per se in the growth of tumors, we compared the growth of tumors of PARP1-wild type and PARP1 knock-down (shRNA approach) BON-1 cells. We also examined the growth suppressive effect of PARP-inhibitor on the response of PARP1-wt cells to chemotherapy (temozolomide and streptozotocin) using the cellular and mouse models. The growth and therapeutic responses in these models were monitored by bioluminescence *in vivo* and by various biochemical, immunohistological and transcriptomic analyses of cells or tumors after sacrifice.
Results
We observed that the treatment with chemotherapeutic agents rapidly activated PARP1 in NET cells and tumors, and PARP inhibitors efficiently blocked this activation. PARP-inhibition increased the cytocidal effect of drugs via suppression of growth and increased cell death due to unrepaired DNA damage in both cellular and tumor models. In the mouse model of liver tumors, a cytostatic dose regime of temozolomide became significantly cytocidal with tumor shrinkage when combined with PARP-inhibitor. Interestingly, we observed that the PARP1 depletion per se suppressed the growth of tumors, although there is no known DNA repair-defect in these cells. The analyses of tumors revealed that PARP1-knckdown decreased Ki67 proliferative index accompanied by alterations in key cell cycle-related genes that control cell growth, increased expression of E-cadherin and increased expression of cell death related genes.
Conclusion
Our results indicate that PARP-inhibition can be a promising strategy for not only potentiating the efficacy of chemotherapy but also for a maintenance therapy to restrict growth of NETs before, during and after chemotherapy.
Acknowledgments
Work supported by CIHR and CHU de Quebec.
Abstract ID 23723
DOI: 10.1530/endoabs.98.B24

B25

A STING Operation in neuroendocrine neoplasms

Erika Eagal[1], Emil Lou[2], Nishant Gandhi[3], Andrew Elliott[3], Vineeth Sukrithan[4], Namrata Vijayvergia[5], Sonam Puri[1], Aman Chauhan[6], Matthew Hadfield[7], Vaia Florou[1], Kajsa Affolter[1], Ari Vanderwalde[3] & Heloisa P. Soares[1]
[1]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [2]University of Minnesota, Minneapolis, MN; [3]Caris Life Sciences, Phoenix, AZ; [4]The Ohio State University, Columbus, OH; [5]Fox Chase Cancer Center, Philadelphia, PA; [6]Sylvester Cancer Center, University of Miami, Miami, FL; [7]Brown University, Providence, RI

Background
Significant advances have been made in the treatment of gastrointestinal (GI-) and pancreatic (P-) NENs. However, the use of immunotherapy is still limited, with most tumors considered immune "cold". The cGAS-STING signaling pathway has emerged as a critical mediator of inflammation and immune-mediated responses, with pathway agonists under development for enhancing immunotherapy. In this study, we evaluated associations between cGAS-STING pathway activity and the molecular and immune landscapes of GI- and P-NENs.
Methods
DNA (592-gene or whole exome) and RNA sequencing (whole transcriptome) were performed on GI- (n =571) and P- (n =294) NEN specimens submitted to Caris Life Sciences (Phoenix, AZ). Immune-high (IH) and low (IL) groups were based on hierarchical agglomerative clustering of STING pathway genes (CCL5, CXCL10 and MB21D1); a STING pathway score (SPS) was defined as the summation of z-scores of these genes. QuanTIseq analysis was used to estimate tumor microenvironment immune cell fractions. Statistical significance was determined using chi-square, Fisher's exact or Mann-Whitney U tests where appropriate and adjusted for multiple comparisons.
Results
Median expression of somatostatin receptors (SSTR) 1 and 2 was reduced in the IH vs IL groups (Table 1). IH samples were enriched for TP53, RB1 and KRAS mutations (Table 1). Interestingly, while mutations in all three genes was associated with high SPS in P-NENs, multiple gene mutations did not significantly affect SPS in GI-NENs. IH tumors were associated with increased expression of immune checkpoint genes, including CD80, CTLA4 and IFNG (3.01-4.16-fold and 4.39-8.24-fold compared to IL in GI- and P-NEN, respectively; all P <0.05) and increased immune cell fractions, such as B-cells (GI- and P-NENs(%): 5 vs 4, P <0.05) and M1 Macrophages (GI-NENs(%): 2 vs 1, P-NENs: 1 vs 0; all P <0.05).
Table 1: Features associated with IH and IL groups.

Features	IH: GI-NENS (n =187)	IL: GI-NENS (n =384)	IH: P-NENS (n =83)	IL: P-NENS (n =211)
SSTR1 (median TPM)	2.11	3.18	2.96	5.3
SSTR2 (median TPM)	5.36	12.58	18.44	29.58
TP53 (% Prevalence)	57.61	29.24	41.46	23.79
RB1 (% Prevalence)	36.72	15.21	31.75	7.59
KRAS (% Prevalence)	23.66	11.78	22.89	6.64

Conclusion
Our results demonstrated that the cGAS-STING pathway activity identifies GI- and P-NENs with an immunogenic profile, which may be augmented by one or multiple mutations in TP53, KRAS and RB1. These results suggest combination of cGAS-STING agonists and immune checkpoint inhibitors may be effective in GI- & P-NENs and warrant further investigation.
Abstract ID 23751
DOI: 10.1530/endoabs.98.B25

B26

Cancer testis antigen and interleukin expression correlates with survival in small bowel neuroendocrine tumors

Y. David Seo MD, Russell G. Witt MD, MAS, Rossana Lazcano MD, Samuel Cass MD, Courtney Hudgens, Khalida Wani, Manoj Chelvanambi PhD, Sarah Johnson MS, Sharia D. Hernandez MD, Daniel M. Halperin MD, Alexander J. Lazar MD, PhD, Jennifer A. Wargo MD, MMSc, Jeannelyn S. Estrella MD & Jessica E. Maxwell MD, MBA
The University of Texas, MD Anderson Cancer Center

Background
Patients with small bowel neuroendocrine tumors (SBNETs) frequently present with metastatic disease, and unfortunately, the range and efficacy of available therapies is limited. Immunotherapeutic checkpoint inhibitors have demonstrated benefit in other malignancies and may also play a role in SBNETs, although relatively little is known about the immune infiltrate in these tumors. Toward a goal of developing novel immunomodulatory strategies, we sought to evaluate the tumor immune microenvironment of SBNETs utilizing Nanostring transcriptional profiling.
Methods
Patients with SBNETs who underwent surgical resection at MD Anderson Cancer Center from 2003 to 2016 were retrospectively analyzed. Clinicopathologic data was collected, and patients were stratified by survival. Overall survival (OS) from date of resection was assessed using the Kaplan-Meier method, and p-values were calculated using the log-rank test. Multivariate (MV) analysis was performed using the Cox proportional hazards model. Transcription expression from bulk RNA was analyzed using the Nanostring PanCancer Immune Profiling Panel.
Results
Patients with SBNETs who underwent surgical resection at MD Anderson Cancer Center from 2003 to 2016 were retrospectively analyzed. Clinicopathologic data was collected, and patients were stratified by survival. Overall survival (OS) from date of resection was assessed using the Kaplan-Meier method, and p-values were calculated using the log-rank test. Multivariate (MV) analysis was performed using the Cox proportional hazards model. Transcription expression from bulk RNA was analyzed using the Nanostring PanCancer Immune Profiling Panel.
Conclusion
High expression of CTA and IL signatures in resected SBNETs identified patients with improved survival agnostic of stage. While CTA expression across multiple tumor subtypes have been implicated in their immunogenicity and potential for therapeutic targeting, this is the first work to identify a clinically relevant signal in SBNET. The concurrent increase of key cytokines (which are known to mediate anti-tumor activity) among CTA-high patients suggests an immune-mediated component to their improved survival. Further work is underway to elucidate the epigenetic mechanisms of CTA expression and silencing, with the goal of validating key CTAs such as PRAME and GAGE1 as predictive and therapeutic targets for immunologic intervention.
Abstract ID 23768

DOI: 10.1530/endoabs.98.B26

B27

Development of GEP-NEN patient derived organoids for therapy screening

Steven D. Forsythe[1], James P. Madigan[1], Stephen Andrews[1], Jaydira del Rivero[2], Jonathan M. Hernandez[3], Naris Nilubol[1] & Samira M. Sadowski[1]
[1]Endocrine Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; [2]Developmental Therapeutics Branch, , National Cancer Institute, National Institutes of Health, Bethesda, MD; [3]Surgical Oncology Program, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background
Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs) are a rare subset of cancers which nevertheless are a rising health burden. Development of new therapies suffers from several bottlenecks, including low patient accrual and poor understanding of tumor characteristics. Patient tumor organoids (PTOs) are a novel model capable of improving screening of patient tissue in an accurate, standardized, and high-throughput capacity. In this study, we utilized patient tumors for creation of high-fidelity PTOs from a variety of GEP-NENs.
Methods
Tumors from patients undergoing clinically guided surgeries were processed within two hours of resection and dissociated into single-cell suspension. Cells were encapsulated into Matrigel and cultured into two groups. The first group was grown for 10 days and assessed for viability then treated with a panel of clinically approved therapies for treatment sensitivity. The second group was grown for long-term expansion and biobanking, followed by characterization using immunohistochemistry and genetic profiling at passage 2 to ensure tumor cell maintenance.
Results
From March 2023-June 2023, six patients provided 14 tumors for PTO development. These included small intestine (n =3), pancreatic (n =2), and gastric (n =1) nueroendocrine tumors. Long-term culture (>3 passages) was successful for 11/14 specimens, with an average passage time of ~4 weeks. PTOs maintained immunohistochemical characteristics of the parent tumor types and demonstrated similar genetic profiles, including neuroendocrine tumor cell markers and grade. The early-stage therapeutic screening was performed for four patients, demonstrating dose-dependent effects and showing clinically dose relevant sensitivity towards small molecule inhibitor therapies including cabozantinib and sunitinib in a patient-dependent manner. Finally, a comparison of treatments between multiple resection sites within the same patient demonstrated variance in treatment responses, suggesting tumor heterogeneity.
Conclusion
Development of GEP-NEN PTOs is feasible for standard of care therapy testing. Further study will lead to continued understanding of therapeutic testing and the development of new therapy options.
Abstract ID 23760

DOI: 10.1530/endoabs.98.B27

B28

Therapies targeting CDK4/6 cause regression, immune cell activation, and sensitization to PD-L1 immunotherapy in pancreatic neuroendocrine tumors

Courtney Kaemmer[1], Shaikamjad Umesalma[1], Chandra Maharjan[1], Jordan Kohlmeyer[1], Joshua Lingo[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 effective therapies are needed to improve the survival of patients with metastatic pancreatic NETs (pNETs). RABL6A is a novel oncogenic driver of pNET pathogenesis. Kinome and phosphoproteome analyses of proliferating (RABL6A-positive) pNET cells, vs arrested (RABL6A-knockdown) controls, demonstrated that cyclin-dependent kinase 4 and 6 (CDK4/6) and MEK kinases are actionable drug targets in growing pNET cells. In agreement, published studies of patient pNETs by immunohistochemistry (IHC) and RNAseq identified robust activation of CDK4/6 and MEK in tumors. In other tumor types, CDK4/6 and MEK inhibitors display synergistic antitumor activity linked with heightened CD8 T cell, plasma cell and/or NK 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, colony formation, and immunoblotting assays. Tumor suppressive effects 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. Single cell RNAseq and multiplex IHC was performed on human pNETs.
Results
In vitro, CDK4/6-MEK inhibitor therapy caused synergistic pNET cell death and pathway inactivation, as measured by retinoblastoma protein (RB1) hypophosphorylation. In vivo, the CDK4/6-MEK combination significantly slowed growth of flank pNET xenografts, yielding a 6-fold extension of average survival (~120 days vs 20 days for control). This combination likewise suppressed (but did not eliminate) pNET growth in a bioluminescence metastasis model and reduced tissue colonization relative to monotherapy controls. By comparison, dual CDK4/6-MEK inhibition in immunocompetent in Pdx1-Cre;$Men1^{fl/fl}$;$Pten^{fl/fl}$ insulinomas caused dramatic tumor regression associated with B/plasma cell infiltration. Pilot analyses demonstrate the presence of B-lineage cells in human pNETs, which in other tumors prognose better survival and response to immunotherapy. Indeed, further tumor regression was achieved in Pdx1-Cre;$Men1^{fl/fl}$;$Pten^{fl/fl}$ insulinomas by combining CDK4/6 inhibitors with anti-PD-L1 blockade.
Conclusion
Combination therapy targeting CDK4/6 and MEK inhibits pNET growth and metastatic colonization. Monotherapies were not effective, in agreement with lack of response to CDK4/6 monotherapy in pNET patient trials. In immune competent Pdx1-Cre;$Men1^{fl/fl}$;$Pten^{fl/fl}$ mice, CDK4/6-MEK inhibition causes significant tumor regression linked with immune activation while CDK4/6 inhibition alone sensitized insulinomas to anti-PD-L1 immunotherapy. These data reveal activation of anti-tumor immunity in pNETs following CDK4/6 and MEK or PD-L1 inhibition. Such data provide compelling pre-clinical rationale for pNET clinical trials testing these combination therapies.
Abstract ID 23715

DOI: 10.1530/endoabs.98.B28

Clinical – Chemo/SSA/Biologics

C1

Clinical impact of unsuccessful subcutaneous administration of octreotide LAR instead of intramuscular administration in patients living with metastatic neuroendocrine tumors

Tharani Krishnan[1], Maria Safro[1], Daniel Moreira Furlanetto[2], Sharlene Gill[1], Joao Paulo Solar Vasconcelos[1], Heather C. Stuart[2], Patrick Martineau[2] & Jonathan M. Loree[1]
[1]BC Cancer Vancouver, Vancouver, BC, Canada,[2]Vancouver General Hospital, Vancouver, BC, Canada

Background
Octreotide LAR is a long-acting somatostatin analogue used in the management of metastatic neuroendocrine tumors (NETs), with antiproliferative and symptom control effects. It requires intramuscular (IM) injection. Missed IM injections can cause subcutaneous nodules (SCNs) on radiologic images. We reviewed the rates of SCNs in a real-world cohort of NETs receiving octreotide LAR and explored treatment outcomes.
Methods
Patients with gastrointestinal (GI) NETs commencing octreotide LAR between August 5, 2010 and March 8, 2018 at a single cancer center in British Columbia were identified from pharmacy records. Patients were included if they had a computed tomography (CT) scan performed at the time of progression and available preceding imaging for review. Fisher's exact test was used to examine predictors of SCNs and Kaplan-Meier curves summarized differences that were compared with log-rank tests in progression free (PFS) and overall survival (OS).
Results
Of 243 GI NETs receiving octreotide LAR, 45 patients had all CT imaging at one site and were available for central review. Median age was 67 years, 53% were female, and SCNs were found in 44% (20/45) of patients. A higher proportion of patients with SCNs were female (65%), although this was not statistically significant (OR 2.36, 95% CI 0.66-8.29, $P=0.23$). Patients over 60 years were numerically but not statistically less likely to develop SCNs than younger patients (OR 0.47, 95% CI 0.15-1.68, $P=0.34$). The mean skin-to-muscle distance and body mass index (BMI) in patients with and without SCNs was 54mm vs 35mm and 29kg/m^2 vs 26 kg/m^2 respectively. There was a significantly increased risk of developing SCNs in patients with a skin-to-muscle distance over 38mm (i.e. the length of the Octreotide LAR needle) (OR 5.09, 95% CI 1.39-16.6, $P=0.02$) and a trend towards increased risk in obese patients (BMI over 30kg/m^2) (OR 5.71, 95% CI 1.26-23.4, P = 0.06). PFS (HR 1.01, 95% CI 0.56-1.78, $P=0.98$) and OS (HR 0.86, 95% CI 0.41-1.8, $P=0.70$) was similar between those with and without SCNs.
Conclusion
Almost half of patients receiving octreotide LAR for GI NETs may develop SCNs, and this is more likely in those with a higher skin-to-muscle distance. Despite this, there was no difference in survival seen between patients with/without SCNs. Factors such as female sex, younger age and obesity may affect body fat distribution and SCN development, and should be considered by clinicians when choosing a somatostatin analogue.
Abstract ID 23383

DOI: 10.1530/endoabs.98.C1

C2

Neuroendocrine tumor metastatic to breast: case report and review of the literature

Jose Augusto Urrego[1], Marcela González Díaz[2], Alfredo Ernesto Romero-Rojas[3], Jonathan Strosberg[4] & Paola Jiménez Vásquez[5]
[1]Internal medicine department, Universidad Nacional de Colombia, Bogotá, Colombia; [2]Radiology department, Instituto de diagnóstico médico, IDIME, Bogotá, Colombia; [3]Pathology department, Los Cobos Medical Center, Bogotá, Colombia; [4]GI Oncology department, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [5]Gastrointestinal and Neuroendocrine tumors department, Centro de tratamiento e investigación sobre Cáncer Luis Carlos Sarmiento Angulo, Bogotá, Colombia

Background
We report a case of a patient with an ileocecal neuroendocrine tumor (NET) metastatic to both breasts, for whom the initial clinical presentation was chronic diarrhea Breast metastases were initially suspected by a 68-Gallium DOTANOC PET/CT and were confirmed by histopathology. We also performed a comprehensive (non-systematic) literature review through which we identified 116 cases of NENs metastatic to breast.
Methods
Case report and comprehensive (non-systematic) literature review.
Results
We performed a comprehensive (non-systematic) literature review through which we identified 116 reported cases of NENs metastatic to the breast, nearly all from case reports or case series. We found that many features of our case were compatible with previous reports: mean age of breast metastases report was 56 years, 89% of cases were caused by NETs, while 11% were NECs, etc.
Conclusion
We report a patient with an ileocecal NET metastatic to both breasts. A comprehensive (non-systematic) review of all cases of breast metastases from NENs indicates that most cases correspond to NETs and originate in the digestive tract. Also, there appears to be no preferred laterality for breast metastases. A correct diagnosis is of paramount importance for proper treatment. To this end, functional imaging, and histology (supported by immunohistochemistry) are of great value.
Abstract ID 23425

DOI: 10.1530/endoabs.98.C2

C3

Real-world evidence of lenvatinib use for treatment of metastatic neuroendocrine neoplasms

Joao Paulo Solar Vasconcelos[1], Jose Eduardo Nunez Rodrigues[2], Ali Zaidi[1], Helia Jafari[1], Tharani Krishnan[1], Sharlene Gill[1], Ann Tan[3], Dan Le[4], Theresa Chan[4], Simon Yu[5], John Paul McGhie[6], Howard Lim[1], Simron Singh[2] & Jonathan Michael Loree[1]
[1]BC Cancer Vancouver, BC, Canada; [2]Sunnybrook Hospital, Toronto, ON, Canada; [3]BC Cancer Abbotsford, BC, Canada; [4]BC Cancer Surrey, BC, Canada; [5]BC Cancer Burnaby, BC, Canada; [6]BC Cancer Victoria, BC, Canada

Background
Metastatic neuroendocrine neoplasms (NENs) constitute a heterogeneous group of uncurable cancers with limited treatment options. Lenvatinib is an oral multiple kinase inhibitor that showed activity in gastroenteropancreatic neuroendocrine tumors in the phase II Talent Trial at a starting dose of 24 mg per day. Although a confirmatory phase III study was never conducted, the drug is available for use off-label.
Methods
We retrospectively reviewed real-world data from patients with metastatic NENs treated with lenvatinib via compassionate use in British Columbia and Ontario, Canada. Descriptive statistics and Kaplan-Meier curves were used to summarize baseline characteristics and outcomes.
Results
From January 2019 to June 2023, 32 patients with metastatic NENs were treated with lenvatinib. Patient characteristics are shown in Table 1. The median prior lines of systemic therapy were 2.5 (range 1-5). Median initial, maximal, and minimal doses (mg) were 12 (range 4-24), 12 (range 8-24), and 8 (range 4-24). The median progression-free survival was 10 months (95% CI, 7.3-12.7) and median overall survival was 18 months (95% CI, 9.9-26.1). Of the 29 (91%) patients who had response assessment, 6 (21%) experienced some tumor burden response, 19 (66%) had tumor stabilization, and 4 (14%) had an increase as the best response. RECIST evaluation will be assessed in the future. The most frequent all-grade side effects reported were hypertension (59%), fatigue (38%), hypothyroidism (22%), diarrhea (19%), hand-foot syndrome (12%), mucositis (12%), and proteinuria (9%). Dose reductions were reported in 11 (34%) patients and treatment interruptions or discontinuation due to toxicity in 7 (22%) and 5 (16%), respectively.
Table 1 – Patient Characteristics at Baseline ($n=32$)

Median Age, years (range)	56 (34-81)
ECOG PS No.(%): 0-1 vs.2 vs. 3	28 (87.5) vs. 3 (9.4) vs. 1 (3.1)
Primary Site No.(%): Pancreas vs. Small Intestine vs. Other	16 (50.0) vs. 11 (34.3) vs. 5 (15.6)
WHO Differentiation No.(%): Well-differentiated: G1 vs G2 vs G3	3 (9.4) vs. 22 (68.8) vs. 5 (15.6)
Poorly differentiated	2 (6.3)
Functional Status No.(%): Functional vs Non-functional	15 (46.9) vs. 17 (53.1)
Prior Systemic Treatment No.(%)	32 (100.0)
Somatostatin Analogue	27 (84.4)
Chemotherapy; Targeted Therapy	27 (84.4); 17 (53.1)
PRRT	11 (34.4)

Conclusion
This real-world cohort demonstrates encouraging evidence of lenvatinib activity in pre-treated metastatic NENs even when used on a more heterogeneous population and at a reduced dose compared to the TALENT trial. The toxicity profile was consistent with prior reports with lenvatinib.
Abstract ID 23468

DOI: 10.1530/endoabs.98.C3

C4

Results from a Phase II study of nanoliposomal irinotecan (nal-IRI) with 5-fluorouracil (5-FU)/leucovorin in refractory advanced high-grade neuroendocrine cancer (HG-NEC)

Sarbajit Mukherjee[1], Robert Ramirez[2], Christos Fountzilas[1], Deepak Vadehra[1], Mary Lynne Tarquini[1], Kristopher Attwood[1] & Renuka Iyer[1]
[1]Roswell Park Comprehensive Cancer Center, [2]Vanderbilt University Medical Center

Background
Metastatic neuroendocrine carcinomas (NECs) have a poor prognosis, and standard first-line chemotherapy combines etoposide (E) and platinum (P) has limited benefit. Currently, there is no standard second-line therapy. Irinotecan-based regimens have shown benefits; hence we explored nanoliposomal Irinotecan (nal-IRI) efficacy in this patient population.
Methods
In this open-label, single-arm, multi-center Phase 2 study, advanced GEP or unknown origin HG-NEC patients with progressive disease/intolerance to 1st line treatment with EP received nal-IRI 70 mg/m2, leucovorin 400 mg/m2 followed by 5-FU 2400 mg/m2 (over 46 hours) every other week till disease progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. Baseline tissue or blood sample was submitted for Next Generation Sequencing (NGS). Subsequently, on treatment, blood samples were collected for circulating tumor DNA (CtDNA) measurement using Foundation One® Liquid assay. The study had Simon's minimax design with a plan to enroll 18 patients in stage 1. Unfortunately, it was closed to accrual due to non-clinical reasons after enrolling 11 patients.
Results
There were $n=11$ treated pts enrolled at two sites, of which nine were evaluable for the primary endpoint. In the overall population, 64% were male, median age (range): 66.7 years (50-87.8), median Ki-67 90% (range 50-100%), primary site: 27% colorectal 18% esophageal, 18% ampullary, 9% pancreatic, 28% other; 73% had liver mets. Among evaluable pts, one (11.1%) had a partial response, and 5 (55.6%) had stable disease, with a disease control rate of 67%. Median PFS was 4.4 months (95% CI: 1.7, 6.7). Median OS was 9.4 months (95% CI: 2.9, 29.3) (with one patient alive at 33 months). Among all treated pts ($n=11$), 9 (82%) had a treatment-related adverse event (AE), with 8 (73%) having grade 3 or higher AEs. The most common AEs were diarrhea (45%), nausea (45%%), vomiting (45%), and fatigue (45%)—no treatment discontinuation due to side effects. Subsequent chemotherapy was administered in 5 (45%) patients. On NGS, the most common variants were: TP53 (89%), CHEK2 (78%), APC (22%), and NF1(22%), and they remained mostly detectable throughout treatment.
Conclusion
A combination of 5-FU and nal-IRI showed efficacy and manageable toxicity in refractory HG-NEC, consistent with NET-02 study results (McNamara, 2022). Ongoing biomarker analysis using CtDNA may identify patients likely to benefit most from this combination. Ipsen Pharmaceuticals and the North American Neuroendocrine Tumor Society funded the trial. Clinical trial information: NCT03736720.
Abstract ID 23469
DOI: 10.1530/endoabs.98.C4

C5

A phase 2 clinical trial of cabozantinib in patients with unresectable and progressive metastatic pheochromocytoma or paraganglioma: The NATALIE trial

Camilo Jimenez, Mouhammed A. Habra, Matthew T. Campbell, Gina Tamsen, Damaris Cruz-Goldberg, James Long, Roland Bassett, Robert Dantzer, Vania Balderrama, Jeena Varghese, Steven Waguespack & Yang Lu
The University of Texas MD Anderson Cancer Center

Background
Metastatic pheochromocytomas and paragangliomas are orphan neuroendocrine tumors. 50% of these tumors are associated with germline mutations of the SDHB gene. SDHB related pheochromocytomas and paragangliomas and many apparently sporadic tumors exhibit abnormal angiogenesis. This trial assessed the efficacy and safety of Cabozantinib, a potent, antiangiogenic, tyrosine kinase inhibitor.
Methods
The Natalie trial is a single arm phase 2 clinical trial. Patients older than 18 years of age with progressive metastatic pheochromocytomas and paragangliomas were treated with Cabozantinib 60 mg daily with dose titration down depending on patient's tolerability. The primary endpoint was objective response rate as per RECIST 1.1. Secondary endpoints included progression free survival, overall survival, safety, blood pressure control, and correlations with germline and somatic genotypes and biochemical phenotypes.
Results
The trial recruited 17 patients. The clinical benefit rate was 94%. The objective response rate was 25%. The medican progression free survival was 16.6 months (95%CI 8.1-34.9 months). Median overal survival was 24.9 months (95%CI lower boundary-23.6 months). 80% of patients exhibited blood pressure improvement. 96% of Cabozantinib related side effects were grade 1-2. Three patients reported grade 3 side effects including hypertension, asymptomatic elevation of pancreatic enzymes, and a rectal fistulae. There were no grade 4 or 5 side effects. Tumors did not have c-met receptor mutations or c-met pathway amplification. Positive responses were reported irrepective of germline genotype.
Conclusion
Cabozantinib is an effective systemic therapy for adult patients with metastatic pheochromocytoma and paraganglioma irrespective of the primary tumor origin and genotype.
Abstract ID 23473
DOI: 10.1530/endoabs.98.C5

C6

The role of somatostatin analogue maintenance therapy in refractory metastatic neuroendocrine tumors (NETs): comparative analysis

A. Mohamed[1], M. Kurian[1], S. Patil[2], S.L. Asa[3], S.H. Tirumani[4], A. Mahipal[1], D. Bajor[1], S. Chakrabarti[1], J.E. Selfridge[1], L.M. Ocuin[1], R.S. Hoehn[5], J. Winter[5], J. Ammori[5], J. Hardacre[5], L.E. Henke[6] & L. Bahar[7]
[1]Department of Medicine, Division of Hematology and Medical Oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [2]Department of Quantitative Health Sciences and Biostatistics, Cleveland Clinic Foundation, Cleveland, OH; [3]Department of Pathology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [4]Department of Radiology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [5]Department of Surgical Oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [6]Department of Radiation Oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [7]Department of Medicine, Division of Hematology and Medical Oncology, Cleveland Clinic Foundation, Cleveland, OH. Corresponding author: Amr Mohamed, MD, amr.mohamed@uhhospitals.org

Background
Somatostatin analogues (SSAs) are the standard of care first line therapy for metastatic well-differentiated neuroendocrine tumors (NETs). They are approved for both alleviating hormone-related symptoms for functional tumors and inhibiting tumor growth. Their anti-proliferative benefit in the refractory setting is debatable due to lack of supportive literature. This systematic review compared efficacy of targeted therapies (Everolimus, Sunitinib, Surufatinib, Lenvatinib, Nintedanib, Pazopanib, Axitinib) with and without SSAs in refractory metastatic NETs.
Methods
15 prospective clinical trials published from 2008 to 2020 (8 used targeted therapy alone, 5 used targeted therapies with SSA and 2 used both) were included in final analysis. In a meta-analytic approach, proportions of a characteristic by therapy subgroup and associated p-value for the subgroup comparison were calculated from random effects models. Similar methods for incidence rates were used to evaluate incidence of progression.
Results
2,495 metastatic well-differentiated NET patients were identified; 1,824 were categorized into group A [patients who received targeted therapy alone 59.5% (n=1,087)] or group B [patients who received combined targeted therapies with SSAs 40.4% (n=737)] and the rest of the patients in these trials received placebo. The median age was 58 years old, and 52.9% were males while 47.1% were females. Primary lesions were pancreas (42%), gastrointestinal (32%), lung and thymus (16%), others/unknown (10%). Pathological grades were G1 (45%), G2 (52%), G3 (3%). There were no significant differences in terms of objective response rate (ORR) between group A 0.096 (95% CI 0.057-0.156), and group B 0.098 (95% CI 0.047-0.192), (P=0.9587). In addition, there was no significant difference in the incidence of progression between the two groups [group A: 0.0646 per person year, (95% CI 0.055-0.074) vs group B: 0.0561 per person year, (95% CI 0.039-0.080), (P=0.473)]. Grade 3 and 4 side effects (fatigue, nausea

and transaminitis) were higher in SSA combination therapy, but sample size was limited due to heterogeneous reporting and low incidence rates.
Conclusion
Addition of maintenance SSAs to targeted therapies was not associated with significant benefit in tumor control in patients with refractory metastatic NETs. These results need to be validated in prospective randomized controlled trials designed to include both survival benefit and associated financial toxicity.
Abstract ID 23660

DOI: 10.1530/endoabs.98.C6

C7

A phase II clinical trial of nivolumab and temozolomide for neuroendocrine neoplasms (NEN): updated overall survival data

Dwight H. Owen, Vineeth Sukrithan, Brooke Benner, Lai Wei, Ashima Goyal, Ye Zhou, Carly Pilcher, Nancy Curtis, Megan Jukich, Emily Schwarz, Himanshu Savardekar, Ruthann Norman, Sarah Ferguson, Barbara Kleiber, Robert Wesolowski, William E. Carson, III, Gregory A. Otterson, Claire F. Verschraegen, Manisha H. Shah & Bhavana Konda
The Ohio State University, Columbus, OH

Background
Treatment options are limited in patients with metastatic neuroendocrine neoplasms (NEN). Combination temozolomide and nivolumab showed encouraging objective response rates of 35.7% in advanced NEN regardless of site of origin, with response rates of 64% in lung NEN and 67% in pancreatic NEN (NCT03728361). We present updated survival data on follow-up from a phase II trial of combination nivolumab and temozolomide in patients with advanced NEN.
Methods
NCT03728361 is a nonrandomized, phase II study of nivolumab and temozolomide in patients with NEN. Any patient with disease progression in the prior 12 months was eligible for enrolment, irrespective of line of therapy. The primary endpoint was response rate using RECIST 1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. OS was estimated using Kaplan – Meier method with median and 95% CI. The survival curves were compared using log-rank test. OS was defined as survival from the start of treatment to death. Patients alive were censored at the last follow-up.
Results
After a median follow-up of 35.8 months (range: 3 – 52.7 months), the median OS was 38.6 months for the entire cohort of 28 patients with NEN (95% CI: 20.7 months - Not Reached (NR)). When classified by site of origin, median overall survival in lung NEN was 38.6 months (95% CI: 8.8-NR), pancreatic NEN was NR (95% CI: 32.3 -NR), and NEN not of lung or pancreatic origin was NR (95% CI: 16.8 months-NR). The difference in OS amongst each of these sites was not statistically significant ($P=0.779$).
Conclusion
The combination of nivolumab and temozolomide demonstrated promising activity in lung and pancreatic NEN. Cohorts were of small sample size thereby limiting generalizability. Comparison with historical controls will require further maturation of survival data. Future randomized studies of the combination in this population are warranted.
Abstract ID 23663

DOI: 10.1530/endoabs.98.C7

C8

Effect of hepatic impairment on pharmacokinetics, safety, and tolerability of oral paltusotine, a small-molecule, selective somatostatin receptor subtype 2 agonist

Rosa Luo MS, Alessandra Casagrande MD, PhD, Sonic Oun BA, Yang Wang MSPH, R. Scott Struthers PhD, Keith Usiskin MD & Alan Krasner MD
Crinetics Pharmaceuticals, Inc., San Diego, CA

Background
Paltusotine is an investigational oral, once-daily, small molecule somatostatin receptor type 2 agonist in development for the treatment of acromegaly and carcinoid syndrome associated with neuroendocrine tumors.
Methods
This multicenter, open-label, phase 1 study enrolled participants with mild, moderate, and severe hepatic impairment based on Child-Pugh classification and matched healthy participants. A single 20-mg oral dose of paltusotine was administered after an overnight fast (≥10 hours). Analysis of paltusotine in plasma was performed using validated liquid chromatography–tandem mass spectrometry. Geometric mean ratios of pharmacokinetic (PK) parameters were calculated from an analysis of variance (primary analysis) with hepatic condition (normal, mild, moderate, severe) as a fixed effect and log transformed PK parameter as the dependent variable. A sensitivity analysis (matched pairs mixed models for repeated measures) accounted for participant age and BMI.
Results
The study enrolled participants with mild ($n=8$), moderate ($n=8$), or severe ($n=6$) hepatic impairment and matched healthy controls ($n=14$). Most participants were male (72.2%); mean age was 57.3 years, and mean BMI was 30.7 kg/m^2. Following single oral administration of 20-mg paltusotine, mean plasma concentration of paltusotine peaked rapidly; median time to maximum concentration was 2.0 hours postdose in healthy controls and 1.6 to 3.0 hours in hepatic impairment groups. Maximum plasma concentration and total plasma exposure of paltusotine were similar across all hepatic impairment groups when compared with healthy participants (Table). Results of the sensitivity analysis were consistent with those from the primary analysis. The most common (≥5% of participants) treatment-emergent adverse events (TEAEs) were diarrhea (16.7%) and headache (5.6%). The incidence of TEAEs was similar across all 4 groups. No participant discontinued the study due to a TEAE, and no serious drug-related TEAEs were reported.
Paltusotine Pharmacokinetics: Geometric Mean Ratios

	Mild Hepatic Impairment ($n=8$)	Moderate Hepatic Impairment ($n=8$)	Severe Hepatic Impairment ($n=6$)
C_{max}, ng/mL	1.35 (0.79-2.31)	0.76 (0.45-1.31)	1.05 (0.58-1.90)
$AUC_{0\text{-inf}}$, ng•h/mL	1.00 (0.60-1.66)	0.75 (0.45-1.24)	0.90 (0.51-1.57)

Values shown are geometric mean ratio (90% CI) for each impairment group versus healthy controls. C_{max}=maximum plasma concentration; $AUC_{0\text{-inf}}$=area under the concentration-time curve from time 0 extrapolated to infinity.
Conclusion
Peak and total plasma exposure, safety, and tolerability profiles of paltusotine were similar in participants with varying degrees of hepatic impairment compared with participants with normal hepatic function. There were no changes in paltusotine plasma exposure that would be considered clinically meaningful or sufficient to warrant dose adjustment for mild, moderate, or severe hepatic impairment.
Abstract ID 23688

DOI: 10.1530/endoabs.98.C8

C9

Anti-apoptosis as a therapeutic strategy in Neuroendocrine neoplasms (NEN): A case report

Vineeth K. Sukrithan, MD[1], Uzair Ahmed[2], Ye Zhou[1], Kerry A. Rogers MD[3] & Bhavana Konda, MD, MPH[1]
[1]Division of Medical Oncology, Department of Internal Medicine, The Ohio State University and Arthur G. James Cancer Center, Columbus, OH; [2]The Ohio State University, Columbus, OH; [3]Division of Hematology, Department of Internal Medicine, The Ohio State University, Columbus, OH

Background
The expression of BCL-2, an anti-apoptotic protein, has been implicated in the aggressive behavior of NENs. Dysregulation of BCL-2 expression, controlled by the pRb1-E2F1 axis, has been linked to the development of various cancers, including NENs. Studies have shown that higher BCL-2 expression is associated with poorer survival outcomes in NEN patients.
Methods
We report a unique case of a patient with a pancreatic neuroendocrine tumor who had an unexpected response to venetoclax as part of a regimen to treat chronic lymphocytic leukemia (CLL).
Results
A 69-year-old woman with CLL that is IgVH unmutated, and has a complex karyotype, del13q on FISH panel, as well as TP53, SF3B1, and NOTCH1 mutations required treatment due to fatigue and progressive lymphadenopathy. On imaging she had bulky retroperitoneal lymphadenopathy and a pancreatic tail mass that was 3.6 x 4.9. This mass was presumed due to her CLL and was 3 x 3.7cm five years earlier. She enrolled in a clinical trial for CLL with acalabrutinib, rituximab, and venetoclax. A CT scan done 6 weeks in treatment when she had only received acalabrutinib and rituxumab showed improved retroperitoneal lymphadenopathy but progression in pancreatic tail lesion to 5.5 x 4.1cm. Venetoclax was subsequently started as planned for the study. A repeat scan 4

weeks into venetoclax revealed decrease in size of the pancreatic tail lesion to 4.2 x 3.0 cm, along with continued decrease in lymphadenopathy. As the mass was unlikely to be her CLL, an upper GI endoscopic ultrasound and fine needle aspiration of the pancreatic tail lesion was performed which revealed a well-differentiated neuroendocrine tumor. The Ki-67 was not estimable due to scant specimen. A Gallium-68 dotatate PET (Ga-PET) scan showed increased uptake in the pancreatic tail, peripancreatic lymph nodes and liver consistent with metastatic disease. The liver lesions were subsequently noted on triple phase imaging of the liver. Venetoclax was discontinued after one year of therapy as specified in the CLL trial. Subsequent imaging showed continued shrinkage in the pancreatic tail lesion to a nadir of 2.8 x 3.2 cm; seen on a scan performed 4 weeks after discontinuation of venetoclax. The pancreatic tail lesion and liver metastasis remained stable for approximately 18 months after stopping venetoclax. Subsequently, the patient experienced progression in two satellite nodules adjacent to the pancreatic tail lesion. A Ga-PET scan confirmed disease progression in the pancreatic tail, peripancreatic lymphadenopathy, and increased multifocal liver activity compared to scans from three years prior. She ultimately achieved a complete remission with undetectable minimal residual disease for her CLL.

Conclusion

We report the first known case of a response to venetoclax in a neuroendocrine tumor. BCL-2 pathway inhibition should be investigated as a therapeutic strategy in NENs.

Abstract ID 23696

DOI: 10.1530/endoabs.98.C9

C10

An ongoing phase I trial of the DLL3/CD3 IgG-like T-cell engager, BI 764532, in patients with DLL3-positive extrapulmonary neuroendocrine carcinomas

Valentina Gambardella[1], Jaume Capdevila[2], Yasutoshi Kuboki[3], Olatunji B Alese[4], Daniel Morgensztern[5], Cyrus Sayehli[6], Miguel F Sanmamed[7], Edurne Arriola[8], Jürgen Wolf[9], Taofeek Owonikoko[10], Mohamed Bouzaggou[11], Eric Song[12], Matus Studeny[13] & Martin Wermke[14]

[1]Department of Medical Oncology, Hospital Clínico Universitario, INCLIVA Biomedical Research Institute, University of Valencia, Valencia, Spain; [2]Department of Medical Oncology, Vall d'Hebron University Hospital & Vall d'Hebron Institute of Oncology, Barcelona, Spain; [3]Department of Experimental Therapeutics, National Cancer Center Hospital East, Kashiwa, Japan; [4]Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; [5]Washington University School of Medicine, St. Louis, MO; [6]Interdisciplinary Study Center with ECTU, Medical Clinic and Polyclinic II of the University Hospital, Würzburg, Germany; [7]Department of Oncology, Clínica Universidad de Navarra, Pamplona, Spain; [8]Department of Medical Oncology, Hospital del Mar-CIBERONC (Centro de Investigación Biomédica en Red de Oncología), 08003 Barcelona, Spain; Cancer Research Program, IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), 08003 Barcelona, Spain; [9]Center for Integrated Oncology, University Hospital of Cologne, Cologne, Germany; [10]UPMC Hillman Cancer Center, Division of Hematology/Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA; [11]Boehringer Ingelheim France S.A.S., Reims, France; [12]Boehringer Ingelheim (China) Investment Co., Shanghai, China; [13]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [14]TU Dresden University of Technology, NCT/UCC Early Clinical Trial Unit, Dresden, Germany

Background

Delta-like ligand 3 (DLL3) is highly expressed on small-cell lung cancer (SCLC) tumors and neuroendocrine carcinomas (NECs). BI 764532 is a DLL3/CD3 IgG-like T-cell engager with potent preclinical activity. NCT04429087 is an ongoing phase I dose-escalation trial of BI 764532 in adults with locally advanced/metastatic DLL3-positive (confirmed centrally) SCLC, extrapulmonary NEC, or large cell neuroendocrine lung carcinoma. Here we focus on patients with extrapulmonary NEC.

Methods

BI 764532 was given intravenously (iv) in 3 regimens: Regimen A (RA; fixed iv dose q3w); RB1 (fixed iv dose qw); RB2 (step-in doses followed by a fixed dose). Treatment continued until progressive disease, unacceptable toxicity, other withdrawal criteria or maximum treatment duration (36 months). Main objective: maximum tolerated dose (MTD) and/or recommended dose for expansion of BI 764532. Other objectives: safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy based on investigator review (RECIST v1.1).

Results

As of 26 March 2023, 107 patients received $\geq$1 dose ($\geq$ 0.03 µg/kg) of BI 764532 (RA: $n=24$; RB1: $n=10$; RB2: $n=73$). Dose limiting toxicities: 1 patient on RA (Grade 3 confusion) and 4 patients on RB2 (Grade 4 cytokine release syndrome [CRS]; Grade 3 CRS; Grade 3 nervous system disorder and Grade 2 infusion-related reaction). MTD has not been reached and dose escalation is ongoing. 41 patients with extrapulmonary NEC have been treated. NEC baseline characteristics: male, 63%; median age, 60 (range 33–77); ECOG PS 0/1, 37/61%; prior PD1/PD-L1 treatment, 17%; $\geq$2 prior lines of treatment, 56%. Treatment-related adverse events (TRAEs; any/Grade $\geq$3): 88/20%. The most common TRAEs (any/Grade $\geq$3) were: CRS (76/2%); pyrexia (22/0%); dysgeusia (17/0%); fatigue (17/2%) and decreased lymphocytes (15/12%). There were no treatment discontinuations due to TRAEs. Across all regimens and dose levels, tumor response data were available for 34 patients with extrapulmonary NEC (gastrointestinal: $n=18$; genitourinary: $n=10$; unknown origin: $n=6$). Overall response rate (ORR)/disease control rate (DCR) was 15/41%. In patients who received $\geq$ target dose of BI 764532 (90 µg/kg; $n=25$), 5 patients responded (all partial responses; gastrointestinal origin, $n=4$; genitourinary origin, $n=1$). ORR was 20% and DCR was 48%.

Conclusions

BI 764532 showed clinically manageable tolerability; MTD has not been reached. Promising efficacy was observed in patients with extrapulmonary NEC. The study is ongoing.

Abstract ID 23713

DOI: 10.1530/endoabs.98.C10

C11

Transformation of low-intermediate grade neuroendocrine tumors into high grade morphology

John D. McGlothlin, MD[1], Saam Dilmaghani, MD[2], Antonious Z. Hazim, MD[3], Timothy J. Hobday, MD[3], Mohamad B. Sonbol, MD[4], Jason S. Starr, DO[5], Rachel A. Eiring, PA-C[3], Rondell P. Graham MBBS[6] & Thorvardur R. Halfdanarson, MD[3]

[1]Department of Internal Medicine, Mayo Clinic, Rochester, MN; [2]Department of Gastroenterology, Mayo Clinic, Rochester, MN; [3]Department of Medical Oncology, Mayo Clinic, Rochester, MN; [4]Department of Medical Oncology, Mayo Clinic, Phoenix, AZ; [5]Department of Medical Oncology, Mayo Clinic, Jacksonville, FL; [6]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

Background

Low- (G1) and intermediate-grade (G2) neuroendocrine tumors (NET) are defined by lower mitotic rates and genetic mutations that rarely cause transformation to high-grade (G3) neoplasm. Yet a proportion of patients with de novo low-grade NETs progress to G3 disease or even neuroendocrine carcinoma (NEC). We aimed to highlight cases of low-grade G1 and G2 NETs that eventually transformed to G3 pathology on repeat biopsy and describe characteristics that portend high-grade transformation.

Methods

We conducted a retrospective study of patients with de novo pathology-proven G1/G2 NETs who eventually transformed to G3 NET after treatment at the Mayo Clinic from 1999 to 2022. Patients were identified by search of pathology reports in the electronic medical record and confirmed to meet WHO criteria. In order to minimize the risk of biopsy sampling error and case misclassification, at least one-month time difference was required between collection of the two biopsy specimens. Data analysis was conducted with RStudio for tests of statistical significance including chi-square and Pearson correlation coefficient testing.

Results

Twenty-five patients were identified with initial G1/G2 NET who subsequently progressed to either G3 NET or NEC. 17/25 (68%) were pancreatic primaries. Median age at diagnosis was 55 years (IQR 42-64) and 11 were male (44%). 16/19 (84%) of patients with G3 NET on follow up had a G2 NET on initial diagnosis and 3/6 of patients with poorly-differentiated NEC (60%) on follow up had a G2 NET on initial diagnosis. Median Ki-67 at initial diagnosis was 8.0 (IQR 4.3-14) and median Ki-67 after transformation was 28.5 (IQR 22-32.9). Median time from initial diagnosis to diagnosis of all high-grade pathology was 7.1 months (IQR 1.2-20.9). Median time from initial diagnosis to diagnosis of poorly differentiated NEC was 1.3 months (IQR 0.9-9.5) and median time from initial diagnosis to well-differentiated G3 NET was 8.1 months (IQR 1.6-23.7). Median length of follow up was 51 months (IQR 30.1-73.5). 11/25 (44%) patients had died by follow-up. 1-year disease specific survival was 83% (CI=0.69-1.0) from initial diagnosis and 5-year disease survival was 55% (CI=0.38-0.88).

Conclusion

Patients with G1/G2 NET on initial biopsy can have G3 NET and NEC on future biopsy signifying either high grade transformation or combined low- and high-grade heterogeneity. Patients who have low-grade to high-grade neuroendocrine transformation are more likely to have G2 pathology on initial diagnosis. When

low-grade to high-grade transformation does occur, outcomes are poorer than for patients with low grade morphology.
Abstract ID 23740

DOI: 10.1530/endoabs.98.C11

C12

Real world use of virtual care for treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

William J Phillips[1], Michelle Pradier[2], Rachel Goodwin[3], Michael Vickers[3] & Tim Asmis[3]
[1]The University of Ottawa, Division of Medical Oncology, Ottawa, ON, Canada; [2]The University of Ottawa, Faculty of Medicine, Ottawa, ON, Canada; [3]The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Background
Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a relatively rare group of tumors. Traditionally, management of unresectable GEP-NETs was performed by in-person assessment at specialized regional cancer centers. The COVID-19 pandemic resulted in an unprecedent shift towards virtual care. The aim of this study is to evaluate the use of virtual care for GEP-NETs after the COVID-19 pandemic at a high-volume academic cancer center.
Methods
This is a retrospective, observational study taking place at The Ottawa Hospital Cancer Center in Canada. Adult patients with unresectable GEP-NETs seen in consultation by medical oncology between June 1, 2019, and March 31, 2023, were included. We collected demographic, clinicopathologic and treatment data by review of the electronic medical records. Visit information was collected using a local administrative hospital database. Descriptive statistical analysis was used to summarize our results.
Results
88 patients met the inclusion criteria. The median age was 65 years. Of patients included, ($n=28$, 41%) were employed at the time of consultation and ($n=22$, 30%) lived in a remote area, defined as $>$ 50km from the closest regional cancer center. The most common primary tumor location was the small bowel ($n=45$, 53%) followed by pancreas ($n=27$, 32%) and colon ($n=11$, 13%), while the most common locations of metastasis included the liver ($n=69$, 78%), distant lymph nodes ($n=35$, 40%) and bone ($n=25$, 28%). The distribution of Ki-67 was $<3\%$ in ($n=21$, 30%), 3-20 ($n=31$, 45%) and >20 ($n=17=,25\%$). Systemic therapies used included somatostatin analogues ($n=85$, 97%), chemotherapy ($n=29$, 33%), targeted therapy ($n=2$, 2%) and peptide-receptor radionucleotide therapy (PRRT) ($n=2$, 2%). Overall virtual care use over the study period was ($n=21$, 25%) for consultations and ($n=568$, 75%) for follow-up visits. Virtual care use for follow-up visits varied by year: 2019 ($n=0$, 0%), 2020 ($n=110$, 87%), 2021 ($n=211$, 97%), 2022 ($n=236$, 65%) and 2023 ($n=11$, 33%).
Conclusion
This study demonstrates that virtual assessment is the predominant modality of patient care in the post-COVID era and is still being used significantly up to the first quarter of 2023. These results highlight the continued importance of virtual assessment in the care of GEP-NET patients and advocate for future work in the area to improve virtual care programs.
Abstract ID 23753

DOI: 10.1530/endoabs.98.C12

C13

Clinical characteristics and molecular profiling of patients with pancreatic mixed acinar-neuroendocrine carcinoma

Cody Eslinger[1], Bobak Seddighzadeh[1], Zaid Elsabbagh[2], Rish Pai[3], Chris Hartley[4], Jason Starr[5], Tanios Bekaii-Saab[6], Thorvardur Halfdanarson[7] & Mohamad Bassam Sonbol[6]
[1]Department of Internal Medicine, Mayo Clinic Arizona, Phoenix, AZ; [2]School of Medicine, Johns Hopkins University, Baltimore, MD; [3]Department of Pathology, Mayo Clinic Arizona, Phoenix, AZ; [4]Department of Pathology, Mayo Clinic Rochester, Rochester, MN; [5]Department of Hematology-Oncology, Mayo Clinic Florida, Jacksonville, FL; [6]Department of Hematology-Oncology, Mayo Clinic Arizona, Phoenix, AZ; [7]Department of Oncology, Mayo Clinic Rochester, Rochester, MN

Background
Pancreatic acinar cell carcinoma (PACC) is a rare cancer, comprising less than 1% of all pancreatic cancers and often presents as a mixed malignancy with a neuroendocrine component. Limited data exists on its clinical and molecular characteristics. This retrospective study aims to provide additional insights to better understand and characterize the disease.
Methods
Patients from the Mayo Clinic with pathology records denoting pancreatic acinar cell carcinoma from years 2002 to 2023 were selected for retrospective review. Demographic data, pathologic information, treatment courses, and next generation sequencing (NGS) when available, were collected.
Results
A total of 54 patients (pts) were identified (78% male, $n=42$). Median age was 63 years old (range 23-88). Histologic subtypes were 70% pure acinar cell carcinoma ($n=38$), 24% mixed acinar-neuroendocrine ($n=13$), and 6% mixed acinar-adenocarcinoma ($n=3$). At diagnosis, 46% presented with metastatic disease ($n=25$), 19% were locally advanced ($n=10$), and 35% were resectable ($n=19$). Early stages were more likely to undergo upfront surgical resection (84%, $n=16$), while locally advanced cancers were frequently treated with neoadjuvant chemotherapy (70%, $n=7$) followed by surgical resection (60%, $n=6$). FOLFIRINOX was chosen as neoadjuvant therapy in 71% of pts ($n=10$), while others received gemcitabine-based therapies. 14 pts had somatic and germline NGS (Table 1) with the following ($n=12$ with targetable mutations): homologous recombination (HR) gene alterations ($n=6$, 3 treated with olaparib), RAF alterations ($n=6$, 2 treated with dabrafenib plus trametinib and 1 with ulixertinib), mismatch repair (MMR) gene alterations ($n=3$, 1 treated with pembrolizumab), and NTRK alteration ($n=1$, ongoing treatment with larotrectinib, 15 months partial response).

Targetable Somatic Alterations ($n=14$)	Germline Testing Results ($n=14$)
HR alterations ($n=6$ pts): ATM (3), BARD1 (1), BRCA2 (2), CHEK2 (1), PALB2 (2), RAD51C (1)	HR alterations ($n=5$ pts): ATM (1), CHEK2 (2), BARD1 (1), PALB2 (1)
MMR alterations ($n=3$ pts): MLH1 (3), MSH3 (1)	
RAF alterations ($n=6$ pts): BRAF V600E (1), KANK4-RAF1 fusion (1), SND1-BRAF fusion (3), TBXAS1-BRAF rearrangement (1)	
NTRK alterations ($n=1$ pt): ETV6-NTRK3 fusion (1)	

Conclusion
In our cohort, half of PACC patients presented with advanced disease. Unlike PDAC, PACC is a genomically diverse disease, with potentially targetable alterations in RAF, HRD, and MMR genes, offering additional therapeutic options for most of these patients. Therefore, somatic and germline testing should be considered for any patient diagnosed with PACC.
Abstract ID 23770

DOI: 10.1530/endoabs.98.C13

C14

Cabozantinib as salvage therapy for well differentiated grade 3 neuroendocrine tumors (G3 NETs)

Rylie R. Schnell[1], Rachel A. Eiring[2], Morgan C. Miller[2], Patrick W. McGarrah[2] & Thorvardur R. Halfdanarson[2]
[1]Mayo Clinic Comprehensive Cancer Center, Rochester, MN; [2]Mayo Clinic Comprehensive Cancer Center, Division of Medical Oncology, Rochester, MN

Background
G3 NETs are a recently recognized entity and although the treatment recommendations largely follow those for grade 1 and 2 NETs, the outcomes of therapy are inferior. Little is known about the optimal therapy sequencing but small studies have suggested a benefit of multikinase inhibitors. Somatostatin analogs, PRRT and chemotherapy have all been reported to have activity but later lines of therapy are needed. In this study, we sought to evaluate the activity of cabozantinib in patients with heavily pretreated G3 NETs.
Methods
Using the Mayo Clinic electronic medical record, we searched for patients with G3 NET who received cabozantinib focusing on patients who were either heavily pretreated or had a very high nuclear grade as measured by Ki-67. Information on baseline patient and tumor characteristics, tolerability and efficacy were extracted.
Results
Five patients (3 women, 2 men) met inclusion criteria. Four had pancreatic primary tumor and one had a NET of unknown primary. The median Ki-67 was 10 (range: 10-55) on the initial biopsy and 56 (range: 29-77) on repeat biopsy prior to starting cabozantinib. All patients had grade progression on repeat biopsy, 3 with Ki67 $>$ 50 on repeat biopsy. All patients had genomic studies and 2 had TMB $>$ 200 m/Mb, presumably temozolomide-induced hypermutation. Four patients had prior somatostatin analogs, and all had PRRT and CAPTEM prior to cabozantinib. Three patients had other chemotherapy prior to cabozantinib (all had irinotecan and oxaliplatin regimens). One patient had everolimus and one patient (with high TMB) had immunotherapy without response. Four patients had a substantial response, but one has not had follow-up imaging. Two have

progressed (after 4 and 9 months) and three are still receiving cabozantinib (after 1, 7 and 10 months) with sustained response in 2 patients. Four patients needed dose reduction for toxicity including the patients who have had response for 7 and 10 months).

Conclusion

Cabozantinib seems to have substantial antitumor activity in this small cohort of extensively pretreated mostly pancreatic G3 NET patients. Despite very high Ki-67 and multiple lines of prior therapy, including chemotherapy and PRRT, responses have been profound and in 2 cases durable. While no patient had to discontinue cabozantinib for toxicity, 4 needed a dose reduction. Cabozantinib may be a viable option for patients with advanced and heavily pretreated G3 NETs and further studies are warranted.

Abstract ID 23772

DOI: 10.1530/endoabs.98.C14

C15

Phase II study of frontline maintenance rucaparib in combination with nivolumab in extensive stage small cell lung cancer

Aman Chauhan[1], Jill Kolesar[2], Donglin Yan[2], Zhonglin Hao[2], Ronald McGarry[2], John Villano[2], Ralph Zinner[2], Ashish Maskey[2], Jordan Miller[2], Timothy Mullett[2], Aman Khurana[2], Xitong Zhou[2], Garima Gupta[2], Daniel Flora[3], Colleen Darnell[3], Richard O'Neil[4], Charles Kunos[2], Lowell Anthony[2] & Susanne Arnold[2]

[1]Sylvester Comprehensive Cancer Center, University of Miami; [2]Markey Cancer Center, University of Kentucky; [3]St Elizabeth Healthcare, Edgewood, KY, [4]Prisma Health Cancer Institute, Greenville, SC

Background

Immune checkpoint inhibitor (ICI) maintenance therapy is the standard of care for frontline management of extensive-stage small cell lung cancer (ES SCLC). However, the overall survival benefit of the addition of ICI maintenance to frontline ES SCLC treatment is modest and further improvement is needed. We hypothesized that the addition of poly (ADP-ribose) polymerase inhibition to ICI maintenance therapy for patients with platinum-sensitive ES SCLC could improve the antitumor efficacy of ICI.

Methods

A single-arm, investigator-initiated phase II trial (NCT03958045) enrolled patients with platinum-sensitive ES SCLC who received frontline maintenance nivolumab 480 mg IV every 4 weeks, and rucaparib, 600 mg PO twice a day after the completion of 4-6 cycles of the platinum doublet. The primary outcome was median progression-free survival. Secondary endpoints included assessment of objective response and adverse effects (AEs) per CTCAE 5.0. Correlative studies included pretreatment and during-treatment immune assays and circulating tumor DNA TP53 mutation status.

Results

42 patients consented, and 33 met eligibility criteria and were treated. All patients received 4-6 cycles of frontline platinum doublet and had at least a partial response by RECIST at enrollment. In the 33 participants, the most common grade 3 and 4 AEs (at least possibly related) were hypokalemia (3%), hyponatremia (3%), elevated alanine aminotransferase (3%), neutropenia (3%) and leukocytopenia (3%). No grade 5 AE was noted. The median PFS (mPFS) was 3 months from the time of enrollment on frontline maintenance (post platinum doublet). The mPFS was 11 months from cycle 1 of the platinum doublet. Overall, 89.8% of patients were alive at 12 months, and 54.4 % of patients were alive at 24 months from the start of the platinum doublet. Currently, 2 patients are on active treatment, and the other two have completed study treatment and are on observation with stable disease.

Conclusion

Maintenance rucaparib combined with immune checkpoint inhibition was tolerable and showed promising activity after completion of frontline chemotherapy in platinum-sensitive extensive-stage small cell lung cancer patients.

Abstract ID 23774

DOI: 10.1530/endoabs.98.C15

C16

Comparison of well-differentiated gastroenteropancreatic grade 3 neuroendocrine tumors (G3NETS): de novo and in the setting of apparent grade progression over time

Bryan Khuong Le[1], Alan Paciorek[2], Farhana Moon[1], Courtney Lawhn Heath[3], Thomas Hope[3], Nicholas Fidelman [3], Claire Mulvey[4], Sheila Lindsay[5], Li Zhang ¬[2], Eric Nakakura[5], Nancy Joseph[6] & Emily K. Bergsland[4]

[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [2]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA; [3]Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA; [4]Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA; [5]Department of Surgery, University of California San Francisco, San Francisco, CA; [6]Department of Pathology, University of California San Francisco, San Francisco, CA

Background

G3NETs demonstrate variable clinical behavior (Ki-67 > 20-100%). Treatment extrapolated from grade 1/2 (G1/2) NETs and neuroendocrine carcinomas depending on clinicopathologic features. Therapy for treatment-emergent G3NETs remains especially ill-defined.

Methods

Retrospective chart review of patients with de novo G3NETs or progressing from low-to-high grade (L-H) (G1/2 at diagnosis and G3 > =3 months later). Treatment patterns compared by Pearson chi-squared tests among patients with complete treatment information. Overall survival (OS) from stage IV G3NETs diagnosis estimated by Kaplan-Meier.

Results

$n = 50$ patients with G3NETs: 18% nonwhite, 46% female, median age at G3 62 (29-81). Primary site: pancreas 60%, other gastrointestinal 22%, unknown 18%. Median follow-up from stage IV G3 48 months (mo). De novo G3NETs in 38% (19/50) with median Ki-67 30% (range 21-70%), Ki-67 < =55% in 79%. Among these, 89% (17/19) stage IV and 11% (2/19) locoregional at diagnosis (treated surgically before developing metastases). Median OS was 35 mo (95% CI 20-54). L-H G3NETs in 62% (31/50): median Ki-67 at G3 diagnosis 38% (21-75%), Ki-67 < =55% in 87%. Among these, 77% (24/31) stage IV at G1/G2 diagnosis. Median time to L-H 58 mo (range 3-391 mo); 97% (30/31) stage IV. Therapy prior to G3 diagnosis: SSA 81%, surgery 48%, liver-directed therapy (LDT) 41%, cytotoxic chemotherapy (CC) 39%, radiation 32%, peptide receptor radionuclide therapy (PRRT) 29%, and targeted agents (e.g. everolimus, sunitinib) 26%. Median OS 16 mo (95% CI 9-22). Treatment for advanced G3 listed in Table 1.

Table 1. First-line (1L) and second-line (2L) treatment for metastatic G3NETs ($n = 44$)

	De novo G3NETs ($n = 19$)		L-H G3NETs ($n = 25$)	
	1L,N(%)	2L,N(%)	1L,N(%)	2L,N(%)
SSA^	**9(47)**	0	**1(4)**	0
Cisplatin/carboplatin-based	8(42)	3(16)	4(16)	2(8)
Other CC*/Immunotherapy	0	7(37)	4(16)	5(20)
Everolimus	0	0	0	2(8)
PRRT	0	1(5)	2(8)	1(4)
Radiation	0	1(5)	2(8%)	3(12)
LDT	0	3(16)	6(24)	4(16)
Surgery (primary or metastasis)	2(11)	2(11)	6(24)	2(8)

*capecitabine/temozolomide, FOLFOX

^Pearson chi-squared test indicated significant differences in 1L ($p < 0.001$)

Conclusion

Higher prevalence of L-H compared to de novo G3NETs was observed at our institution. While there is extensive overlap, de novo G3NETs more commonly treated with SSA. Further research is needed to compare the outcomes and molecular underpinnings of apparent de novo G3NETs vs L-H, and the impact of primary tumor site, Ki67, and prior therapy. Understanding these differences will help elucidate whether these subtypes are truly distinct entities (with one being treatment-emergent) or simply reflect the natural history of the disease and intrapatient heterogeneity.

Abstract ID 23806

DOI: 10.1530/endoabs.98.C16

C17

Argentinian registry of gastric neuroendocrine tumors: A closer look at type 1

Ana Oviedo[1], Romina Luca[2], Claudia Bestani[3], Andrés Rodriguez[2], Federico Waisberg[2], Carla Ypa[4], Greta Catani[2], Andrea Acosta[1], Julian Maquieira[1], Teresa Pombo[6], Mirta Kujaruk[5], Guillermo Méndez[1] & Juan O'Connor[2]

[1]Oncology Unit, Gastroenterology Hospital "Dr. Carlos Bonorino Udaondo", Buenos Aires, Argentina; [2]Medical Oncology Department, Alexander Fleming Institute, Hospital, Buenos Aires, Argentina; [3]Gastroenterology Unit, Gastroenterology Hospital "Dr. Carlos Bonorino Udaondo", Buenos Aires, Argentina; [4]Medical Oncology Department,

Oncology Hospital "Maria Curie", Buenos Aires, Argentina; [5]Pathology Unit, Gastroenterology Hospital "Dr. Carlos Bonorino Udaondo", Buenos Aires, Argentina; [6]Pathology Department, Alexander Fleming Institute, Hospital, Buenos Aires, Argentina

Background
Gastric neuroendocrine tumors (gNETs) are relatively uncommon. Represent up to 23% of all digestive neuroendocrine neoplasms. The majority are incidentally diagnosed from histology of 'simple' gastric polyps identified at endoscopy. There are 3 groups of gNETs: types 1, 2 and 3 with different pathogeneses, biological and clinical behaviors. It is worth mentioning that recent reports suggest a fourth type of gNETs[1]. Type I represents 75–80% of all gNETs and are mostly related to chronic atrophic gastritis, which is reflected by the presence of multiple small lesions in about 65% of cases. They are usually of indolent behavior and characterized as non-functioning and well differentiated NETs. Nevertheless, rare cases of negligible risk of metastases ($<5\%$)[2] poorly differentiated tumors and prognosis have been described in the literature. We aimed to explored clinicopathological characteristics of type I gNETs and explored prognostic factors associated with progression free survival (PFS) in patients that were followed in two referenced centers in Argentina.
Methods
This study was part of a multicentric and retrospective register of patients with gNETs diagnosis from 2009 to 2023. Descriptive statistics was used to summarize main patient characteristics, including mean and standard deviation. PFS was calculated considering the interval between tumor interventions, which included endoscopic resections. Survival data was analyzed using the Kaplan-Meier method, and we evaluated the presence of prognostic factors using uni and multivariate Cox regression models.
Results
Of the 81 assessable patients with gNETs, 61(75.3%) were type 1. Mean age at diagnosis was 53.5 years (SD +/-13.2), 45(73.7%) were women. Most frequent localization was gastric corpus 34(55.7%). Cromogranin A and synaptophysin were positive in 54(93.1%) cases. Histological grade was G1 in 29 (50.9%) patients. Anti-parietal and anti-intrinsic factor autoantibodies were positive in 35 (57.4%) and 8 (13.1%) patients, respectively. Mucosal and distant relapse were observed in 15(24.5%) and 2(5.6%), patients respectively. Median follow-up was 85.2 months (95% CI 40-NR). Median PFS(PFSm) was 42.73 months CI95% (30-74m). No differences in PFS were observed in patients according to different subgroups including high serum gastrin ($P=0.14$), localization ($P=0.67$; corpus 35.9 (18.4-NR) vs fundus 64.86 (23.1-NR)), and endoscopic vs surgical treatment ($P=0.97$). Distant relapse had been found in 3.2% ($n=2$) of this cohort. Considering the median follow up of 86 months, a distant relapse free survival of 100% was estimated. Multivariate models did not show a specific prognostic factor associated with PFS.
Conclusion
Our study represents one of the largest gNETs cohorts reported in Latin America. No prognostic factors for PFS were identified in uni or multivariate models. Most patients received surgical or endoscopic treatment in at least one point of their treatment care plan, and only 2 events of distant recurrence were identified. The complexity of these tumors should be discussed in a multidisciplinary board of neuroendocrine tumors and further studies are required to facilitate the identification of the genetic and molecular information of the disease, thereby enabling the development of new effective diagnostic and therapeutic strategies advances in the treatment of gNETs.

TYPE 1 GASTRIC NET	N 61	%
Mean age	53.5 years (SD +/- 13.2)	
Sex		
• Male	16	26.%
• Female	45	73.7%
Lesion size		
• <10 mm	42	68.8%
• 10-20 mm	20	32.7%
• >20 mm	1	1.6%
Type lesions		
• Single polyps	30	49.1%
• Multiple polyps	28	45.9%
• Ulcerated lesions	1	1.6%
• Unknown	2	3.2%
Localization		
• Corpus	34	55.7%
• Cardias	13	21.3%
• Antrum	4	6.6%
• Greater curvature	2	3.3%
• Lesser curvature	1	1.6%
• Unknown	3	4.9%
IHC Staining		
• Cromogranin A +	54	93.1%
• Synatophysin +	54	93.1%
Mitotic count		
• <2	33	55.9%
• 2-20	3	5.1%
• >20	3	5.1%
Ki67 index		
• <2	33	55.9%
• 3-20	13	22.4%
• Unknown	12	19.6%
Histological grade		
• G1	33	55.9%
• G2	10	17.5%
Intestinal metaplasia		
• Positive	34	58.6%
• Negative	9	15.5%
• Mixed	3	5.2%
• Unknown	12	20.7%
Pseudopyloric metaplasia		
• Positive	18	32.1%
• Negative	9	16.1%
• Unknown	29	51.8%
Deep invasión		
• Mucosa	10	17.5%
• Submucosa	29	50.9%
• Muscularis propia	8	14%
• Unknown	10	17.5%
Histopathological patterns		
• LVI (+)	3	5.1%
• PNI (+)	1	1.7%
• Unknown	57	93%
Margins after resection		
• R0	16	27.6%
• R1	20	34.5%
• Unknown	47	81%

Abstract ID 23810
DOI: 10.1530/endoabs.98.C17

Clinical – Nuclear Medicine/ Interventional Radiology/Imaging

C18

[68Ga] DOTA-TATE (NETSpot) PET/CT Imaging of Pulmonary Neuroendocrine Tumors

Rolf Grage MD, Matt Dudgeon MD, Akash Sharma & Ephraim Parent
Department of Radiology, Mayo Clinic FL

Background
Neuroendocrine tumors (NETs), also known as carcinoid, comprise a heterogeneous group of malignancies that arise from neuroendocrine cells throughout the body, most commonly originating from the gastrointestinal tract and lungs. Lung NETs originate from pulmonary neuroendocrine cells (PNECs) that occur as individual cells or small clusters, accounting for approximately 25% of primary lung neoplasms. Lungs NETs can be classified into four subtypes: well-differentiated, low-grade typical carcinoids (TCs); well-differentiated, intermediate-grade atypical carcinoids (ACs); poorly differentiated, high-grade large cell neuroendocrine carcinomas (LCNECs); and poorly differentiated, high grade small cell lung carcinomas (SCLCs). Lung NETs are considered a distinct family of tumors with shared morphologic characteristics. There is evidence to suggest that TCs and ACs are morphologically distinct from LCNECs and SCLCs. Some TCs and ACs develop in patients with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), a rare pre-neoplastic lesion characterized by the associated of pre-invasion hyperplasia of PNECs and neuroepithelial bodies in the respiratory epithelium. Carcinoid tumors express somatostatin receptors, which allows for imaging with the use of [68Ga] DOTA-TATE (NETSpot) PET/CT and FDG PET/CT. These studies image the uptake of somatostatin by the tumor rather than the actual tumor and acquire a maximum standardized uptake value (max SUV).
Methods
We obtained permission from the Institutional Review Board for this retrospective review. The Mayo Florida registry was searched with chart review that looked at the max SUV of patients with pulmonary NETs who received [68Ga] DOTA-TATE (NETSpot) PET/CT imaging. We identified multiple patients with biopsy proven pulmonary NETs. Tumor imaging characteristics, pathology, and associated findings were reviewed, analyzed, and recorded.
Results
Patient Characteristics
Seventeen patients had biopsy proven lung NET, 12 cases of typical and 5 cases of atypical carcinoid. The demographics are summarized in Table 1. Most lesions where found in the lung parenchyma with a couple in the hilum.
Radiologic Data
CT, [^{68}Ga] DOTA-TATE (NETSpot) PET/CT, and FDG PET/CT imaging were reviewed with max SUV measurement included in Table 1. Max SUV of all lesions ranged from 1.2 – 57.5. Representative images are included on Figure 1a, 1b, and 2. Twelve patients were diagnosed with typical carcinoid with the highest uptake of 57.5, range of max SUV of 3.6-57.5. Five patients were diagnosed with atypical carcinoid, range of max SUV of 1.2–6.2. Of the 3 patients with DIPNECH, one had pathology of atypical carcinoid and 2 were found to be typical carcinoid. The patients with typical carcinoid were found to have a higher max SUV than atypical carcinoid.
Pathological Data
Typical carcinoid lesions had a lower Ki-67 than atypical carcinoid.
Conclusion
[68Ga] DOTA-TATE (NETSpot) PET/CT can identify patients with pulmonary neuroendocrine tumors with high specificity and sensitivity. The maximum SUV seems to decrease as the disease progresses, which is in line with common knowledge. Maximum SUV is not necessarily involved in the grading of these tumors; however it may give a marker about the extent of disease and whether there is a recurrence. The results need to be further verified in a larger sample size and with clinical follow up to correlate PET characteristics and outcomes.
Abstract ID 23387
DOI: 10.1530/endoabs.98.C18

C19

The Impact of Post-Treatment Imaging in Peptide Receptor Radionuclide Therapy

Surekha Yadav, MD[1], Courtney Lawhn-Heath, MD[1], Sheila Lindsay, NP[1,2], Rebecca Mirro, RN[1,2], Emily K. Bergsland, MD[2,4] & Thomas A Hope, MD[1,3,4]
[1]Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA; [2]Department of Medicine, Division of Medical Oncology, University of California San Francisco, CA; [3]Department of Radiology, San Francisco VA Medical Center, San Francisco, CA; [4]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, CA

Background
A small portion (11%) of radioactive decay of 177Lu involves the emission of gamma photons, allowing for post-treatment imaging. Despite this capability, most centers do not routinely conduct post-treatment imaging. It is not well recognized that qualitative findings from post-PRRT imaging can influence clinical management. The aim of this study was to evaluate the rate of change in management from post treatment imaging.
Methods
100 patients who received 177Lu-DOTATATE for metastatic well-differentiated NETs at our institution between 2016 and 2021 retrospectively analyzed. Included patients received minimum two cycles & underwent 24-hour post-therapy SPECT/CT imaging after each cycle. Scans were compared to baseline post-cycle 1 images to assess response, divided into four groups: 1: Marked reduction in tumor volume; 2: Reduction but with residual disease; 3: Stable disease; 4: Development of new SSTR positive lesions. Changes in management, were grouped into major and minor. Major: PRRT stopped due to progressION, stopped due to marked response, delayed for targeted treatment of new/growing lesion, and stopped due to lab values. Minor: PRRT continued despite of borderline low/low lab value, characterization of pseudoprogression, and hydronephrosis noted leading to stent placement.
Results
100 patients were analyzed. 84% had GEP NET (bronchial 6%, others 10%). 36% were Grade 1, 58% were Grade 2 & 6% were Grade 3. 64% received four cycles, 21% received three cycles and 15% received two cycles. Most patients (78% in post-cycle 2, 78.8% in post-cycle 3, and 73.4% in post-cycle 4 images) exhibited qualitatively stable disease on SPECT/CT over the course of PRRT. Post-therapy SPECT/CT resulted in a change in management in 27%. In 77% of those cases, post-therapy imaging led to major changes. Patients with a higher tumor grade had a higher proportion of change in management. However, no significant relationship was noted between the tumor grade and the impact on management.

Grade	Total (n =100)	Major (n =21)	Minor (n =6)	All (n =27)
G1	36% (36)	11% (4)	8% (3)	19% (7)
G2	58% (58)	22% (13)	5% (3)	26% (16)
G3	6% (6)	67% (4)	0	67% (4)

Table 1: Break down of change in management by Grade in patients with NETs that underwent post therapy SPECT imaging.

Conclusion
In a considerable proportion of patients (27%), post-treatment SPECT/CT imaging resulted in a change in management. The rate of change was higher in patients with higher-grade tumors. Although post-treatment imaging is typically discussed in the setting of dosimetry, qualitative impact of post-treatment imaging is common.
Abstract ID 23467
DOI: 10.1530/endoabs.98.C19

C20

Yttrium 90 transarterial radioembolization of neuroendocrine liver metastasis

Gavin Yuan[1,2], Elena Petre[1], Etay Ziv[1], Amgad Moussa[1], Adrian Gonzalez Aguirre[1], Jonathan Latzman[1], Diane Reidy[1], Nitya Raj[1] & Erica Alexander[1]
[1]Memorial Sloan Kettering Cancer Center, [2]New York Medical College

Background
To determine the safety and efficacy of Yttrium 90 (Y90) transarterial radioembolizations (TARE) for neuroendocrine liver metastasis (NLM) and elucidate factors that affect outcomes.
Methods
Retrospective analysis of 39 patients with NLM in a single center who underwent 65 Y90 TAREs with glass or resin microspheres between April 2012 and December 2022. There were 17 male and 22 female with a mean age at time of treatment of 65.5 years (SD ±12.25), range 40-89 years). Primary anatomic site for tumor included pancreas (n=16), small bowel (n=7), rectal (n=4), lung (n=5), NET of unknown origins (n=4), colon (n=1), renal (n=1), and gastric (n=1). MSK-IMPACT next generation sequencing was collected when available. Survival outcomes were local tumor progression (LTP) and overall survival (OS) calculated based on time of treatment; these were measured via Kaplan-Meier method. Cox proportional hazards model and the log rank test were used to estimate differences between groups. Complications were graded via Common Terminology Criteria for Adverse Events (CTCAE).
Results
Median local tumor progression free survival (LTPFS) was 12.43 months (95%CI: 6.8-17.97 months). Higher tumor grade was associated with lower LTPFS (p=.094). Stratified by anatomic site, LTPFS for lung tumors was the longest (median: 33.73 months; 95%CI: 0.4-NR months), followed by pancreatic (median: 17.17 months; 95%CI: 6.13-26.33 months), rectal (median: 11.07 months; 95%CI: 0.67-NR months), small bowel (median: 7.43 months; 95%CI: 4.17-NR months), other anatomic sites (median: 4.4 months; 95%CI: 1-11.03

months), and NET of unknown origins (median: 3.97 months; 95%CI: 2.87-NR months). Differences in LTPFS between anatomic sites were statistically significant ($P=0.04$). The median overall survival for all patients was 33.67 months (95% CI 15.67-57.2 months). Survival hazard ratio (SHR) for tumor burden >50% compared to tumors <50% of the liver volume was 2.23 (95% CI: 0.92-5.41, $P=0.076$). Prescence of DAXX mutation was associated with longer survival (SHR .57, 95%CI .19-.1.76, p=.329), while presence of TP53 mutations (SHR 1.78 95% CI .51-6.28, p=.369) and WT mutation (SHR 2.67, 95% CI .93-7.63, p=.068) were associated with worse survival outcomes. Two patients developed complications within 30 days. One patient developed fatigue, nausea and epigastric pain requiring hospital stay (grade 1), and another developed bilateral motor and sensory loss due to spinal infarct (grade 3).

Conclusion

Y90 radioembolization offers a safe and effective treatment option for patients with neuroendocrine liver metastasis. Higher tumor burden and tumor mass portends a poorer prognosis while DAXX mutation was associated with better outcomes following Y90 radioembolization.

Abstract ID 23476

DOI: 10.1530/endoabs.98.C20

C21

Ratio of total uptake volume on DOTATATE vs FDG PET as a predictive marker of treatment efficacy of Lu-177-DOTATATE in metastatic pheochromocytoma

Frank I. Lin[1], Jaydira Del Rivero[1], Jorge Carrasquillo[1], Inna Shamis[1], Joy Zou[1], Baris Turkbey[1], Abhishek Jha[2], Joanna Klubo[3], Steve Adler[1], Esther Mena[1], Liza Lindenberg[1], Clara Chen[4], Peter Herscovitch[4], Corina Millo[4] & Karel Pacak[2]

[1]National Institutes of Health, National Cancer Institute; [2]National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development; [3]National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; [4]National Institutes of Health, Clinical Center

Background

Pheochromocytoma/Paraganglioma (PPGL) are rare neuroendocrine tumors that expresses somatostatin receptors (SSTR) and can be treated with radiolabeled somatostatin analogues such as Lu-177-DOTATATE. Ga-68-DOTATATE PET scans show the distribution and density of SSTR+ tumors, and F-18-FDG PET scans show hypermetabolism in lesions. Total uptake volumes (TUV) for each respective scan can be obtained consistently and semi-automatically using standardized workflow in imaging software such as MIM, and the relative TUV ratio of the DOTATATE vs FDG scans is obtained and analyzed in this study.

Methods

F-18-FDG and Ga-68-DOTATATE PET scans are performed as per the phase 2 clinical trial evaluating the use of Lu-177-DOTATATE in patients with metastatic pheochromocytoma (NCT03206060). Per the study's protocol, FDG (10 mCi) and DOTATATE (6 mCi) PET scans are obtained at baseline. The primary clinical end point is progression free survival (PFS). A workflow was built in MIM Software where lesions are automatically contoured into regions of interest (ROIs) using a SUV threshold (that was arbitrarily determined to screen out most physiologic uptake) of > 5.0 for the FDG and > 23.0 for the DOTATATE PET scans. The resultant ROIs were manually reviewed by a trained Nuclear Medicine physician and adjusted as needed. A ratio of the TUV from the DOTATATE over the FDG PET scans was then calculated and used for this analysis.

Results

Interobserver variability evaluation of three blinded independent Nuclear Medicine physician readers showed the variability in TUV obtained using the semi-automated MIM workflow was less than 10%. On average, the time required to perform a TUV calculation was 3-5 minutes per scan. Thirty-six patients from NCT03206060 are included in this analysis. The ratio of the DOTATATE SUV to FDG SUV ranged from 0.22 (uptake on FDG scan > DOTATATE) to 4911 (uptake on DOTATATE >> FDG scan). The mean PFS is 21.0 and mean OS is 31.0 months for all patients. Using a ratio of 2.0 as a cutoff, patients whose TUV ratio is < 2.0 ($n=13$) have a mean PFS of 17 months and OS of 26 months while those having a ratio of > 2.0 ($n=23$) have a mean PFS of 23.0 and OS of 35 months. The c-index between DOTATATE-FDG TUV ratio and PFS is 0.693 ($P=0.002$), and is 0.674 (p=.045) between TUV and OS.

Conclusion

The TUV ratio of DOTATATE PET over the FDG PET reflects underlying tumor biology and may be used as a predictive marker of treatment efficacy of Lu-177-DOTATATE.

Abstract ID 23658

DOI: 10.1530/endoabs.98.C21

C22

Phase 2 trial of lu-177-DOTATATE in metastatic or inoperable pheochromocytoma/paraganglioma: interim analysis results

Frank I. Lin[1], Jaydira Del Rivero[1], Jorge Carrasquillo[1], Inna Shamis[1], Joy Zou[1], Baris Turkbey[1], Abhishek Jha[2], Joanna Klubo[3], Ya-ting Teng[4], Esther Mena[1], Liza Lindenberg[1], Clara Chen[5], Peter Herscovitch[5], Corina Millo[5] & Karel Pacak[2]

[1]National Institutes of Health, National Cancer Institute; [2]National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development; [3]National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; [4]Uniformed Services University School of Medicine; [5]National Institutes of Health, Clinical Center.

Background

Pheochromocytoma/Paraganglioma (PPGL) are rare neuroendocrine tumors that expresses somatostatin receptors (SSTR) and can be treated with radiolabeled somatostatin analogues such as Lu-177-DOTATATE. This study is the first prospective study to examine the safety and efficacy of Lu-177-DOTATATE in the treatment of metastatic or inoperable PPGL in a phase 2 clinical trial setting, and results from a planned interim analysis are presented.

Methods

This is an open-label, single-arm phase 2 study being conducted at the National Institutes of Health to evaluate the efficacy and safety of Lu-177-DOTATATE in patients with PPGL (NCT03206060). Patients are divided into 2 cohorts (SDHx or apparent sporadic). The primary endpoint is Progression Free Surival (PFS) rate at 6 months after starting treatment. Eligibility includes having SSTR+ tumor, histologically-confirmed diagnosis, and evidence of progression by RECIST 1.1 within 12 months of study enrollment. Anatomic scans as well as both F-18-FDG and Ga-68-DOTATATE PET scans are acquired at baseline, 4 weeks after the second cycle of Lu-177-DOTATATE, 8 weeks after the fourth cycle, and then every 3 months (anatomic scans) to 6 months (PET scans). The study opened for enrollment in August 2017 and is conducted using a Simon two-stage optimal design. An interim analysis is built-in when each of the cohort reaches 18 participants, and the study will continue onto the second stage if 11 or more out of 18 patients meet the primary endpoint. Full accrual for the study will be 90 patients, 45 per cohort.

Results

36 patients (18 per cohort) were evaluated for safety and efficacy. For the sporadic cohort, 16 patients achieved stable disease (SD) while 2 had partial response (PR) by RECIST 1.1 at 6 months. In the SDHx cohort, 10 patients had SD, 3 patients had PR, and 5 patients had progression at 6 months. In conglomerate 31/36 (86%) met the primary study end point, and the median PFS is 21.0 months. Rates of adverse and serious adverse events (SAE) attributable to Lu-177-DOTATATE were similar to those previously reported in other studies such as NETTER-1, with hematologic SAEs being the most common. Catecholamine release syndrome (flushing, hypertension, tachycardia, constipation) is observable starting as early as during Lu-177-DOTATATE infusion and persisting for days to weeks after treatment, with 10% incidence of grade 3+ events. Peak risk appears to be within 24-48 hours of infusion and is likely related to significant surge in serum catecholamine levels (median increase=60%, max increase 10x baseline) in this time frame. In select high risk patients, elective ICU intervention is advisable. Despite the acute increases and associated symptoms, however, catecholamine levels in most patients return to baseline by Day 28.

Conclusion

Interim analysis results demonstrate that Lu-177-DOTATATE has high efficacy and good safety profile when used to treat metastatic PPGL, especially in patients with no associated genetic mutations. While catecholamine crisis related to surging serum catecholamine levels can be observed, levels usually return to near baseline and patients can be safety treated.

Abstract ID 23659

DOI: 10.1530/endoabs.98.C22

C23

Phase 1/2 study of Lu-177-DOTATATE in combination with olaparib in metastatic or inoperable GI neuroendocrine tumors - first results

Frank I. Lin[1], Jaydira Del Rivero[1], Jorge Carrasquillo[1], Inna Shamis[1], Joy Zou[1], Baris Turkbey[1], Joanna Klubo[2], Esther Mena[1], Liza Lindenberg[1], Clara Chen[3], Peter Herscovitch[3], Corina Millo[3] & Karel Pacak[4]

[1]National Institutes of Health, National Cancer Institute; [2]National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; [3]National Institutes of Health, Clinical Center; [4]National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development

Background
GI neuroendocrine tumors express somatostatin (SSTR) receptors, and the radioloabeled SSTR analog Lu-177-DOTATATE is an FDA-approved systemic treatment for those with metastatic disease. Olaparib is a poly (ADP-ribose) polymerase inhibitor (PARPi) which inhibits cells from repairing damaged DNA, especially single-stranded DNA breaks caused by beta particle emissions from the radioactive decay of Lu-177. We report the first results of a phase 1/2 study evaluating the safety and efficacy of Lu-177-DOTATATE in combination with olaparib.
Methods
This is an open-label, single-arm, single-center phase 1/2 study being conducted at the National Institutes of Health (NCT04086485). Phase 1 is a standard 3 + 3 design where Lu-177-DOTATATE is being given at the FDA-approved fixed dose of 200 mCi x 4 cycles 8 weeks apart and the olaparib undergoes escalation at the 50mg bid, 100mg bid, 200mg bid, and 300mg bid levels. Olaparib is given daily starting 2 days prior to the administration of each Lu-177-DOTATATE until 28 days post, for a total of 30 days for each Lu-177-DOTATATE administration. Eligibility criteria includes SSTR + tumors, histologically confirmed diagnosis, and progressive disease by RECIST 1.1 within 36 prior to enrollment. As part of the study, both FDG and DOTATATE PETs are acquired at baseline and at the completion of treatment. The study opened for enrollment in September 2022 and will require 33 patients for full accrual.
Results
One patient with metastatic neuroendocrine tumor of the pancreas has been enrolled and completed treatment on study, at the 50mg bid olaparib dose level. First set of restaging scans at 4 weeks after the second cycle of Lu-177-DOTATATE shows decrease in some tumors up to 17% but overall stable disease by RECIST 1.1, while restaging at end of 4 cycles showed continued decrease in tumor size but still RECIST SD. The combination was well-tolerated with AE profile similar to previous reported. Only grade 1 hematotoxcity was seen. Transient grade 3 hyperglycemia was noted but likely due to dietary non-compliance over the holidays, although causal relationship to treatment cannot be completed ruled out. Baseline WBC, Hgb, and platelets were 6.77k, 15.7, and 608k, respectively, and were 5.99k, 14.7, and 459k, respectively (all values within normal range) at 4 weeks after the second cycle of Lu-177-DOTATATE, and 3.77k, 13.8, and 401k by end of therapy.
Conclusion
The combination of Lu-177-DOTATATE and olaparib shows early evidence of efficacy and is well-tolerated in this limited data set. More data is needed to confirm and refine these findings.
Abstract ID 23664

DOI: 10.1530/endoabs.98.C23

C24

68Ga-DOTATATE/18F-FDG dual PET: Utility of the NETPET score in management of G2-3 WD NENs

Jose E. Nunez[1], David L. Chan[2], Roshini Kulanthaivelu[3], Vanessa Murad[3], Simron Singh[1] & Ur Metser[3]
[1]Sunnybrook Health Sciences Centre, [2]University of Sydney, [3]University Health Network

Background
The clinical heterogeneity of G2 and G3 well-differentiated GEP-NENs make it difficult to choose an effective treatment plan, highlighting the need of molecular imaging in the treatment of NETs patients. It has been suggested that a dual-tracer 68Ga-DOTATATE/18F-FDG grading scoring system could be a useful imaging biomarker. This pilot study aims to validate the prior observation from Chan et al. (BJC 2022) of variability in NETPET scores in G2-G3 WD GEP NENs and assess the impact of dual tracer PET on management.
Methods
Patients with G2-G3 WD GEPNENs referred for 68Ga-DOTATATE PET at the University Health Network were enrolled to this prospective, single-arm study for performance of 18F-FDG PET. 40 patients were planned to receive 18F-FDG PET with a pre-FDG and post-FDG management plan. Primary outcome was to describe the percentage of patients in whom management was changed as a result of the FDG PET. Clinical follow-up followed the routine clinical schedule determined by the treating physician. Specific changes in management (e.g. SSA to chemotherapy or vice versa) and change in treatment modality (e.g. systemic to PRRT or vice versa) were reported.
Results
Forty patients were enrolled (9 small bowel, 17 pancreas, 11 other GI primaries and 3 unknown). The median age was 62 (23-88). 40% of patients had Grade 3 WD NEN. The median Ki-67 index was 12%. Patients with NETPET scores P0, P1, P2, P3, P4 and P5 represented 5%, 12.5%, 62.5%, 5%, 10% and 5% of the overall population respectively. Specific changes in management represented 60% of cases. Change in treatment modality represented 47.5% of cases. The change of treatment modality within P0, P1, P2, P3, P4 and P5 groups was 50%, 80%, 40%, 50%, 50% and 50% respectively.
Conclusion
The addition of FDG PET to DOTATATE PET resulted in treatment modality change in 47.5% of patients. These descriptive findings are hypothesis generating and will help inform design of a future prospective trial to assess the impact of dual tracer PET directed management on patient outcomes.
Abstract ID 23666

DOI: 10.1530/endoabs.98.C24

C25

A pilot study of pembrolizumab and peptide receptor radionuclide therapy for patients with metastatic well-differentiated neuroendocrine tumors

Nicholas Fidelman MD, Bridget P. Keenan MD, PhD, David Y. Oh MD, Lawrence Fong MD, Kira Chan BS, Li Zhang PhD, Emily K. Bergsland MD & Thomas A. Hope MD
University of California San Francisco

Background
Expected progression free survival (PFS) for patients with grade 3 well-differentiated neuroendocrine tumors (WD NET) treated with peptide receptor radionuclide therapy (PRRT) is approximately 9 months, and objective response rate (ORR) is 35%. Response rate to single agent immune checkpoint inhibitors (ICI) for patients with G1-3 NET is $<15\%$. Delivery of targeted radiation using PRRT may potentiate the anti-tumor immune response. The purpose of this study is to evaluate safety and efficacy of the combination of PRRT and PDL-1 inhibitor pembrolizumab in high risk NET.
Methods
In a single arm prospective pilot study, adult patients with WHO grade 2 or 3 (Ki-67 index $>$ 10%) metastatic NET of any primary site received concurrent pembrolizumab 200mg every 3 weeks up to 35 doses and up to 4 doses of ^{177}Lu-DOTATATE PRRT (200mCi) at 8 week intervals. Treatment was terminated in the event of disease progression, performance status deterioration, and/or intolerable toxicity. Primary endpoint was best observed objective response rate (ORR) by RECIST v.1.1. Secondary endpoints were PFS and safety.
Results
A total of 26 patients (15 men, median age 60 years) with grade 2 (Ki-67 index 10-20%, 6 patients) or grade 3 (Ki-67 index 21-70%, 20 patients) WD NET (15 pancreas, 6 small bowel, 3 lung, 2 other primary sites) were included. As of June 25, 2023, 13 patients have been on study for more than 24 weeks, of whom four have demonstrated PR, with all patients having shrinkage of their disease (mean 27% decrease in RECIST measurable lesions). Of the 13 patients who have been on study less than 24 weeks, three have discontinued due to progression, and 10 patients remain on trial. Grade 3 adverse events included cytopenias related to PRRT in four patients and diabetes mellitus attributable to pembrolizumab in one patient. Updated safety, PFS, and ORR analyses will be reported.
Conclusion
Preliminary results indicate that combination treatment with ^{177}Lu-DOTATATE PRRT and pembrolizumab is well tolerated and leads to durable disease control in a subset of patients.
Abstract ID 23671

DOI: 10.1530/endoabs.98.C25

C26

A pilot study of pembrolizumab and embolization or 90Y radio-embolization for patients with metastatic well-differentiated neuro-endocrine tumors

Nicholas Fidelman MD, Lawrence Fong MD, Li Zhang PhD & Emily K. Bergsland MD
University of California San Francisco

Background
Well-differentiated neuroendocrine tumors (WD-NET) have a relatively low tumor mutation burden and do not commonly express the programmed death ligand 1 (PD-L1), characteristics which may limit the anti-tumor activity of PD-L1 inhibitors in this disease. Response rate to single agent immune checkpoint inhibitors (ICI) for patients with G1-3 NET is $<15\%$. The intensity of anti-tumor immune response may be enhanced by addition of liver-directed therapy (LDT), such as embolization or ^{90}Y radioembolization targeting one or several liver

lesions. This pilot study aimed to evaluate whether combining pembrolizumab with LDT results in abscopal effects for patients with WD-NET.
Methods
In a prospective pilot study, adult patients with WHO grade 1-3 (Ki-67 index <30%) metastatic NET of any primary site received concurrent pembrolizumab 200mg every 3 weeks up to 35 doses and a single session of either liver transarterial embolization (TAE) with spherical polyvinyl alcohol particles (PVA) or transarterial radioembolization (TARE) with Yttrium-90 glass microspheres. Embolotherapy was performed for the purpose of tumor antigen exposure to the immune system and targeted no more than one liver segment. Patients with liver lesions <5cm were treated with TAE, while patients with lesions >5cm were treated with TARE. Treatment was terminated in the event of disease progression, performance status deterioration, and/or intolerable toxicity. Primary endpoint was overall response rate (ORR) at disease site(s) not targeted by embolotherapy (abscopal response). Secondary endpoints were PFS and safety.
Results
A total of six patients (4 women, median age 59 years) with grade 2 (Ki-67 index 5-17%, 5 patients) or grade 3 (Ki-67 index 23%, 1 patient) WD-NET from ovary, small bowel, thymus, rectum, lung, and pancreas primary sites were included. Enrollment to TAE and TARE groups was halted after 3 out of 8 planned patients were recruited into each group due to slow accrual. No abscopal responses were observed. PFS was 6 and 10 months for patients in TAE group, and 1, 2, and 5 months in TARE group. Grade 3 pneumonitis occurred in one patient 17 days following TAE and required hospital admission and corticosteroids. Another patient was admitted to the hospital for grade 3 nausea, vomiting, and fatigue five days following TARE.
Conclusion
Combination therapy with pembrolizumab and TAE or TARE did not lead to abscopal responses in a small group of patients with metastatic WD-NET.
Abstract ID 23674

DOI: 10.1530/endoabs.98.C26

C27

ETCTN 10388: A first in human Phase I Trial of Triapine and Lutetium Lu 177 DOTATATE in Well-Differentiated Somatostatin Receptor-Positive Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

Aman Chauhan[1], Susanne Arnold[2], Jill Kolesar[2], William Carson[3], Heidi Weiss[2], Donglin Yan[2], Riham El Khouli[2], Aman Khurana[2], Jan Beumer[4], Heloisa Soares[5], Mary Mulcahy[6], Thorvardur Halfdanarson[7], Daneng Li[8], Heather Jacene[9], Percy Ivy[10], Elise Kohn[10], John Wright[10], Larry Rubinstein[10], Charles Kunos[2], Lowell Anthony[2] & Bhavana Konda[3]
[1]Sylvester Comprehensive Cancer Center, University of Miami; [2]Markey Cancer Center, University of Kentucky, Lexington, KY; [3]Ohio State University, Columbus, OH; [4]University of Pittsburgh, Pittsburgh, PA; [5]Huntsman Cancer Center, Salt Lake City, UT; [6]Northwestern, Chicago, IL; [7]Mayo Clinic, Rochester, MN; [8]City of Hope, Duarte, CA; [9]Dana Farber, Boston, MA; [10]NCI CTEP, Bethesda, MD

Background
Radiation is a potent inducer of DNA double-strand breaks, and ribonucleotide reductase (RNR) is the rate-limiting enzyme in the synthesis and repair of DNA, making RNR-targeted therapy a rationale therapeutic strategy for radiosensitization. ETCTN 10388 (NCT04234568) evaluated safety and efficacy of the combination of lutetium 177 DOTATATE, a beta-emitting radionuclide in combination with triapine, a ribonucleotide reductase (RNR) inhibitor.
Methods
This study was a multicenter phase 1 dose escalation trial [using the Bayesian optimal interval design (BOIN)] of triapine in combination with fixed dose lutetium Lu 177 DOTATATE for well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumor (GEP-NETs) after the failure of at least one line of prior systemic cancer treatment with an expansion cohort at the recommended phase 2 dose (RP2D). Oral triapine (100mg, 150mg, 200mg) was administered once daily on days 1-14 and Lu-177 DOTATATE [200 mCi] intravenously on day 1 of every 56-day cycle. A total of 4 cycles were administered. Response and adverse effects were assessed per RECIST and CTCAE 5.0, respectively. Exploratory correlative studies included tumor somatic and germline mutation testing, RNA sequencing, pharmacokinetics, deoxynucleosides and circulating cell free DNA analysis. Primary endpoints were safety and RP2D.
Results
Overall, 31 patients were enrolled between 6 sites, 15 in the dose escalation phase and 16 in the dose expansion phase. Adverse events (AE) were assessed in all 31 patients per CTCAE 5.0. One DLT in dose level 1, seven DLTs in dose level 2, and one grade 5 DLT in dose level 3 were observed. The RP2D of the combination is triapine 150 mg QD (dose level 2) on days 1-14 in combination with Lu-177 DOTATATE on day 1 of every 56-day cycle. Detailed safety and adverse event data will be presented at the meeting. There were 28 patients evaluable for efficacy, of which 6 (21%) achieved a partial response. At 12 months, 6 patients had progressed, while 22 (86%) remained progression free. Median PFS has not been reached. PK data were available for 12 patients enrolled in the dose escalation cohort. The geometric mean (SD) $AUC_{0\text{-}inf}$was 1159 (1.22) μg/L•h for the 100mg dose level and 1862 (1.76) μg/L•h for the 150 mg dose level, suggesting that exposure increased with dose, and inter-patient variability was as expected for an oral agent.
Conclusion
The combination of triapine and Lu-177 DOTATATE was safe with preliminary efficacy signals, which will be further evaluated in ETCTN 10558, a randomized phase 2 study that is comparing the effectiveness of triapine and Lu-177 DOTATATE to Lu-177 DOTATATE alone.
Abstract ID 23693

DOI: 10.1530/endoabs.98.C27

C28

ETCTN 10450: A phase I trial of peposertib and lutetium 177 DOTATATE in well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Aman Chauhan[1], Jill Kolesar[2], Donglin Yan[2], Daneng Li[3], Aman Khurana[2], William Edgar Carson[4], Susanne M. Arnold[2], Steven Gore[5], Larry Rubinstein[5], Elise C. Kohn[5], S. Percy Ivy[5], Ying Xiao[6], Yuni Dewaraja[7], Heloisa P. Soares[8], Jan Hendrik Beumer[9], Bhavana Konda[4], Vineeth Sukrithan[4] & Lowell Brian Anthony[2]
[1]Sylvester Comprehensive Cancer Center, University of Miami; [2]Markey Cancer Center, University of Kentucky; [3]City of Hope National Comprehensive Cancer Center, Duarte, CA; [4]The Ohio State University, Columbus, OH; [5]National Cancer Institute Division of Cancer Treatment and Diagnosis, Rockville, MD; Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD; [6]University of Pennsylvania, Department of Radiation Oncology, Philadelphia, PA; [7]University of Michigan, Ann Arbor, MI; [8]Hunstman Cancer Hospital, University of Utah, Salt Lake City, UT; [9]University of Pittsburgh, Pittsburgh, PA

Background
Radiolabeled somatostatin analogs provide a means of delivering targeted radiation with a high therapeutic index to NETs that express somatostatin receptors (SSTRs). We hypothesize that the addition of an effective radiation sensitizer could help improve the antitumor activity of Lutathera. Radiation is a potent inducer of DNA damage. The primary repair mechanism of radiation-induced double-stranded breaks (DSBs) is the nonhomologous end-joining (NHEJ) pathway, in which the DNA-PK (Deoxyribonucleic acid protein kinase) complex plays a pivotal role. Upregulation of DNA-PK promotes the repair of DSBs leading to tumor radio-resistance preclinically and clinically. Thus, DNA-PK is an important molecular target for inhibiting DSB repair and enhancing the cytotoxicity of radiation. Peposertib is a selective inhibitor of DNA-PK that targets tumor cell DNA damage repair and survival by blocking NHEJ.
Methods
This is an investigator-initiated, NCI-sponsored, multicenter phase 1 trial of peposertib and Lutetium 177 DOTATATE in well-differentiated somatostatin receptor-positive GEP-NETs after the failure of at least one line of prior systemic treatment. Peposertib was administered orally from D1-21 with each dose of PRRT. The primary endpoint is to evaluate recommended phase II dose (RP2D) with the help of BOIN design. Secondary endpoints are to evaluate the safety, pharmacokinetics, and clinical activity (ORR and PFS). We are also evaluating Lu-177 DOTATATE dosimetry in collaboration with NIH IROC.
Results
13 patients were treated in the dose escalation phase. A total of three dose-limiting toxicities were noted. One patient had transient grade 3 elevation of ALT on dose level 2, and two patients developed anaphylactic reactions on dose level 3. These patients came off Peposertib per protocol but continued Lutathera (PRRT). Peposertib PK parameter values observed in this trial were comparable to previous reports. The peposertib exposure in our four patients dosed at 150 mg BID was C_{max} 572 (1.92) μg/L, and AUC 2744 (2.01) μg/L□h, while previously reported values are 610 μg/L, and 2960 μg/L□h, respectively. Similarly, dose-normalized C_{max}, T_{max}, and apparent clearance (38-55 L/h vs 30-60 L/h) were comparable. In PBMC's, the IC_{50} for DNA-PK was reported to be around 200 ng/mL, a value exceeding in all patients at 100 mg (the MTD) and 150 mg BID, though the plasma C_{min} fell below this IC_{50} in most patients. The limited dose range evaluated in our trial, combined with the high between-patient variability

precluded a definitive assessment of dose linearity by either absolute exposure or metabolic ratio.
Conclusion
Based on DLT data, PK data, and concern for anaphylaxis with dose level 3, dose level 2 (100 mg PO BID, Days 1-21)was assigned as RP2D. The expansion cohort for additional safety analysis and dosimetry sub-study is now open for enrollment at 6 sites within the US.
Abstract ID 23695

DOI: 10.1530/endoabs.98.C28

C29

Small bowel ischemia in patients with midgut neuroendocrine tumors after treatment with 177Lutetium-Dotatate

Eleonora Pelle, MD[1], Taymeyah Al-Toubah, MPH[1], Ghassan El-Haddad, MD[2] & Jonathan Strosberg, MD[1]
[1]Department of Gastrointestinal Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL; [2]Diagnostic Imaging and Interventional Radiology, Moffitt Cancer Center and Research Institute, Tampa, FL

Background
^{177}Lutetium (Lu)-Dotatate is a safe and well tolerated treatment for metastatic gastroenteropancreatic (GEP) NETs. However, radiation can cause transient inflammation/swelling of tumors which can result in toxicity. Treatment-related small bowel obstruction associated with mesenteric or peritoneal disease has been described. We investigated the potential for intestinal ischemia in ^{177}Lu-Dotatate treated patients.
Methods
Clinical records of patients with midgut NETs treated with ^{177}Lu-Dotatate at our institution between April 2018 and December 2022 were reviewed.
Results
Among the cases reviewed, we identified 2 patients who developed bowel ischemia/perforation shortly after their initial treatment with ^{177}Lu-Dotatate. Both patients had metastatic small bowel NET with prominent mesenteric mass encasing/obstructing the mesenteric vessels and preexisting symptoms of post-prandial abdominal pain.
Conclusion
Acute bowel ischemia may be a rare complication of PRRT in patients with mesenteric arterial or venous obstruction from mesenteric metastasis.
Abstract ID 23700

DOI: 10.1530/endoabs.98.C29

C30

Novel alternate (Alt) response criteria for early outcome prediction in pancreatic (P) neuroendocrine tumors (NETs): utilizing banked imaging and radiomics

Ishara Lareef[1], Namrata Vijayvergia[1], Elizabeth Handorf[1], Pamela L. Kunz[2], Emil Alkim[3], Lauren M. Burke[4], Paul Catalano[5], Noah Graham[5], Laura Levin[1], Weier Li[1], Caitlin Meeker[1], Daniel Rubin[3], Anush Sridharan[1], Peter J. O'Dwyer[6], Terence Z. Wong[7] & Jordan Anaokar[1]
[1]Fox Chase Cancer Center, Philadelphia, PA; [2]Yale, School of Medicine, New Haven, CT; [3]Stanford University, Stanford, CA; [4]UNC Chapel Hill, Chapel Hill, NC; [5]Dana-Farber Cancer Institute, Boston, MA; [6]University of Pennsylvania, Philadelphia, PA; [7]Duke Cancer Center, Durham, NC

Background
Evaluating treatment (Tx) Response in NETs using CT/MRI scans can be difficult. Previous studies, including the E2211, have shown improved progression-free survival (PFS) but no significant difference in Rp as measured by RECIST 1.1 (R1.1) criteria. Therefore, it is difficult to determine Tx effectiveness with short-term imaging, further complicated by differences in imaging protocols and inter-reader variability. Incorporating tumor density, using smaller threshold changes in tumor size, and novel quantitative features may be more sensitive and precise than R1.1 (e.g. CHOI in GIST) but have not been studied for NETs.
Methods
Banked CT images from the E2211 trial were repurposed to study novel criteria. Three radiologists provided a R1.1 assessment. Density and radiomic features were calculated from a 2D region of interest in the portal venous phase (as per CHOI Criteria Patients were classified as responders (PR), stable disease (SD), or progressive disease (PD) based on R1.1 and CHOI and compared with PFS to determine the best predictor. Radiomic features were analyzed using pyradiomics. Wilcoxon tests were used to compare scan quality by center type, agreement was measured using Cohen's Kappa, and predictive value was quantified using the c-statistic and AUC for time-varying outcomes.
Results
67 patients had their scans repurposed for the study. Inter-reader agreement for overall imaging studies was fair, with only 5 of 9 PD cases noted by reviewer 1 being agreed upon by reviewer 2 (proportional agreement for PD = 0.56) and a Kappa of 0.6 (95% CI 0.41 – 0.79). The CHOI Criteria showed improved prediction of PFS compared to R1.1 (12-month AUC 0.75 for CHOI vs 0.69 for R1.1, c-statistic 0.66 vs 0.64, $P = 0.22$), and was able to predict improved PFS for PR vs SD at the first interval scan. This was not seen with R1.1 (table). Radiomics and texture analysis found that adding the radiomic feature of Zone Entropy improved predictive ability of CHOI criteria for PNET disease evaluation.
Conclusion
This study using repurposed banked imaging from an NCTN trial found that there was significant variability in image interpretation, and that the R1.1 Criteria was poorly correlated with Rp in PNETs. The CHOI Criteria emerged as a better alternative as it may have a better correlation with PFS and ability to predict outcomes at the point of first disease assessment. Importantly, CHOI Criteria can be easily applied in clinical practice to inform treatment decisions. Further research is needed to confirm these findings and define its therapeutic importance.
Abstract ID 23705

DOI: 10.1530/endoabs.98.C30

C31

High-specific-activity iodine-131-meta-iodo-benzylguanidine for the treatment of advanced pheochromocytoma and paraganglioma: a real-world study

Ruaa Al-Ward[1,2,3], Vania Balderrama Brondan[1], Sahar Sawani[1,2], Roland Bassett[4], Guofan Xu[5], Steven G. Waguespack[1], Jeena Varghese[1], Mouhammed Amir Habra[1], Yang Lu[5] & Camilo Jimenez[1]
[1]Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas, MD Anderson Cancer Center, Houston, TX; [2]Section of Endocrinology, Diabetes and Metabolism, Baylor College of Medicine, Houston, TX; [3]Department of Neuroendocrinology, Diabetes and Metabolism, Methodist Hospital, Houston, TX; [4]Department of Biostatistics, The University of Texas, MD Anderson Cancer Center; [5]Department of Nuclear Medicine, The University of Texas, MD Anderson Cancer Center

Background
Metastatic pheochromocytomas and paragangliomas are rare neuroendocrine tumors with limited treatment options. We studied the efficacy and safety of off-label High-Specific-Activity I-131-meta-iodobenzylguanidine (HSA-I-131-MIBG) in routine clinical practice.
Methods
This is a retrospective cohort study. The primary endpoint is objective response rate (ORR) as per RECIST v1.1. Secondary endpoints are blood pressure control, safety, overall and progression free survival rates, duration of response, and correlations with genetic background.
Results
25 patients were studied. 62% were men. Median age at the time of treatment was 43 years (range 18-82). 68% had hormonally active tumors.52% previously received antineoplastic treatment. 60% received two doses of HSA-I-131-MIBG. Median duration of follow up was 19 months (2-61). 24 patients were evaluable for radiographic response. The ORR was 33%, including two patients with complete response (CR). The disease control rate (DCR) was 83%. Median time to response was 12.5 months (95% CI, 4.6 to 25.1). Twelve patients had sporadic disease; ORR was 25% and DCR was 92%. Twelve patients had hereditary disease (SDHB, VHL, RET); ORR was 42%, DCR was 75%. Two SDHB carriers achieved CR. Plasma metanephrines normalized in 27%, improved by at least 50% in 45%. 16 patients had hypertension; blood pressure normalized leading to discontinuation of antihypertensive therapy in 56% of patients with hormonally active tumors and hypertension. The most common adverse events were grade I/II nausea/vomiting and transient bone marrow suppression. One patient developed premature ovarian failure. Grade III/IV myelosuppression was seen in 28% of patients. One patient had a fatal pneumonitis (probably related) and 1 patient had grade 5 gastrointestinal bleeding (not related).
Conclusion
HSA 131-I-MIBG is associated with a high DCR regardless of underlying genetic mutation. Severe adverse events are mainly transient and correctable bone marrow insufficiencies.
Abstract ID 23706

DOI: 10.1530/endoabs.98.C31

C32

Myelodysplasia and leukemia instances after PRRT: Experience from a tertiary institution

Nikolaos Trikalinos, MD[1,2], Michael De La Iglesia, MD[1,2], Vikas Prasad MD, PhD[3], Manik Amin, MD[4], Kyle Winter, BSN, RN[1,2], Justin Schutte MSN, FNP-C, AOCNP[1,2] & Hyun Kim, MD[1]
[1]Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO; [2]Siteman Cancer Center, St Louis MO; [3]Mallinckrodt Institute of Radiology, Washington University in St Louis, St Louis, MO; [4]Department of Medical Oncology, Dartmouth-Hitchcock Medical Center, Lebanon, NH

Background
Peptide receptor radionuclide therapy (PRRT) was introduced in 2018 as one of the major advances in treatment of patients with neuroendocrine neoplasms (NENs). Initial results from the NETTER-1 trial suggested a very low percentage of secondary hematological malignancies, including myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). We sought to confirm that data in a large institutional database.
Methods
Under an institutional IRB we perused the data from every patient who underwent PRRT at Washington University in St Louis. We identified patients with a subsequent diagnosis of MDS or AML. We extracted data on basic demographics, treatment details and lag time from PRRT end to hematological malignancy diagnosis.
Results
A total of 176 patients were treated between 2017 and 2021. Eight patients (4 male, 4 female) or 4.5% were diagnosed with MDS/AML by hematopathology while another one had a strong suspicion of MDS. All but one patient had received 4 fractions of PRRT. MDS was the most common diagnosis (5/8) followed by AML (2/8) and one patient with aplastic anemia. Cases appeared at a rate of 1-2 per year. Latency periods ranged from 5 months to 5 years and 3 months, with AML cases diagnosed at 2 years and 3 months and 4 years and 10 months post end of PRRT. Three patients are alive while 5/8 have expired. Cytogenetic analyses are underway.
Conclusion
In a real-life setting we have identified a rate of 4.5% MDS/AML post PRRT, with leukemia cases appearing more than 2 years post end of treatment so far. The latency to hematological malignancy diagnosis can reach more than 4 to 5 years post end of PRRT and thus cannot entirely be attributed to radionuclide treatment. An updated analysis with cytogenetic panels and consideration of prior and follow-up treatments is underway.
Abstract ID 23721

DOI: 10.1530/endoabs.98.C32

C33

DOTATATE PET/CT imaging in prostate cancer: incidental observations and potential future implications

Ahmed E Salem MD, PhD, Heloisa P. Soares MD, Gabriel C Fine MD & Kathryn A Morton MD.
Hunstman Cancer Hospital, University of Utah, Salt Lake City, UT

Background
Hormonally-refractory, lethal forms of PCa may express neuroendocrine features, including PCa with neuroendocrine differentiation (NEDPCa) and treatment emergent small cell neuroendocrine PCa (tSCNC). We hypothesize that some lethal metastatic PCa may show higher expression of SSTR than of PSMA and that a dual imaging approach with PET radiopharmaceuticals targeting these moieties will enable informed selection of patients for the future corresponding therapeutic radiopharmaceutical construct.
Methods
Our center has performed hundreds of DOTATATE (68Ga or 64Cu) PET-CT scans for NETs. We have noted a wide variety of patterns of uptake in the prostate.
Results
The data was mined from a deidentified file and is IRB exempt. Various patterns of prostate uptake have emerged as men age. These include increased uptake in the transitional zone indicative of benign prostatic hyperplasia (BPH), and uptake confined to the peripheral zone (which accounts for 70-75% of PCa's) In one patient, a new diagnosis of widespread metastatic prostate adenocarcinoma with bone metastases was identified by DOTATATE PET. The maximum SUV of the bone lesions was 17.2 and 10 in the prostate. In a review of 20 GEP NET patients with 68Ga DOTATATE scans, normal average values for SUVmax (+/- SD) were 6.9 (+/- 1.8) for liver, 22.1 (+/-10.7) for adrenal, 24.2 (+/- 7.9) for spleen, 21.9 (+/- 8.5) for kidney, 1.3 (+/- 0.8) for skeletal muscle, and 2.0 (+/- 0.4) for blood pool. There is a wide range of SUVmax for moderately and well-differentiated GEP NETs, averaging 37.7 (+/- 20.6). Uptake by the bone metastases was within 1 SD of the mean for moderately/well-differentiated GEP NETs, and within the mid-range of reports of SUVmax in primary and metastatic lesions with 68Ga PMSA-11. It was also within the range of tumor:liver ratios selected for the Netter-1 trial of 177Lu DOTATATE for treatment of GEP NET, which constituted the basis for FDA approval. In NED PCa, we hypothesize that uptake may be even higher, supporting the potential for efficacy of 177Lu DOTATATE treatment of mCRPC in select patients.
Conclusion
PCa as well as BPH demonstrate uptake of DOTATATE. Dual tracer PET imaging with SSTR and PSMA targeting agents may therefore inform which target would be better expressed and provide an ideal personalized medicine approach both in characterizing the phenotype of mCRPC, as well as in directing therapy, potentially toward 177Lu PSMA or 177Lu DOTATATE.
Abstract ID 23743

DOI: 10.1530/endoabs.98.C33

C34

Comparative assessment of 111in-octreotide scintigraphy, 68GA-DOTATOC PET/CT and 18F-FDG PET/CT in the staging and management of neuroendocrine tumors (NETs)

Ali Zaidi, Brendan Chia, Marilyn Zhou, Gale Ladua, Pavithraa Ravi, Ingrid Bloise, Sara Harsini, Don Wilson, Francois Benard, Patrick Martineau & Jonathan M Loree
BC Cancer Agency, Vancouver, BC, Canada

Background
Accurate imaging is essential for NETs. 111In-octreotide scintigraphy, 68Ga-DOTATOC PET/CT and 18F-FDG PET/CT are the most commonly used modalities. This study compared the three modalities to ascertain the added value of newer functional imaging approaches.
Methods
A retrospective review was performed on patients who underwent 68Ga-DOTATOC PET/CT and 18F-FDG PET/CT between 07/2018 and 03/2023 as part of a clinical trial at BC Cancer. Patients with 111In-octreotide scintigraphy within one-year prior to their DOTATOC and FDG scans were included if all three scans included the number of detected lesions. Descriptive statistics were used to evaluate the three modalities.
Results
Of the 102 patients identified, 45.1% were female and median age at diagnosis was 61 years (IQR 51-69). The most common primary sites were small intestine (44.1%), pancreas (17.6%), unknown (12.7%), lung and stomach (both 9.8%). Median time between octreotide and DOTATOC scans was 120 days (IQR 66-203) and 4 days (1-11) between DOTATOC and FDG scans. DOTATOC had the highest positive scan rate of 73.5% (75/102, 95% CI [63.9, 81.8]) and a mean number of detected lesions of 5.75 ($p < 0.001$) compared to octreotide (53/102, 52.0%, 95% CI [41.8, 62.0]) with a mean of 1.98 lesions and FDG (34/102, 33.3%, 95% CI [24.3, 43.4]) with a mean of 2.00 lesions. The most common imaging profiles were Octreotide+DOTATOC+FDG- (28/102, 27.5%), Octreotide-DOTATOC-FDG- (20/102, 19.6%), Octreotide+DOTATOC+FDG+ (19/102, 18.6%) and Octreotide-DOTATOC+FDG- (16/102, 15.7%). Among patients with an initial negative octreotide scan ($n=49$), 59.2% (29/49) showed positive findings on one or both of DOTATOC or FDG (16/49, 32.7% DOTATOC only; 1/49, 2.0% FDG only; 12/49, 24.5% both), with a median DOTATOC Krenning score of 3 (range 1-4). In patients with either a positive octreotide or DOTATOC scan ($n=81$), lesion count concordance was observed in 13.6% (11/81), with DOTATOC exhibiting a higher lesion count in 87.1% (61/70) of the discordant scans. Among patients with at least one positive scan ($n=\82$), only 6.1% (5/82) had a higher lesion count on FDG. In patients metastatic at baseline ($n=65$), DOTATOC and FDG were able to detect liver and bone lesions not observed on octreotide in an additional 17 (13/17, 76.5% DOTATOC only; 2/17, 11.8% FDG only; 2 both) and 9 (7/9, 77.8% DOTATOC only; 2/9, 22.2% both) patients, respectively.
Conclusion
These findings highlight the potential benefit of incorporating 68Ga-DOTATOC PET/CT with/without 18F-FDG PET/CT for improved detection of NETs compared to 111In-octreotide scintigraphy.
Abstract ID 23755

DOI: 10.1530/endoabs.98.C34

C35

Institutional retrospective review of peptide receptor radionuclide therapy use in metastatic paragangliomas and pheochromocytomas

Yee Lan Wong PA-C, & James Thomas MD, PhD.
Medical College of Wisconsin

Background
Metastatic paragangliomas (PGL) and pheochromocytomas (PCC) are rare neuroendocrine diseases with an incidence of 2 to 8 people per million, a prevalence between 1:2500 and 1:6500 and a strong hereditary disposition. However, due to the rarity of the disease, there is relatively limited data on treatment options, including radionuclide therapy using radioisotope analogs of MIBG and dotatate. There are a few published small series on clinical benefits of treating PGL and PCC with peptide receptor radionuclide therapy (PRRT).
Methods
In this retrospective review of our PRRT patients, treated between May 2018 to March 2023, we have identified a total of 9 patients with histologically confirmed biopsies of either PGL or PCC. We evaluated the 9 patients in terms of number of PRRT cycles completed, time to progression and overall survival.
Results
A total of 9 patients were reviewed. Majority of the patients (6 out of 9) had completed all 4 cycles of PRRT, while 2 of the 9 patients had progressed after 2 cycles of PRRT and 1 of the 9 patients did not complete cycle #4 due to severe anemia. Of the 6 patients that had completed all 4 cycles of PRRT, 1 had progressed within a year of completion of PRRT, 1 was lost in follow-up, 2 had progressed by 26 months and 2 still with durable response. Interestingly, 1 of the 6 patients who had completed all 4 cycles of PRRT and with durable response had ^{131}I-MIGB 4 years prior to PRRT. Of the 6 patients who had completed all 4 cycles of PRRT, 4 patients are alive, 1 lost in follow-up and 1 decreased (more than 36 months after completing PRRT).
Conclusion
With limited data on the use of PRRT in PGL and PCC, we examined our treated PRRT patients from May 2018 to March 2023 and had identified 9 PGL and PCC patients. Although our sample size is small, we conclude that this therapy appears safe and may be beneficial as a treatment option for metastatic PGL and PCC.
Abstract ID 23756

DOI: 10.1530/endoabs.98.C35

C36

Utility of 68Ga-DOTATATE for Grade 3, Poorly Differentiated Gastroenteropancreatic Neuroendocrine Carcinoma

Eric Pletcher MD, Ashley Russo MD, Teodora Dumitra MD, Louise Thomson MD, Andrew Hendifar MD, Jun Gong MD & Alexandra Gangi MD
Cedars-Sinai Medical Center

Background
68Ga-DOTATATE is the preferred imaging modality for evaluating neuroendocrine tumor (NET) receptor status and metastatic disease. Poorly differentiated NETs, now referred to as neuroendocrine carcinoma (NEC), less frequently express SSTR, and typically have greater avidity on 18F-FDG-PET given the lack of SSTR. In this retrospective study, we examine the utility of 68Ga-DOTATATE for Grade 3, NEC.
Methods
Thirty-four patients were diagnosed with Gastroenteropancreatic (GEP) NEC from 2012-2022. Radiographic imaging was ordered at the discretion of the treating physician. Patients with well-differentiated NETs were excluded. The imaging modalities used at the time of diagnosis and during surveillance were noted. When possible, the imaging findings on 68Ga-DOTATATE and 18F-FDG-PET were compared.
Results
25 of the 34 primary tumors were pancreatic (73.5%), 5 were small bowel (14.7%), 2 were rectal (5.9%) and 2 were gastric (5.9%). Twenty patients (58.8%) had 18F-FDG-PET as their initial staging functional imagining modality while 7 patients (20.6%) had a 68Ga-DOTATATE. Six patients had both 68Ga-DOTATATE and 18-FDG-PET either at the time of diagnosis or during surveillance. Of these 6 patients, 2 had newly identified bony metastasis and one had additional liver metastasis not seen on the 18F-FDG-PET. One of the two patients with bony metastasis had a Ki67 proliferation index $< 3\%$ with a mixed acinar carcinoma and one patient had small-cell type NEC with a Ki-67 proliferation index not reported. Nine of 20 patients (45%) had their imaging modality changed from 18F-FDG-PET to 68Ga-DOTATATE during the surveillance period. Of these nine patients, 68Ga-DOTATATE was ordered for three patients for localization of an unknown primary, three patients for preparation of octreotide or liver-directed therapy, and three patients for evaluation of disease progression and treatment response.
Conclusion
68Ga-DOTATATE PET may have superior sensitivity in detecting bony metastatic disease secondary to Gastroenteropancreatic NEC and can be used in combination with 18F-FDG-PET to further characterize suspicious lesions.
Abstract ID 23757

DOI: 10.1530/endoabs.98.C36

C37

Initial Experience Using 0.55T MRI for Detection of Liver Metastases in NET Patients

Isabelle Remick[1], Thomas Armstrong Hope[1], Michael Ohliger[1], Cheng William Hong[1], Yang Yang[1], Emily Bergsland[1], Courtney Lawhn Heath[1], Pan Su[2] & Pedro Itriago-Leon[2]
[1]University of California San Francisco, [2]Siemens Healthineers

Background
0.55T MRI is a new MRI technology offering increased patient accessibility with a wider bore (80cm) and reduced acoustic noise. We compared the sensitivity of liver metastases detection on gadoxetate-enhanced 0.55T MRI to ^{68}Ga-DOTATATE PET/CT while evaluating patient experience.
Methods
Nine patients with neuroendocrine liver metastases were imaged using gadoxetate-enhanced 0.55T MRI (MAGNETOM Free.Max, Siemens Healthineers, Erlangen, Germany). Eight patients also received 68Ga-DOTATATE PET/CT and five received 3.0T MRIs for comparison. The presence of liver metastases was assessed on CT, PET from PET/CT, diffusion weighted imaging (DWI), and hepatobiliary phase imaging (HBP), and positivity rates were compared. Up to five lesions measuring under 1 cm and five over 1cm per patient were included for analysis. Maximum standardized uptake values (SUVmax) of DOTATATE PET/CT were determined. Sound pressure level (SPLmax) of DWI and HBP were measured at 0.55T and 3.0T by placing a decibel meter 2m from each magnet's front panel and SLPmax was calculated over five repetitions.
Results
Nine patients (average age 63 [5 female, age range 47-75]) with 69 total liver lesions were successfully imaged at 0.55T MRI. 63 lesions were visualized at 0.55T and 42 were seen on DOTATATE PET/CT. Mean SUVmax of hepatic lesions was 18.7 $\pm$ 10.5 on DOTATATE PET/CT. HBP and DWI at 0.55T had increased detection of liver metastases over DOTATATE PET/CT. Qualitatively, HBP was superior on 0.55T compared to 3.0T for 4/5 patients.
Table 1. Sensitivity for the detection of liver lesions by imaging technique broken down by lesion size.

	0-1cm	>1cm	Total
0.55T HBP	88%	100%	94%
0.55T DWI	85%	94%	90%
3.0T HBP	89%	100%	94%
CT	44%	82%	65%
DOTATATE PET	67%	75%	71%

SPLmax was significantly lower for DWI and HBP sequences on a 0.55T system (DWI 76.3 $\pm$ 0.6 dB, HBP 78.5 $\pm$ 1.1 dB) compared to a 3.0T system (DWI 86.6 $\pm$ 1.1 dB, HBP 90.5 $\pm$ 1.3 dB) (p value < 0.0001).
Conclusion
Routine imaging of patients with neuroendocrine tumor metastases is feasible at 0.55T with HBP imaging showing an increased detection rate for hepatic metastases compared to ^{68}Ga-DOTATATE PET/CT. Low-field MR imaging has potential to improve patient experience without sacrificing diagnostic capability.
Abstract ID 23759

DOI: 10.1530/endoabs.98.C37

C38

Are there any clinical factors associated with PRRT-refractoriness in NET patients?

Garima Gupta[1], Rina Yadav[1], Donglin Yan[1], Lowell Anthony[1], Robert Ramirez[2] & Aman Chauhan[3]
[1]University of Kentucky Markey Cancer Center, [2]Vanderbilt University Medical Center, [3]University of Miami Sylvester Cancer Center

Background
Peptide receptor radionuclide therapy (PRRT) with Lutetium-177 DOTATATE (LUTATHERA) is an effective treatment option for somatostatin receptor (SSTR)

positive metastatic gastroenteropancreatic neuroendocrine tumors (NETs) and has also demonstrated antitumor activity in SSTR positive NETs from other primary sites. While the median progression free survival (mPFS) is around 29 months, there is a subset of patients who are refractory to PRRT and demonstrate progression within one year of treatment completion. Since literature from United States on Lutetium-177 DOTATATE refractory disease is limited, we specifically wanted to study clinicopathological factors that may correlate with primary PRRT-refractory disease.
Methods
Retrospective analysis of 163 patients with NETs who underwent PRRT at University of Kentucky between January 2018 until December 2022 was performed. Sixty-one progressors were identified and 39 were included in the final analysis. Primary PRRT-refractoriness was defined as radiographic progression within 12 months of last PRRT treatment. Univariate and multivariate analysis using logistic regression were performed to determine if tumor grade, primary tumor origin, carcinoid syndrome, number of metastatic sites, metastatic peritoneal disease, prior systemic therapies, history of surgical debulking, prior chemotherapy, prior liver directed therapy (LDT) and prior tumor resection were associated with PRRT-refractoriness. Subgroup analyses were also performed to explore the aforementioned associations.
Results
Patients who had unknown cause of death ($n=14$), demonstrated clinical progression but no radiographic progression ($n=2$) or received less than 3 doses of PRRT ($n=6$) were excluded from the final analysis. There were 21 patients in the primary PRRT-refractory group and 18 patients in the PRRT-sensitive group. The median time to progression (TTP) was 163 days and 624 days in the PRRT-refractory group and PRRT-sensitive group, respectively. No statistically significant ($p<0.05$) associations were found between the studied clinicopathological factors and PRRT-refractoriness. On subgroup-analysis performed several different ways including patients with tumor grade 2 or higher, lung/pancreatic primary, no history of surgical debulking, presence of peritoneal metastasis, lines of prior systemic treatment more than or equal to 3 and prior chemotherapy did not reveal significant associations.
Conclusion
This study did not identify any association between pre-specified clinicopathological factors and PRRT-refractoriness in NET patients. Larger multi-center studies are needed to further explore this clinical question.
Abstract ID 23769

DOI: 10.1530/endoabs.98.C38

C39

Repeat peptide receptor radionuclide therapy in neuroendocrine neoplasms: a NET center of excellence experience

Udhayvir Singh Grewal, MD[1], Alexander Paschke, MD[2], Joseph Dillon, MD[1] & Chandrikha Chandrasekharan, MD[1]
[1]Holden Comprehensive Cancer Center, [2]University of Iowa Hospitals and Clinics

Background
Lu177 DOTATATE Peptide Receptor Radionucleotide Therapy (PRRT) was FDA approved in the United States in 2018, however, the data for the safety and efficacy of repeat PRRT are almost exclusively from European centers. We present an updated experience with repeat PRRT in a cohort of US patients.
Methods
We used our single-center longitudinal IRB approved neuroendocrine tumor (NET) registry to identify patients who had been previously treated with at least 1 dose of PRRT (PRRT 1, either Lu 177 DOTATATE or Y90 DOTATOC) and following disease progression were retreated with a second course of PRRT (PRRT 2). Patients who received alpha PRRT were not included.
Results
A total of 153 patients received Lu-177 DOTATATE PRRT at our institution, out of which, 13/153 (8.5%) patients received repeat PRRT. 2/13 patients were excluded due to lack of follow up. All patients included were White (11/11, 100%). Median age of the participants was 65 years (IQR 63, 67) and 54.5% (6/11) patients were females. Most patients had grade 2 (9/11,81.8%) followed by grade 1 NET (2/11, 18.2%) and all except one patient included had a gastroenteropancreatic origin NET (10,11, 90.9%). 45.5% (5/11) patients received Lu-177 DOTATE PRRT only both for PRRT1 and PRRT 2, while 54.5% (6/11) patients received Y90 DOTATOC PRRT for PRRT1. Median number of lines of therapies before PRRT1 and PRRT2 were 2 (IQR 2,5) and 1 (IQR 1,2) respectively. Patients received a median of 3 (IQR 2, 4) and 3 (IQR 1,4) cycles for PRRT1 and PRRT2 respectively. At first restaging scan after PRRT1 (3-6 months), 54.5% and 45.5% patients had partial response (PR) and stable disease (SD) respectively. At first restaging scan after PRRT2 (3-6 months), 45.5%, 27.3% and 9.1% patients had SD, progressive disease (PD) and PR respectively; 2/11 patients (18.2%) died before first restaging scan. Median PFS for PRRT1 ($n=11$) was 22.5 months (IQR 12.7, 30.7). Median PFS ($n=5$) for PRRT2 was 10.9 months (IQR 10.05, 25.7). PFS was not reached for 1 patient after PRRT2. 1 (9.1%) patient each developed grade 2 nephrotoxicity and grade 3 thrombocytopenia after PRRT2.
Conclusion
To our knowledge, this is the first of its kind analysis describing the safety and effectiveness of repeat PRRT in a US cohort. We show that repeat PRRT may benefit select patients and has an acceptable safety profile. Larger prospective clinical studies are required to identify patient groups that are more likely to benefit from repeat PRRT.
Abstract ID 23779

DOI: 10.1530/endoabs.98.C39

C40

Evaluation of long-term hepatic adverse events in patients receiving Peptide Receptor Radionuclide Therapy (PRRT) following BLAND embolization

Udhayvir Singh Grewal, MD[1], Alexander Paschke, MD[2], Joseph Dillon, MD[1] & Chandrikha Chandrasekharan, MD[1]
[1]Holden Comprehensive Cancer Center, [2]University of Iowa Hospitals and Clinics

Background
Clinicians are concerned about increased hepatotoxicity in patients who received hepatic artery bland embolizations (TAE) and subsequent Peptide Receptor Radionuclide Therapy (PRRT). The body of literature describing the safety of PRRT following prior TAE is very limited. The purpose of this study is to evaluate the degree of long-term liver toxicity in patients who received PRRT in addition to previous hepatic embolizations for liver dominant disease.
Methods
Retrospective review was conducted for mNET patients who received at least 1 cycle of PRRT with 177Lu-DOTATATE between 4/2018 and 02/2022 with and without prior hepatic bland embolization (TAE). Patients were followed for at least 6 months after their last PRRT cycle. Most recent clinical, imaging and laboratory findings including hepatic CTCAE v5.0 were compared to pre-PRRT.
Results
238 patients (126 M, 112 F, mean age=64) with mNET (G1:78, G2:137, G3:19, unknown: 27) of different primary sites (12 foregut, 137 midgut, 11 hindgut, 60 pancreas, 1 lung, 17 unknown) underwent at least 1 cycle of PRRT. 171 patients had at least 6 months of follow-up, 110 of whom were embolization naïve and 61 who had prior TAE. Median follow up was 22 months (range: 6-43). Patients with prior TAE had higher liver tumor burden on average (<25%: 40, 25-50%: 16, 50%+: 5) than patients without prior TAE (<25%: 90, 25-50%: 15, 50%+: 5) ($P=0.058156$). 7 patients in TAE naïve group exhibited long-term G3 hepatotoxicity (bilirubin, AST, ALT, ALP) compared to 6 patients who had prior TAE (bilirubin, AST, ALP) ($P=0.4118$). Similarly, there was no significant difference in grade 4 hepatotoxicity between cohorts; 2 patients in the TAE naïve group had G4 hepatotoxicity (bilirubin, AST) while 1 in the prior TAE group had transient G4 toxicity (bilirubin) ($P=0.9319$).
Conclusion
Even though mNET patients who undergo TAE prior to PRRT often have a higher liver tumor burden than their embolization naïve counterparts, these patients have low risk of long-term high-grade hepatotoxicity. Patients with liver dominant metastatic mNET can safely receive PRRT after bland TAE.
ABSTRACT ID 23802

DOI: 10.1530/endoabs.98.C40

C41

Spectrum of therapy-related clonal cytopenias and neoplasms after exposure to Lutetium-177-Dotatate

Stephanie L Pritzl[1], Yael Kusne[2], Thorvardur R Halfdanarson[3], Timothy Hobday[3], Mohamad Bassam Sonbol[2], Ayse Tuba Kendi[4], Abhishek Mangaonkar[1], Naseema Gangat[1], Mithun Shah[1] & Mrinal M Patnaik[1]
[1]Mayo Clinic, Department of Internal Medicine, Division of Hematology, Rochester, MN; [2]Mayo Clinic, Division of Hematology and Medical Oncology, Phoenix, AZ; [3]Mayo Clinic, Department of Oncology, Division of Medical Oncology, Rochester, MN; [4]Mayo Clinic, Department of Radiology, Division of Nuclear Medicine, Rochester, MN

Background
Peptide receptor radionuclide therapy (PRRT) is a form of targeted systemic radiopharmaceutical therapy that has been approved for treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors. Persistent hematologic dysfunction is a recognized potential long-term toxicity after PRRT, including the development of hematologic malignancies and persistent cytopenias. Therapy-related myeloid neoplasms (t-MN) are a well-recognized entity that arise after exposure to DNA damaging therapy for an unrelated condition and are associated with poor outcomes. Therapy-related acute lymphoblastic leukemia and therapy-related clonal cytopenias (t-CC) have also been recognized as clinically distinct entities.
Methods
We characterized our institutional experience on the spectrum of therapy-related neoplasms/clonal cytopenias in individuals with neuroendocrine neoplasms (NENs) who have received at least one dose of Lutetium-177-Dotatate. Clinical characteristics and outcomes were retrospectively reviewed. Bone marrow biopsies, cytogenetic studies and somatic mutation profiling were reviewed.
Results
A total of 346 patients received at least one dose of PRRT at Mayo Clinic-Rochester. Of these, 8 patients (2.3%) were noted to have an established diagnosis of a therapy-related neoplasm or clonal cytopenia; 1.4% with a therapy-related myeloid neoplasm. The median age at the time of first PRRT treatment was 61 years (range, 51-69) and 62.5% were male. The type of NENs included 3 (37.5%) small bowel, 2 (25%) pancreatic, 1 (12.5%) gastric, 1 (12.5%) unknown primary, and 1 (12.5%) pheochromocytoma. Four patients (50%) also had exposure to an alkylating agent. Five patients (63%) developed a therapy-related myelodysplastic syndrome, 1 patient (12.5%) developed B-cell acute lymphoblastic leukemia, and 2 patients (25%) developed t-CC. The median latency from first PRRT treatment to development of a therapy-related hematologic malignancy or clonal cytopenia was 18.5 months (range, 8-42); the median latency for t-CC and therapy-related neoplasm was 25.5 and 18 months, respectively. All patients received 4 cycles of PRRT. The median latency from time of first alkylator exposure to development of a therapy-related neoplasm was 68.5 months (range, 6-144). Cytogenetic analyses revealed recurrent high-grade chromosomal damage in 80% of the patients with a t-MN. Somatic mutations were identified in 6 (85.7%) of 7 assessable patients, with the most commonly mutated gene being BCOR (33%). Four patients (50%) were alive at last follow-up.
Conclusion
Prospective studies are needed to help better understand and predict patients at risk for developing therapy-related neoplasms after PRRT and factors impacting latency for transformation.
Abstract ID 23803
DOI: 10.1530/endoabs.98.C41

C42

Treatment with Lutetium in a real-world setting: How does it affect patient experience and their time-toxicity?

María Romina Luca[1], Eliana Cecilia Vazquez[2], Federico Waisberg[1], Greta Catani[1], Ana Oviedo[3], Martina Musumeci[4], Andres Rodriguez[1], Marcos Bortz[1], Federico Esteso[1], Matias Chacon[1], Juan Manuel Óconnor[1] & Silvina Racioppi[4]

[1]Medical Oncology Department, Alexander Fleming Institute, Hospital, Buenos Aires, Argentina; [2]Nuclear Medicine Theranostics and Molecular Imaging Department, Alexander Fleming Institute, Buenos Aires, Argentina; [3]Oncology Unit, Gastroenterology Hospital "Dr. Carlos Bonorino Udaondo", Buenos Aires, Argentina; [4]Nuclear Medicine Theranostics and Molecular Imaging Department, Alexander Fleming Institute, Buenos Aires, Argentina

Background
Lutetitum-177 (Lu-DOTATE) is an approved treatment regimen for patients with advanced neuroendocrine tumors (NETs). Improving patient experience is one of main goals of a cancer treatment plan. "Time-toxicity" describes the period that patients spend in doing administrative or medical procedures, including medical visits, scans, lab analyses, emergency room admissions, drug applications and hospitalizations. Modern therapies are usually approved after an improvement of progression and overall survival are showed in clinical trials. It is expected that "time-toxicity" may allow physicians to determine how much "home" time is gained after initiating different treatments. Our purpose was to describe clinical characteristics, safety and efficacy results in an institutional cohort of patients that received Lu-DOTATATE and to determine the "time-toxicity", describing how much Lu-DOTATATE treatment may have been associated with health services utilization.
Methods
This was an institutional cohort of patients that received Lu-DOTATATE in Alexander Fleming Institute, Buenos Aires, Argentina. Adverse events were registered as per CTCAE 4.0 criteria, and "time-toxicity" was evaluated considering Author's definitions. Progression free survival was calculated with the Kaplan Meier method, from the first Lu-DOTATATE application to radiological disease progression.
Results
A total of 21 patients were included (Male 66%, Median age 55). Primary tumor site was small bowel and pancreas for 47.6% and 33.3% of the cohort, respectively. 61.9% of tumors were Grade 2. 38% received Lu-DOTATATE as a second-line treatment and 42.8% as a third or more treatment line. 53% of the population received 4 treatment applications. Median interval between diagnosis to Lu-DOTATATE initiation was 206 days (SD: 414,6). The median total treatment duration was 194 days (IQR 162-215). The time toxicity of this cohort was 5.67%, which corresponds to a total of 11 (IQR 8-18) days. This period involved 1 day for cancer specialist consultation, 2 days for lab analysis, 4 days due to hospitalizations, and 4 days for body scans. Adverse events were observed in 33% of the patients. Overall tumor response and disease control rates were 19%, and 66.6%. The progression free survival rate at 18 months was 70.7% (CI95% 43-100)
Conclusion
New measures are essential to incorporate a better view of how patient experience is affected due to cancer treatments. Lu-DOTATATE was associated with appropiate disease control rates and low time-toxicity in a real-world scenario. We consider that is necessary to incorporate the patient's voice to better assess which efficacy measures are needed to guide treatment decisions and highlight patient experience during cancer care.
Abstract ID 23807
DOI: 10.1530/endoabs.98.C42

Clinical – Surgery/Applied Pathology

C43

Accuracy of DOTATATE PET imaging in the preoperative planning of small bowel neuroendocrine tumor resection

Chi Zhang, MD[1,2], Hallbera Gudmundsdottir, MD[2,3], Hiroaki Takahashi, MD, PhD[4], Courtney Day, MS[2], Amy Glasgow, MHA[2], Nabil Wasif, MD, MPH[1], Patrick Starlinger, MD[3], Susanne Warner, MD[3], Travis Grotz, MD[3], Rory Smoot, MD[3], Mark Truty, MD[3], Sean Cleary, MD[3], Michael Kendrick, MD[3], David Nagorney, MD[3], Patrick Navin, MB, BCh[4], Thorvardur R. Halfdanarson, MD[5] & Cornelius Thiels, DO, MBA[2,3]
[1]Mayo Clinic Department of Surgery, Phoenix, AZ; [2]The Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery Rochester, MN; [3]Mayo Clinic Department of Surgery, Rochester, MN; [4]Mayo Clinic Department of Radiology, Rochester, MN; [5]Mayo Clinic Division of Medical Oncology, Rochester, MN

Background
Small bowel neuroendocrine tumors (sbNETs) incidence is on the rise. Given that sbNETS are often multifocal with high risk of regional nodal metastasis, open resection with lymphadenectomy is the gold standard approach as it offers manual palpation of the entire small bowel. We evaluated the accuracy of preoperative DOTATATE PET/CT in estimating the number of lesions and the presence of nodal disease compared to postoperative pathology findings. We hypothesize that it may allow for the safe transition to total MIS approaches.
Methods
A multicenter analysis was performed on patients with sbNETs who underwent preoperative DOTATATE PET imaging and surgery between 1/2016-8/2022. All patients underwent extracorporeal small bowel anastomoses. Preoperative imaging reports and blinded secondary imaging reviews were compared to the final postoperative pathology reports. Descriptive statistics were applied.
Results
One-hundred and four patients met inclusion criteria. Pathology showed 53 (51%) patients had multifocal sbNETs and 96 (92%) had nodal metastases. The original preoperative DOTATATE PET imaging identified multifocal sbNET in 28 (27%) patients and LN metastases in 80 (77%) patients. Based on the original radiology reports, sensitivity for multifocal sbNET identification was 45%, specificity was 92%, positive predictive value (PPV) was 86%, and negative predictive value (NPV) was 62%. For identification of LN metastases, sensitivity was 82%, specificity was 88%, PPV was 99%, and NPV was 29%. The blinded re-review of DOTATATE PET imaging identified 48 (52%) patients with multifocal sbNETs and 82 (88%) with LN metastases. Sensitivity and specificity were 71%, PPV was 75%, and NPV was 67% for multifocal sbNET identification. Sensitivity was 92%, specificity was 87%, PPV was 96%, and NPV was 36% for LN metastases identification.
Conclusion
Although DOTATATE PET imaging is specific and relatively accurate, the sensitivity and NPV are insufficient to guide surgical planning. Preoperative use should not replace open palpation to identify additional synchronous lesions or to omit regional lymphadenectomy.
Abstract ID 23197
DOI: 10.1530/endoabs.98.C43

C44

Real-time prospective DAXX/ATRX testing of 186 consecutive surgically resected pancreatic neuroendocrine tumors reveals loss of expression correlates with distant metastasis

Phoenix D Bell, Katelyn Smith[1], Alessandro Paniccia[1], Kenneth K Lee[1], James F Pingpank[1], Melissa Hogg[2], Herbert J Zeh[3], Marina N Nikiforov[1], Aatur D Singhi[1] & Amer H Zureikat[1]
[1]University of Pittsburgh Medical Center, [2]Northshore University Hospital, [3]UT Southwestern Medical Center

Background
Pancreatic neuroendocrine tumors (PanNETs) are a heterogeneous group of neoplasms with increasing incidence and unpredictable behavior. Whole-exome sequencing studies of metastatic PanNETs have found recurrent genomic alterations in DAXX and ATRX, which correlate with corresponding loss of protein expression. Loss of DAXX/ATRX in PanNETs is reported to be associated with several, adverse clinicopathologic features and poor patient disease-free survival (DFS). However, prior studies have been retrospective in nature and, therefore, the aim of this study was to prospectively evaluate the status of DAXX/ATRX among surgically resected PanNETs and assess its prognostic clinical significance.
Methods
Within a timeframe of 5 years, 186 consecutive patients underwent surgical management for a primary PanNET. This patient cohort included 175 non-functional PanNETs, 10 insulinomas, and 1 somatostatinoma. Additionally, 7 patients had multiple endocrine neoplasia type 1 (MEN1) and 1 patient had von Hippel Lindau (VHL) syndrome. The status of DAXX/ATRX was immunohistochemically evaluated as part of routine pathologic assessment for each surgically resected PanNET. The results of DAXX/ATRX staining were correlated with standard clinicopathologic features and patient follow-up that ranged from 5 months to 5 years (median, 2.25 years).
Results
Loss of DAXX, ATRX, both proteins, or either protein within the prospective cohort was identified in 26 (14%), 21 (11%), 1 (1%), and 46 (25%) cases. DAXX/ATRX loss was associated with tumor size of >2.0 cm (94% vs 56%, $P<0.001$), higher WHO grade (41% vs 14%, $P<0.001$), perineural invasion (72% vs 29%, $P<0.001$), lymphovascular invasion (87% vs 42%, $P<0.001$), synchronous distant metastasis (26% vs 9%, $P=0.004$), and the development of metachronous distant metastases (35% vs 6%, $P<0.001$). No statistical significance was observed between DAXX/ATRX status and functional status or predisposing syndrome. Among patients without synchronous distant metastases ($n=162$, 87%), the 3-year DFS for patients with DAXX/ATRX-negative PanNETs was 65% as compared to 95% for DAXX/ATRX-positive PanNETs. By multivariate analysis to include WHO grade, T-stage, and N-stage, loss of DAXX/ATRX was a negative, independent prognostic factor for DFS ($P=0.023$).
Conclusion
Consistent with retrospective studies, the detection of DAXX/ATRX loss in surgically resected PanNETs was associated with multiple adverse clinicopathologic features and an increased risk of patients developing distant metastatic disease. While continued long-term follow-up is being accrued for this study cohort, the assessment of DAXX/ATRX should be clinically considered in the prognostic evaluation of surgically resected PanNETs.
Abstract ID 23368
DOI: 10.1530/endoabs.98.C44

C45

Grade progression in gastrointestinal neuroendocrine tumors

Bryan Hill-Fung Lau[1], Farhana Moon[2], Nancy Joseph[3], Eric Nakakura[4], Bryan Khuong Le[2], Stephanie Wang[1], Li Zhang[1,5] & Emily Bergsland[6]
[1]School of Medicine, University of California San Francisco, San Francisco, CA; [2]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [3]Department of Pathology, University of California San Francisco, San Francisco, CA; [4]Department of Surgery, University of California San Francisco, San Francisco, CA; [5]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA; [6]Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA

Background
Gastrointestinal neuroendocrine tumors (GI NETs) are subdivided into grades (G) G1-G3 based on Ki-67 proliferation index (%) (G1 <3%, G2 3-20%, and G3 $>$ 20%) or mitotic rate, with tumor grade informing prognosis and treatment. Grade progression (GP) over time in GI and pancreatic NETs has recently been identified, with low(G1/2)-to-high(G3) grade progression (L-to-H) the most clinically relevant form. L-to-H is associated with worse survival, yet the timeframe, incidence rate and risk factors remain largely unknown. This study aims to determine the incidence and potential predictors of L-to-H in tubal GI NETs.
Methods
We conducted a retrospective review of the medical records of patients with stage I-IV GI or unknown primary NETs diagnosed between 2009-2023 identified from an IRB-approved NET database. Patients with low-grade (G1/2) NET at diagnosis and at least two metachronous (at least 3 months apart) tumor biopsies with Ki67 staining were included. Demographic and clinicopathologic characteristics were compared between groups using Chi-squared test and Mann-Whitney test for categorical and continuous variables, respectively.
Results
Out of 354 total patients, 99 had metachronous tumor biopsies with Ki-67 staining; 82 had low-grade (G1/2) NET at diagnosis and were included in the analysis (median follow-up 5.9 yrs, median age 58 yrs, 51% female, 73% White, 17% Hispanic, 61% stage IV, 33% with functional tumor). Overall, 77 (94%) patients exhibited low-to-low (L-to-L), meaning low grade at diagnosis and on serial biopsy; 5 (6%) exhibited L-to-H. There were no differences in age, sex,

race, ethnicity, follow-up time, primary tumor site, tumor functional status, or initial stage/Ki-67/grade between L-to-L and L-to-H groups.

Characteristic	Total (n =82)	L-to-L (n =77)	L-to-H (n =5)	p-value
Primary tumor site N(%)	10(12)	10(13)	0(0)	0.441
Stomach	55(67)	52(68)	3(60)	
Small bowel	5(6)	4(5)	1(20)	
Colon/Rectum	2(2)	2(3)	0(0)	
Other	10(12)	9(12)	1(20)	
Unknown				
Grade at diagnosis N(%): G1	52(63)	49(64)	3(60)	0.870
G2	30(37)	28(36)	2(40)	
Ki-67 at diagnosis, median(range)	2(0.1,18)	2(0.1,18)	1(1,3.2)	0.189
Subsequent Ki-67, median(-range)	**2.9 (0.3, 44.5)**	**2.4(0.3,20)**	**38(29.7,44.5)**	**<0.001**

Conclusion
This single-center retrospective cohort study reveals a 6% incidence of L-to-H over time in GI NETs. Ongoing work will integrate factors such as time to 2nd biopsy, prior therapy, reasons for 2nd biopsy, and site of biopsy (primary vs. metastasis). Results of this study provide insight into the natural history of GI NETs and risk factors associated with L-to-H. Additional work is needed to understand the molecular mechanisms underlying L-to-H progression in this disease.

Abstract ID 23472
DOI: 10.1530/endoabs.98.C45

C46

Peptide receptor radionuclide therapy improves survival in patients who progress after resection of gastroenteropancreatic neuroendocrine tumors

Luis C. Borbon[1], Scott K. Sherman[1], Patrick Breheny[2], Po H. Ear[1], Yusuf Menda[3], Chandrikha Chandrasekharan[4], Andrew M. Bellizzi[5], Thomas M. O'Dorisio[4], Joseph S. Dillon[4] & James R Howe[1]
[1]Department of Surgery, University of Iowa Hospitals and Clinics, Iowa City, IA; [2]Department of Biostatistics, The University of Iowa, Iowa City, IA; [3]Department of Radiology, University of Iowa Hospitals & Clinics, Iowa City, IA; [4]Department of Internal Medicine, University of Iowa Hospitals & Clinics, Iowa City, IA; [5]Department of Pathology, University of Iowa Hospitals & Clinics, Iowa City, IA

Background
Peptide Receptor Radionuclide Therapy (PRRT) is effective for gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) and received FDA approval after demonstrating improved progression-free-survival (PFS) in advanced midgut NETs. We investigated a two-decade experience with PRRT, hypothesizing that PRRT confers PFS and overall-survival (OS) advantages in patients who progress after surgery.
Methods
A single-institutional NET database was reviewed for patients who had resection and/or cytoreduction of GEP-NETs and later had disease progression according to RECIST 1.1 criteria. The Kaplan-Meier method assessed PFS and OS, calculated from progression after surgery for the no-PRRT group or start of PRRT for PRRT recipients. Cox regression with time-dependent covariates controlled for immortal time bias and other confounders.
Results
Among 237 patients identified, 95 received PRRT while 142 did not. There were no differences in sex, T- or N-stage, tumor grade/differentiation, primary site, or time to first progression; 94% of PRRT patients had metastases at diagnosis vs. 77% in the non-PRRT group. Among PRRT recipients, 60 received PRRT soon after first progression ("Upfront", median 4.6 months) while 35 received later PRRT ("Delayed" as 2nd- 4th line therapy at median 24.5 months). Median PFS from the start of PRRT was longer for both groups (32.0 and 34.3 months, respectively) compared with the no-PRRT group (11.0 months, $P<0.001$). Importantly, median OS was longer for the Upfront PRRT group (53.7 vs. 38.4 months in the no-PRRT group; $P=0.01$), and in both pancreatic (PNET) and small bowel-primary (SBNET) subgroups (Table). Time-dependent covariate analysis revealed a lower risk of death associated with PRRT (HR=0.61; 95%-CI 0.39-0.95; $P=0.028$) after adjusting for sex, age, M-stage, tumor grade, and primary site.
Table: PFS and OS by treatment category in 237 GEP-NET patients progressing after surgery.

	Median PFS (months)	p-value*	Median OS (months)	p-value*
PRRT Upfront (n =60)	32.0	<0.001	53.7	0.01
PRRT Delayed (n =35)	34.3	<0.001	48.7	0.2
No PRRT (n =142)	11.0	—	38.4	—
SBNET PRRT (n =65)	32.0	<0.001	40.5	0.02
SBNET No PRRT (n =79)	12.4	—	29.8	—
PNET PRRT (n =27)	34.3	<0.001	123.4	0.08
PNET No PRRT (n =52)	10.6	—	56.6	—

SBNET=Small bowel NET; PNET=Pancreatic NET. *p-value by log-rank test compared with No PRRT.
Conclusion
The strategy of surgical resection and cytoreduction followed by PRRT after progression appears to confer superior PFS and OS in SBNET patients, and PFS in PNET patients. The PFS benefit of PRRT was seen whether it was given Upfront or Delayed after failure of other lines of therapy.

Abstract ID 23486
DOI: 10.1530/endoabs.98.C46

C47

Surgical cytoreduction vs systemic therapy in patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETS): NCDB analysis

A. Mohamed[1], A. Fasih[2], L.M. Ocuin[2], J. Winter[2], J. Ammori[2], J. Hardacre[2], A. Mahipal[1], D. Bajor[1], S. Chakrabarti[1], S.L. Asa[3], J.E. Selfridge[1], S.H. Tirumani[4], L.E. Henke[5] & R.S Hoehn[2]
[1]Department of Medicine, Division of Hematology and Medical Oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [2]Department of Surgical Oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [3]Department of Pathology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [4]Department of Radiology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; [5]Department of Radiation Oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, OH.
Corresponding author: Amr Mohamed, MD, amr.mohamed@uhhospitals.org

Background
The role of surgical cytoreduction for metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is considered an area of debate due to lack of prospective data. While retrospective and single institution analyses demonstrated higher survival rates associated with surgical cytoreduction, there was no comparison with systemic therapies alone in these studies. The aim of this analysis of the National Cancer Database (NCDB) was to evaluate the survival benefit of surgical cytoreduction compared to systemic therapy alone in metastatic GEP-NETs.
Methods
Patients with stage IV well differentiated GEP-NETs were identified using the NCDB (2004-2020). Patients were stratified according to age, gender, grade, primary site, and facility type. Patients who received surgical cytoreduction with or without systemic therapies were compared to those who only received systemic therapies in univariate analysis. Associations between treatment characteristics and median overall survival (OS) were compared using Kaplan-Meier (KM) curves and Cox proportional hazards modeling.
Results
3,183 stage IV GEP-NET patients were identified: 49.5% (n=1,574) males and 50.5% (n=1,609) females, with median age 62 years old. 66.7% (n=2,124) had hepatic metastases. 69.8% (n=2,222) of patients received cytoreduction alone, 23.4% (n=747) received systemic therapy alone, and 6.7% (n=214) received both. Patients who received cytoreduction alone or combined with systemic chemotherapy had higher median OS compared to systemic therapy alone (140.9 months vs 96.2 months vs 51.6 months, $P<0.001$ respectively). Cytoreduction was associated with higher median OS for patients with both G1/2 and G3 tumors (table 1). Regarding primary tumor, both midgut and pancreatic NETs had higher OS with surgical cytoreduction compared with systemic therapy alone (table 1). When stratified according to facility type, patients who received surgical

cytoreduction at academic hospitals seemed to have better OS compared to community-based hospitals (table 1). Compared to academic hospitals, treatment at community-based hospitals was associated with inferior OS following cytoreduction (HR: 2.77, 95% CI: 1.20-6.41) but similar survival with chemotherapy alone (HR: 1.88, 95% CI: 0.39-9.06).
Conclusion
Patients with metastatic GEP-NETs who had surgical cytoreduction experienced higher median OS compared to patients treated with only systemic therapy, regardless of primary tumor site or histologic grade. Academic centers were also associated with higher median OS. These results need to be validated in future prospective studies.
Abstract ID 23661

DOI: 10.1530/endoabs.98.C47

C48

Predictors of low-to-high grade progression in pancreatic neuroendocrine tumors

Stephanie J. Wang[1], Farhana Moon[2], Nancy Joseph[3], Eric Nakakura[4], Bryan Khuong Le[2], Li Zhang[1,5] & Emily Bergsland[6]
[1]School of Medicine, University of California San Francisco, San Francisco, CA; [2]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [3]Department of Pathology, University of California San Francisco, San Francisco, CA; [4]Department of Surgery, University of California San Francisco, San Francisco, CA; [5]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA; [6]Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA

Background
Pancreatic neuroendocrine neoplasms (panNENs) are heterogeneous, with grade (G) defined by Ki67 proliferation index (<3% G1, 3-20% G2, >20% G3) or mitotic rate. The G3 NEN subgroup is further divided into well differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NEC). Grade progression can occur over time, with low-to-high grade progression (L-to-H; G1/2 to G3) the most clinically relevant form. It is associated with shorter overall survival (OS) and occasional dedifferentiation into NEC. However, little is known about the timeframe over which L-to-H occurs or what drives this change, adding uncertainty to individual clinical management and complexity to use of archived biopsies for clinical trial inclusion.
Methods
We conducted a retrospective review of patients with stage I-IV G1-3 panNENs diagnosed between 2010-2021 and identified from an IRB-approved NET database. Patients with at least two serial tumor biopsies (with Ki67 staining) over 3 months apart were eligible.
Results
Of 318 cases, 76 patients (23.9%) had metachronous tumor biopsies with Ki67 staining (median follow-up 6.8 yr), and 66/76 (86.8%) were initially diagnosed with low grade NET (median Ki67 4.6%, range 1.0-20.0%). Of these, 23/66 (34.8%) showed grade progression, with 16/66 (24.4%) demonstrating L-to-H. Over a median 2.3 years, L-H patients experienced a median Ki67 increase of 27.0% to a median subsequent Ki67 of 31.0% (range 21.0-60.0%). In comparison, $n=50$ low-to-low (L-to-L) patients were diagnosed as low grade and remained so upon serial biopsy, with a median Ki67 change of 0% between serial biopsies a median 2.3 years apart. L-to-H patients were more likely to display heterogeneity on DOTA PET imaging ($P=0.003$), receive more lines of therapy prior to subsequent biopsy ($P=0.04$), and have a change in disease behavior trigger a biopsy ($P=0.008$), more often via percutaneous techniques rather than surgical resection ($P=0.02$). Time to serial biopsy, median follow-up, sex, race, functional status and stage at diagnosis did not differ significantly between groups. L-to-H was associated with worse OS from metastatic disease than L-to-L ($P=0.002$).
Conclusion
In patients with G1/2 panNET undergoing serial biopsies, 24.4% demonstrated L-to-H. Clinicians should be aware of the potential for L-to-H over time, particularly if the patient is heavily pretreated, or has heterogeneous uptake on DOTA PET scan or suspicious clinical behavior. Our findings highlight the potential limitations associated with use of archival tissue for clinical trial eligibility. Additional work is needed to understand the molecular mechanisms underlying L-to-H, optimal therapy, and incidence in extrapancreatic NETs.
Abstract ID 23675

DOI: 10.1530/endoabs.98.C48

C49

Post-procedure outcomes of liver-directed therapy of neuroendocrine liver metastases

Léamarie Meloche-Dumas[1], Frédéric Mercier[2], Victoria Barabash[3], Calvin Law[1,4], Simron Singh[3,4], Sten Myrehaug[3,4], Wing Chan[5] & Julie Hallet[1,4]
[1]Department of Surgery, University of Toronto, Toronto, ON, Canada; [2]Department of Surgery, Université de Montréal, Montréal, QC, Canada; [3]Sunnybrook Research Institute, Toronto, ON, Canada; [4]Susan Leslie Clinic for Neuroendocrine Tumors - Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [5]ICES, Toronto, ON, Canada

Background
While there have been major advances in the care of neuroendocrine tumors (NETs), there is still no widely adopted therapeutic sequencing in metastatic NETs. The roles and benefits of locoregional treatments need reassessment, in order to define a modern therapeutic algorithm. We examined contemporary short-term outcomes of liver-directed therapy for metastatic NETs.
Methods
We conducted a population-based retrospective cohort study of patients with metastatic NETs (2000-2019) undergoing liver embolization (LE) or liver resection (LR). Outcomes were 30-day major morbidity (Clavien-Dindo grade 3-5) and/or re-admission (composite) and length of hospital stay. Modified Poisson regression accounting for clustering at the hospital level examined factors associated with outcomes in both treatment groups.
Results
Overall, 1,224 LEs and 502 LRs were performed for 5,159 patients with metastatic NETs. Median length of hospital stay was 1 day (IQR 1-4) for liver embolization and 7 days (IQR 5-9) for liver resection. 30-day major morbidity and re-admission occurred after 213 LEs (17.4%) including 40 (3.3%) deaths, and 138 LRs (27.5%) including 11 (2.2%) deaths. There were 25 (2%) LEs followed by infectious complications. Factors independently associated with increased risk after LE were prior LE treatment (adjusted relative risk- aRR 0.62; 95%CI 0.44-0.88), rural residence (aRR 0.43; 95%CI 0.20-0.91) and high comorbidity burden (aRR 1.85; 95%CI 1.34-2.54). The only factor independently associated with increased risk after LR was metachronous metastases (RR 0.60; 95%CI 0.37-0.98).
Conclusion
In this contemporary cohort, LE was associated with mortality similar to that of LR. Prior LE, rural residence, comorbidities, and metachronous metastatic diagnosis were associated with higher risk of major morbidity and re-admission. This information is important when discussing the use of and choice of liver-directed therapies in the multi-disciplinary management of metastatic NETs. Further characterization of long-term outcomes and patient-reported outcomes will further support decision-making, counselling, and patient preparation.
Abstract ID 23682

DOI: 10.1530/endoabs.98.C49

C50

Phenotype Genotype Correlation in Multiple Endocrine Neoplasia Type 1

Charlita Worthy, Nayan U. Vikram, Rana Tora, James Welch, Anisha Ninan, Lynn Bliss, Craig Cochran, Lee S Weinstein, William F. Simonds, Jenny E. Blau, Sunita K. Agarwal & Smita Jha
National Institutes of Health, Bethesda, MD

Background
The presence of a genotype-phenotype correlation in patients with MEN1 remains controversial with conflicting data from different centers. Furthermore, about 10-30% patients have genotype-negative (GN)-MEN1. Here, we evaluate the presence of genotype-phenotype correlation in our cohort of comprehensively phenotyped patients with MEN1. In addition, we compare the phenotype of GN-MEN1 and genotype-positive (GP)-MEN1 patients and investigate somatic mosaicism as a cause of GN-MEN1.
Methods
Index patients (first patient in kindred to be diagnosed with MEN1) or probands (first patient from kindred to be evaluated at our center) from kindreds with GP-MEN1 were identified. Germline variants in GP-MEN1 patients were categorized into high-impact (nonsense, frameshift, splice site, whole or partial gene deletion) or low-impact (missense or in-frame indels) groups. GN-MEN1 patients showed no mutations in MEN1 or other PHPT genes (CASR, RET, CDKN1B, CDC73, AIP, GNA11, AP2S1, GCM2). All patients underwent testing for tumor biomarkers, imaging and evaluation for Zollinger-Ellison syndrome (ZES). Whole exome sequencing was performed on multiple tumors from 13 GN-MEN1 patients.

Results
We identified 160 patients with GP-MEN1 (96 females) and 42 (31 females) with GN-MEN1. Among GP-MEN1, 97 had high impact and 34 had low-impact mutations. Mean age at last follow-up was 56 (±14) years for GN-MEN1 and 52 (±16) years for GP-MEN1 patients. All patients with high-impact mutations had PHPT (58% had recurrent disease), 70% had pituitary tumors (35% with macro-adenomas) and 63% developed GEP-NETs (24% with distant metastases). In comparison, 88% patients with low-impact mutations developed PHPT (48% with recurrent disease), 77% developed pituitary tumors (21% with macro-adenomas) and 75% developed GEP-NETs (24% with distant metastases). Among the GN-MEN1 patients, 38/42 developed PHPT - 3/38 (8%) had recurrent disease. In GP-MEN1, 103/107 developed PHPT - 62/103 (60%) with recurrent disease. Median age of index presentation with PHPT was significantly different between the two groups (27.5 years in GP-MEN1 vs 53 years in GN-MEN1, $p < 0.05$). 33/42 GN-MEN1 patients had a pituitary adenoma (22/33 functioning – 9/22 prolactinomas; 8/22 GH-secreting). In comparison, 72/103 GP-MEN1 patients developed a pituitary adenoma (37 functioning – 30/37 prolactinomas, no GH-secreting tumors). In the GN-MEN1 group, 12/42 (29%) patients developed a gastro-entero-pancreatic (GEP)-NET. In comparison, 64/98 (65%) patients with GP-MEN1 had a GEP-NET. Somatic variants in MEN1, CDC73 or CDKI were observed in six tumors. However, these variants were not seen in a second tumor/s or germline DNA from the patient.
Conclusion
Patients with GP-MEN1 have distinct characteristics with younger age of onset, greater likelihood of recurrent PHPT and co-occurrence of GEP-NETs in comparison to GN-MEN1. No apparent correlation in phenotype between high-impact vs. low-impact mutations is noted. Our findings do not support somatic mosaicism as a cause of GN-MEN1.
Abstract ID 23684

DOI: 10.1530/endoabs.98.C50

C51

A prospective phase ii single-arm trial on neoadjuvant peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE followed by surgery for pancreatic neuroendocrine tumors (NeoLuPaNET)

Stefano Partelli[1], Luca Landoni[2], Mirco Bartolomei[3], Alessandro Zerbi[4], Chiara Maria Grana[5], Ugo Boggi[6], Giovanni Butturini[7], Riccardo Casadei[8], Claudio Bassi[2] & Massimo Falconi[1]
[1]Pancreatic Surgery Unit, Pancreas Translational and Clinical Research Center, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, 20132 Milan, Italy; [2]General and Pancreatic Surgery Department, Pancreas Institute, University and Hospital Trust of Verona, Verona, Italy; [3]Nuclear Medicine Unit, Oncological Medical and Specialist Department, University Hospital of Ferrara, 44124 Cona, Italy; [4]Pancreatic Surgery Unit, IRCCS Humanitas Research Hospital, Milan, Italy; [5]Radiometabolic Therapy Unit, Division of Nuclear Medicine, IRCCS European Institute of Oncology, 20141 Milan, Italy; [6]Division of General and Transplant Surgery, University of Pisa, Italy; [7]Department of Surgery, Pederzoli Hospital, Peschiera, Italy; [8]Department of Surgery, S Orsola-Malpighi Hospital, Bologna, Italy

Background
Surgical resection of Nonfunctioning Pancreatic Neuroendocrine Tumor (NF-PanNET) is curative in most of the cases. Neoadjuvant treatments in patients with resectable NF-PanNET at high-risk of recurrence have never been investigated. Aim of this study was to test the safety and efficacy of neoadjuvant PRRT with ^{177}Lu-DOTATATE followed by surgery in patients with resectable high-risk NF-PanNET.
Methods
This was a multi-center single-arm phase 2 trial. Treatment was PRRT with ^{177}Lu-DOTATATE (Lutathera®) followed by surgery in patients with high-risk of recurrence resectable NF-PanNET. "High-risk NF-PanNET" was defined by the presence of at least one of the following characteristics: tumor size > 4 cm, nearby organ/s invasion, Ki67 > 10%, vascular invasion, single liver metastasis, nodal involvement. The primary endpoints were postoperative morbidity and mortality. The secondary endpoint was the rate of objective radiological response.
Results
Among 34 patients screened, 31 were enrolled in the study. Twenty-six (84%) patients tolerated 4 cycles of ^{177}Lu-DOTATATE whereas 4 patients did not complete 4 cycles for adverse events or unsafe absorbed dose. One patient voluntary interrupted treatment after 2 cycles and 2 patients refused to undergo surgery after ^{177}Lu-DOTATATE. No patient had progressive disease after neoadjuvant ^{177}Lu-DOTATATE. A partial radiological response was observed in 18 patients (58%) whereas 13 patients (42%) had stable radiological disease. Overall, 29 patients underwent surgery after a median period of 119 days (113–142.5 days) from the last cycle of ^{177}Lu-DOTATATE. Surgical resection of NF-PanNET was achieved in 28 patients (96.5%) whereas one patient underwent only exploratory laparotomy for unresectable vascular invasion. Pancreaticoduodenectomy ($n = 11$) and distal pancreatectomy ($n = 11$) were the most frequent types of operation. At final histology, the majority of patients who underwent resection had a NF-PanNET G2 ($n = 16$) and a nodal involvement (N1) was present in the 52% of cases. There was no postoperative mortality. Severe postoperative complications occurred in the 24% of patients and postoperative pancreatic fistula was the most frequent complication after surgery (34%).
Conclusion
Neoadjuvant PRRT with ^{177}Lu-DOTATATE followed by surgery for NF-PanNET is safe and effective demonstrating evidence of a high rate-of radiological response. (ClinicalTrials.gov registration: NCT04385992).
Abstract ID 23692

DOI: 10.1530/endoabs.98.C51

C52

Translational potential of a receptor-targeted contrast agent for fluorescence-guided applications in pancreatic neuroendocrine tumors

Solmaz AghaAmiri[1], Jeannelyn S. Estrella[2], Mark W. Hurd[2], Servando Hernandez Vargas[1], Sukhen C. Ghosh[1], Ali Azhdarinia[1] & Naruhiko Ikoma[2]
[1]The Brown Foundation Institute of Molecular Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX; [2]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX. Drs. Azhdarinia and Ikoma are co-corresponding authors

Background
Accurate intraoperative localization of primary and metastatic pancreatic neuroendocrine tumors (pNETs) is challenging, and molecularly driven fluorescence-guided surgery could significantly improve surgical outcomes with given the overexpression of somatostatin receptor subtype-2 (SSTR2). We developed an optimized SSTR2-targeted fluorescent agent, MMC(FNIR-Tag)-TOC, which expressed excellent targeting specificity and pharmacokinetics, as the lead compound for clinical development. To bridge the gap between preclinical and clinical development of MMC(FNIR-Tag)-TOC, we implemented a fluorescence-guided pathology strategy to (i) examine the binding of our agent to human tumors and (ii) investigate its potential use for delineation of surgical margins.
Methods
We obtained whole tissue sections ($n = 8$) from pNET patients who underwent curative-intent pancreatectomy from the Institutional Tissue Bank at The University of Texas MD Anderson Cancer Center after Institutional Review Board approval. The tissues were snap-frozen and serially sectioned into 5 μm frozen sections for ex vivo staining with MMC(FNIR-Tag)-TOC as described in the supplemental file. The stained sections were scanned for fluorescence signal using a near-infrared fluorescence imaging system (Odyssey, LI-COR). Sequential sections from each specimen were also stained with standard hematoxylin and eosin (H&E) and immunohistochemistry (IHC) for SSTR2 (ab134152, Abcam, 1:1000 dilution) to allow morphologic evaluation of tumor and normal tissues and to assess SSTR2 expression in the samples, respectively. We performed qualitative analysis and evaluated the correlation between the fluorescence staining pattern and SSTR2 distribution in the tumor and surrounding normal areas of the sections.
Results
Six tissue sections contained tumor only, and two samples contained both tumor and normal pancreas. SSTR2 IHC staining was positive in tumor cells, with strong and widespread staining intensity in all cases except one**,** where variable intensity was seen, as indicated by areas of both strong and weak staining in the tumor. SSTR2 staining showed minimal background staining in pancreatic acinar cells (normal pancreas), while highlighting islets of Langerhans. Fluorescence imaging showed excellent co-localization of MMC(FNIR-Tag)-TOC with SSTR2-positive areas that was confined within the tumor boundary, as confirmed by H&E and IHC staining.
Conclusion
Our findings showed that MMC(FNIR-Tag)-TOC has high specificity for human pNET tissues. The observed fluorescence signal was largely correlated with SSTR2 IHC staining and accurately represented pNET tumor extension, which suggests strong utility for fluorescence-guided applications. Accordingly, we plan to extend our research into the clinical arena and initiate a first-in-human trial to investigate the feasibility of using MMC(FNIR-Tag)-TOC for FGS in patients with pNETs.
Abstract ID 23710

DOI: 10.1530/endoabs.98.C52

C53

Abstract Withdrawn

DOI: 10.1530/endoabs.98.C53

C54

Tissue section thickness of Ki67 immunohistochemistry does not have a correlative effect on pancreatic neuroendocrine tumor grading

Moreen Ng[1], John Sinard[1], John Kunstman[2], Pam Kunz[3] & Joseph Misdraji[1]
[1]Department of Pathology, Yale University School of Medicine; [2]Department of Surgery, Yale School of Medicine; [3]Department of Medicine, Section of Medical Oncology, Yale School of Medicine

Background
Despite the widespread use of immunohistochemistry (IHC), there are debates on how pre-analytic variables influence diagnostic results, including the effect of varying tissue section thickness. Scant literature suggests that tissue thickness can affect stain interpretation, including nuclear stains that rely on assigning tumor cells to the positive category, such as Ki-67, and raise the question of whether tissue section thickness should be standardized for some diagnostic or prognostic tests. Grading of pancreatic neuroendocrine tumors (pNET) relies on Ki-67 score, with 3% being the threshold between grade 1 and 2. The goal of our study is to determine if variations in tissue section thickness affect calculation of Ki67 proliferation index that could affect tumor grade assignment in pNET.
Methods
Five pNET resection specimens were selected. Sections for Ki67 were cut at 2um, 3um, 4um, and 5um, and stained with antibodies for Ki-67. Ki-67 score was determined by taking high-magnification photographs of a tumor and the corresponding area in slides cut at different microns. Using manual counting, the number of Ki-67 positive tumor nuclei was divided by the total number of tumor nuclei to calculate a Ki-67 score.
Results
The total number of tumor nuclei present in a high-power photograph tended to decrease as the tissue thickness decreased; mean number of tumor cell nuclei counted across the 5 cases for 5um, 4um, 3um, and 2um sections was 1415, 1330, 1242, and 1319 nuclei, respectively. Ki67 score for each case by tissue section is provided in Table 1.
Table 1. Ki-67 score by slide section thickness for five cases of pNET.

	5um	4 um	3 um	2 um
Case 1	5.59	5.21	4.38	4.12
Case 2	2.92	3.29	3.81	3.03
Case 3	0.90	1.04	1.25	1.00
Case 4	1.07	1.45	1.46	1.16
Case 5	5.29	6.74	7.80	6.30

Conclusion
Based on our study, thinner tissue sections did not correlate with lower Ki-67 score. Assignment of pNET grade does not require standardization of tissue thickness section for manual calculation of Ki-67 score.
Abstract ID 23734

DOI: 10.1530/endoabs.98.C54

C55

Association of long-term PPI use with low-risk gastric neuroendocrine tumor

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

Background
Gastric neuroendocrine tumors are rare neoplasms, comprising approximately 2% of all gastric tumors, and develop from enterochromaffin-like (ECL) cells in the gastric mucosa. Type I and II develop due to hypergastrinemia and ECL cell hyperplasia; type III typically occur sporadically, tend to be more aggressive, present metastatically in $>$ 50% of cases, have normal fasting gastrin levels, and vary histopathologically from well- to poorly differentiated tumors. While long-term proton pump inhibitor (PPI) use has been known to lead to chronic hypergastrinemia, only a few cases of gastric NETs associated with PPI use are reported, and the classification of these cases remains undefined.
Methods
Retrospective study of all gastric NETs seen at MCC between 1/2008 and 9/2021. Patients (pts) with clear type I and type II gastric carcinoids, and poorly differentiated NECs were excluded. Data was collected on pts with type 3 gastric NETs, including PPI use, gastrin levels (both on and off PPI), pathologic features, and the presence of metastatic disease.
Results
76 patients met eligibility criteria. 51% had long-term PPI use defined as $>$ 1 year of consecutive treatment. All had well-differentiated tumors; 33 grade 1, 35 grade 2, 4 grade 3 & grade unknown in 4. Median ki67% was 4.5 (range 1 – 40). Of patients on long-term PPI, 21 (54%) had normal gastrin levels off PPI: 7 pts had mildly elevated gastrin, and the remaining patients did not have a gastrin level while off PPI (or had no gastrin level available). Among 37 patients who received long-term PPI, 4 (10%) had metastatic disease, whereas the remaining patients without long-term PPI use, 68% had metastatic disease ($p<0.0001$).
Conclusion
Gastric NETs diagnosed in patients with long-term PPI use tend to be less aggressive than those occurring sporadically and may represent a separate subtype of gastric NETs that is biologically more similar to type 1 than type 3.
Abstract ID 23765

DOI: 10.1530/endoabs.98.C55

C56

Comparative gene expression and pathway analysis of neuroendocrine neoplasms in relation to clinical outcomes and tumor location

Bahar Laderian[1], Bahar Saberzadeh Ardestani[2], Yanwen Chen[1], Amr Mohamed[3], Ying Ni[1] & Prabhjot Mundi[4]
[1]Cleveland Clinic, [2]Mayo Clinic, [3]Seidman Cancer Center-University Hospitals, [4]Columbia University Medical Center

Background
Neuroendocrine malignancies are heterogeneous cancers with varied clinical outcomes. The molecular landscape driving this heterogeneity has not yet been fully characterized. We aimed to investigate the gene expression profiles of neuroendocrine neoplasms, in relationship to baseline clinicopathological features and clinical outcomes, to elucidate underlying biology and potential therapeutic targets.
Methods
Patients with neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) treated at the Cleveland Clinic (2000-2022) with molecular profiling ($n=79$) were identified. Quantified gene expression profiles were retrospectively retrieved from Tempus or Caris. Clinicopathological characteristics were obtained from the electronic health record. Statistical analyses were performed using R v.4.0.5 and R package Limma was used to identify differential gene expression. Tempus and Caris data were analyzed separately. Pathway analysis using gene set collections from the molecular signatures database (MSigDB) was performed by gene set enrichment analysis.
Results
The cohort consisted of 41 patients with NECs and 38 NETs. Among NETs, 14 (37%) had Ki67 $>$ 20%. The most common primary sites for NETs were small bowel ($n=19$, 50%) and pancreas ($n=8$, 21%), while for NECs colorectal ($n=9$, 23%) and bladder/prostate ($n=9$, 23%). Among NETs, ARX, IRX2, and NOL4 were differentially overexpressed in pancreatic origin vs small bowel (Benjamini Hochberg (BH)-corrected $P<0.01$), while CGA, TBC1D30, and DTNA were significantly underexpressed (BH $P<0.01$). ITGB4 and CTNNB1 were differentially over-expressed in colon vs other primaries (BH $P<0.05$). Pathway analysis using the "cancer hallmarks", "gene ontology", and "KEGG pathway" gene sets in MSigDB, demonstrated that short survival ($<$2 years) in stage IV NET was associated with marked activation in MYC, oxidative phosphorylation, and ribosome/ribonucleoprotein complex formation pathways and deactivation in G-protein coupled and neuroactive ligand receptor signaling pathways (BH $P<0.00001$). In NETs with ki67 $>$ 20% , cell cycle mediators (E2F, G2M checkpoint, and MYC), oxidative phosphorylation, and glycolysis pathways were activated, while inflammatory pathways (TNF-alpha, IFN-gamma, and JAK-STAT signaling) were deactivated (BH $P<0.00001$). In NECs, short survival was associated with marked activation of cell cycle mediators, oxidative phosphorylation, MTOR signaling, and DNA repair pathways, and deactivation of epithelial to mesenchymal transition (EMT), inflammatory (TNF-alpha and IFN-gamma), cell adhesion, and cytokine interaction pathways (BH $P<0.00001$).
Conclusion
Our analysis revealed differential expression of potentially targetable genes in NECs and NETs. Dysregulation of EMT, TNFα signaling, interferon, and E2F pathways in specific subsets of neuroendocrine malignancies could be used for future precision therapy development.
Abstract ID 23785

DOI: 10.1530/endoabs.98.C56

C57

Perioperative management of carcinoid crisis: protocol for a modified Delphi international expert consensus statement with patient engagement

Julie Hallet[1,2], Fahad Alam[3,4], Flavio Rocha[5], Jaydira Del Rivero[6], Stefano Partelli[7], Jonathan Koea[8], Stephanie Ladowski[3,4], Chadi Saliba[3,4] & Rodney Pommier[5]

[1]Department of Surgery, University of Toronto, Toronto, ON, Canada; [2]Susan Leslie Clinic for Neuroendocrine Tumors – Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [3]Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, ON, Canada; [4]Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [5]Oregon Heath & Science University Department of Surgery, Division of Surgical Oncology, Knight Cancer Institute, Portland, OR; [6]Developmental Therapeutics Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; [7]Pancreatic Surgery Unit, Pancreas Translational and Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy; [8]Department of Surgery, North Shore Hospital, Takapuna, Auckland, New Zealand

Background
Patients with neuroendocrine tumors (NETs) are at risk of carcinoid crisis when undergoing operations, which is associated with adverse post-operative outcomes. There is no contemporary guideline regarding the perioperative management of patients at risk of carcinoid crisis. Moreover, recent evidence has challenged traditional management with somatostatin analogs preparation and avoidance of beta-adrenergic medication. Therefore, specific guidance is needed to provide evidence-based care and improve the quality of surgical care for patients with NETs. Using a modified Delphi consensus methodology, we aim to establish expert consensus regarding the perioperative management of patients undergoing operations for NETs at risk of carcinoid crisis (loco-regional or metastatic midgut and broncho-pulmonary NETs).
Methods
An international expert panel representing surgical oncology, anesthesiology, medical oncology, endocrinology, and patient partners will be assembled. A literature review and summary was performed and will be presented to the panel to support voting rounds. A first survey round will ask panelists to assess the relevance of items (e.g. preparation, monitoring) to be included in the statement and suggest additional items. Statements will then be generated for items assessed as relevant. Panelists will score their agreement with each statement using a 7-point Likert scale during 2 to 3 survey rounds, aiming for $\geq$70% consensus for (dis)agreement. A final in-person round will be held to review and re-score items that did not reach consensus. Dissent and sentiment analyses will be conducted to explore if scoring was influenced by the make-up of the panel. Finally, a public consultation will be held for stakeholders (interested patients, care partners, healthcare professionals, and members of the public) to provide feedback on the final statement, using elements of the AGREE-REX tool as a framework.
Results
The literature review was conducted and an international panel of 59 experts has been assembled. The first survey round for assessment of items' relevance is set for August 2023. The final expert consensus statement is expected by March 2024, with stakeholders' consultation to take place in March to May 2024.
Conclusion
The proposed modified Delphi expert consensus will fill an important gap in the perioperative management of patients with NETs at risk of carcinoid crisis. It will contribute to standardization of care and improvement of outcomes for this patient population. The international panel and unique patient and public engagement strategy will contribute to the external validity and applicability of the resulting expert consensus statement.
Abstract ID 23788

DOI: 10.1530/endoabs.98.C57

C58

Do Pancreatic Well-differentiated Neuroendocrine Tumor (NET) Progress to Poorly-differentiated Neuroendocrine Carcinoma (NEC)?

Nancy Joseph[1], Sarah Umetsu[1], Sanjay Kakar[1], Stephanie J. Wang[2], Eric Nakakura[3], Alan Paciorek[4], Bryan Khuong Le[5], Farhana Moon[5] & Emily Bergsland[6]

[1]Department of Pathology, University of California San Francisco, San Francisco, CA; [2]School of Medicine, University of California San Francisco, San Francisco, CA; [3]Department of Surgery, University of California San Francisco, San Francisco, CA; [4]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA; [5]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [6]Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA

Background
Grade 3 pancreatic neuroendocrine tumor (G3-PanNET) and neuroendocrine carcinoma (PanNEC) are both defined by Ki67$>$20% and/or mitoses $>$20 per 2mm2. PanNET and PanNEC are thought to be molecularly distinct entities and progression from PanNET to PanNEC is considered rare. MEN1, ATRX, DAXX, and TSC1/2 mutations are common in PanNET, while TP53, RB1, KRAS, and SMAD4 mutations are typical of PanNEC. Immunostains for ATRX/-DAXX/p53/Rb aid in the classification of G3-NET v NEC, and history of prior or concurrent G1/G2-NET is thought to support a G3-NET diagnosis. We have observed multiple G3 neuroendocrine neoplasms (NENs) with alterations in both NET and NEC genes, raising questions about how these cases should be classified and managed.
Methods
Next generation sequencing was performed on 31 pancreatic G3-NENs that were classified as G3-NET during routine pathology review at UCSF. An additional 20 cases of ambiguous pancreatic G3-NEN were also sequenced. Of the ambiguous cases, 10 had alterations in NET genes and were included yielding a total of 41 cases that were either diagnosed as G3-NET or were ambiguous but harbored NET alterations. Several matched prior G1/G2-NETs ($n=5$) were also sequenced.
Results
Of the 41 cases, 23 (56%) had history of a prior G1/G2-NET and received prior therapies, whereas the other 44% were G3 at diagnosis and treatment naive. 88% (36/41) had alterations in NET genes including in MEN1 (63%), DAXX/ATRX (37%), and TSC1/2 (31%). 27% (11/41) had alterations in both NET genes and TP53; 3 of these 11 (3/41 overall; 7.3%) had co-alteration of TP53 and RB1. Of the 11 cases with alterations in TP53 +/- RB1, 8 (73%) had prior G1/G2-NET (5 of which were also sequenced). All G1/G2 priors demonstrated shared identical mutations with the matched G3 NET in at least one NET gene, but none had alterations in TP53 or RB1.
Conclusion
Our study demonstrates that 20% of G3-PanNET harbor alterations in TP53 and another 7.3% harbor co- alteration of TP53 and RB1. Our data suggest that TP53 and RB1 alterations emerge during grade progression to G3-NET, most often (73%) in the setting of previously treated G1/G2-NET. These data raise many questions: 1) Should G3-NET with TP53 and/or RB1 alterations be classified and treated as NEC? 2) Do specific prior therapies increase the risk of acquiring TP53 and/or RB1 alterations? 3) Are outcomes worse in G3-NET with or without TP53 and/or RB1 alterations? Further studies are needed to answer these important questions.
Abstract ID 23800

DOI: 10.1530/endoabs.98.C58

C59

High grade medullary thyroid carcinoma predicts greater lymph node burden in the ipsilateral lateral neck

Aradhya Nigam[1], Bin Xu[2], Philip M. Spanheimer[3], Ian Ganly[1], R. Michael Tuttle[4], Richard J. Wong[1], Ashok R. Shaha[1], Ronald A. Ghossein[2] & Brian R. Untch[1]

[1]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY; [3]Department of Surgery and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; [4]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

Background
The International Medullary Thyroid Carcinoma Grading System (IMTCGS) is a newly established grading system for medullary thyroid carcinoma and is predictive of disease-specific outcomes. When compared to low-grade tumor patients, patients with high-grade tumors have worse locoregional recurrence rates and overall survival. We aimed to investigate how tumor grade impacts neck lymph node burden and post-resection recurrence patterns in MTC.
Methods
A retrospective cohort analysis was performed at a single tertiary care cancer center (Memorial Sloan Kettering Cancer Center, New York, NY) between 1/1/1986 to 12/31/2017. Thyroid specimens were categorized as high-grade if they on pathologic review were found to have: a mitotic index $\geq$ 5 per 2mm^2, Ki67 $\geq$ 5%, and/or necrosis present. Competing risk modelling was used to analyze post-resection local recurrence, distant recurrence, and survival. Significance was set at a p-value$<$0.05.

Results

Amongst 122 patients, 98 (80.3%) low-grade and 24 (19.7%) high-grade patients were evaluated. A similar proportion of low-grade (73%) and high-grade (75%) patients underwent central neck dissection ($P = 0.2$), although the median number of involved lymph nodes in the central neck was greater in high-grade patients (4.5, IQR 0.3-11.2 vs 1.0, 0-2.0; $P < 0.05$). Ipsilateral lateral neck dissection (ILND) was performed in a significantly greater proportion of high-grade patients (71%) than low-grade patients (45%; $P < 0.05$) owing to regional disease identified preoperatively. Amongst patients who underwent ipsilateral lateral neck dissection, the median number of involved lymph nodes was significantly greater in high-grade patients (6.0, 4.0-19.0) than low-grade patients (4.0, 1.0-6.0; $P < 0.05$). Competing risk modelling was subsequently performed to compare disease-specific outcomes between high- and low-grade patients who underwent ILND (Table 1). High-grade patients who underwent ILND had observed worse local recurrence (5yr incidence: 56% vs 19%), distant recurrence (5yr incidence: 38% vs 0%), and overall survival (60% vs 97%) when compared to low-grade patients.

Table 1. Cumulative Incidence at 5 Years of Local and Distant Recurrence Amongst Patients Who Underwent Ipsilateral Lateral Neck Dissection Stratified by Grade

Outcome	ILND for Any Reason			ILND for Known Disease		
	Cumulative Incidence at 5 years	95% CI		Cumulative Incidence at 5 years	95% CI	
		Low	High		Low	High
Local Recurrence						
Low Grade	14%	6%	27%	19%	8%	35%
High Grade	56%	27%	77%	56%	28%	77%
Distant Recurrence						
Low Grade	3.2%	0%	14%	0%	-	-
High Grade	37%	13%	62%	38%	13%	62%

Conclusion

Patients with high-grade MTC demonstrate worse initial lymph node burden in the central and ipsilateral lateral neck compartments. Despite lymph node dissection in patients with known regional disease, high-grade patients experience worse disease recurrence and survival compared to low-grade patients. Tumor grading remains an important factor in the evaluation of MTC patients that undergo surgical resection and can guide postoperative surveillance strategies.

Abstract ID 23801

DOI: 10.1530/endoabs.98.C59

Population Science

P1

Rising incidence of bronchopulmonary neuroendocrine tumors

Alan Paciorek[1,2], Farhana Moon[2], Bryan Khuong Le[2], Li Zhang1,[3], Paige Steiding[2], Emily Bergsland[4] & Claire Mulvey[2,4]
[1]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA; [2]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [3]School of Medicine, University of California San Francisco, San Francisco, CA; [4]Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA

Background
The epidemiology of typical (TC) and atypical carcinoid (AC) bronchopulmonary neuroendocrine tumors (pulmNETs) is not well understood. We aim to describe the incidence of pulmNETs and differences by sex and race and ethnicity (R&E) in the diverse state of California.
Methods
All patients with malignant pulmNETs diagnosed from 1992-2019 in the population-based California Cancer Registry were identified by histology (ICD-O-3 code 8240 for TC or 8249 for AC) and topography (bronchus or lung). Annual age-adjusted incidence rates (AIR) by patient or tumor characteristic were calculated, compared using incidence rate ratios (IRR), and described using JoinPoint regression temporal trend and annual percent change (APC).
Results
Among 6,276 pulmNET patients identified, almost all (92%) were TC. Most (69%) were diagnosed with local stage, 18% with regional, and 12% with distant metastases. Most (78%) self-identified as Non-Hispanic (NH) White, 16% as Hispanic, 3% Asian/Pacific Islander (API), and 3% NH Black. The vast majority (69%) were women. One in five was diagnosed before age 50, and two in five at the time of diagnosis resided in a neighborhood with the highest socioeconomic status tertile. Surprisingly, the AIR sharply increased starting year 2013, resulting in a large APC (8.09 during 2013-2019 with 95% confidence interval (CI) [4.39,11.93]) and a high final overall AIR in 2019 (0.94 per 100,000 persons). During the most recent five-year block, the AIR for women (1.16) was more than twice that for men (0.53), with a statistically significant IRR (2.18 with 95% CI [1.96,2.42]). Other pronounced incidence disparities are seen by R&E, as presented in the Table. Latest 5-year age adjusted incidence rates (AIR) from 2015-2019 by race and ethnicity and incidence rate ratio (row/column) with Tiwari 95% confidence interval

	API	Hispanic	NH black	NH white
N:	110	373	94	1,264
AIR:	0.31	0.67	0.75	1.14
API	1	**0.46 [0.37,0.57]**	**0.41 [0.31,0.55]**	**0.27 [0.22,0.33]**
Hispanic	**2.17 [1.74,2.73]**	1	0.90 [0.71,1.14]	**0.59 [0.52,0.67]**
NH black	**2.43 [1.81,3.25]**	1.12 [0.87,1.41]	1	**0.66 [0.52,0.82]**
NH white	**3.69 [3.02,4.54]**	**1.70 [1.50,1.92]**	**1.52 [1.22,1.91]**	1

Conclusion
We found incidence rates of pulmNETs rising faster now than a decade ago, and differences by sex and R&E. Most pronounced is the disproportionately higher AIR for women. The NH White population has higher AIR than other R&Es, and API has far lower AIR than other R&Es. The reasons for these wide differences in incidence are unclear, and further research is needed to better understand the mechanisms causing disparities.
Abstract ID 23690

DOI: 10.1530/endoabs.98.P1

P2

Renal neuroendocrine tumors: a single center clinicopathologic and molecular analysis

Guillaume J Pegna, Erik Mittra, Nadine Mallak, Adel Kardosh, Emerson Chen, Charles Lopez & Rodney Pommier
Oregon Health and Science University

Background
Renal neuroendocrine tumors (NETs) are a particularly rare subset of NETs, with fewer than 100 cases described in the literature. Of these, next generation sequencing (NGS) findings have been described in fewer than 10 cases, all but one of which had grade 1 disease.
Methods
A single-center, IRB-approved retrospective analysis of patients with grade 2 or 3 well-differentiated renal NETs treated at our institution from 2016-2023 for whom NGS data was available was conducted. Clinical, radiographic, and pathologic data including NGS were abstracted from the electronic medical record.
Results
A total of three patients were found and the median age at diagnosis was 42.7 years (range 24.2-51.7 years). The presenting symptom was back/flank pain in two patients and hematuria in the third. One patient had a horseshoe kidney. All patients had large primary renal tumors measuring >9cm at the time of diagnosis and metastatic disease at or shortly following diagnosis. Clinical, radiologic, and molecular findings are described in the table below.
Table 1: Clinicopathologic and molecular characteristics

	Patient 1	Patient 2	Patient 3
Tumor Grade (Ki-67 index)	2 (8%)	3 (>20%)	3 (22%)
Pathogenic mutation	TP53	None	None
Dotatate PET Imaging uptake	Heterogenous	Homogenously +	Heterogenous
Nephrectomy	Yes	Yes	No
Liver Debulking	No	Yes	Yes
Liver embolization	Yes	Yes	No
Systemic therapies	SSA	SSA, Lu177*, Lenvatinib*	SSA, everolimus, CT
Alive	Yes	Yes	No
Diagnosis to last follow-up (years)	1.7	10.5	2.1

Abbreviations: PET positron emission tomography, SSA somatostatin analogue, Lu177 lutetium 177 dotatate, CT capecitabine/temozolomide. *confirmed radiographic response
Conclusion
This retrospective analysis includes to our knowledge the largest cohort of patients with grade 2 or 3 renal NETs for whom NGS analysis is reported to date. In this cohort, known pathogenic mutations were infrequent and no actionable mutations were found. These tumors demonstrated heterogeneous clinical behavior and radiographic characteristics.
Abstract ID 23698

DOI: 10.1530/endoabs.98.P2

P3

Factors affecting patient knowledge and awareness about neuroendocrine tumors

Sahithi Sonti, Shailesh Advani & Renuka Iyer
Department of Medicine, Roswell Park Comprehensive Cancer Center

Background
Neuroendocrine Tumor (NET) patients are the fastest growing population of cancer patients, hence we wanted to assess if there are gaps in patient knowledge and awareness of their disease. To improve our understanding of the factors affecting patient knowledgeability, we looked at their educational level, satisfaction with educational materials provided at initial diagnosis, other sources used for awareness, and their level of accessibility to education materials about NETs.
Methods
The Roswell Park NET Biobank has enrolled 154 participants to date and answered questionnaires capturing demographics, patient finances, clinical information, quality of life and access to NET educational materials. Patients were asked to record their responses to the question "How knowledgeable do you feel regarding NETs?" on a 4-point scale: Not at all, Somewhat, Very and Extremely. We combined responses into "low levels" (Not at all/Somewhat) and "high levels" (Very/Extremely) for statistical analysis. We ran multivariable logistic regression models to identify demographic and clinical correlates of patient self-report of NET knowledge levels. These models were adjusted for patient's age, gender, marital status, education level, comorbidity burden, level of education/counselling provided to patient's regarding NETs, resources available and their overall level of satisfaction about their accessibility to NET resources. $P < 0.05$ was considered to be statistically significant.
Results
Of the 154 respondents, 123 (79.8%) reported having low levels of knowledge regarding their NET diagnosis. In the multivariable logistic regression model, we found that older patients (OR: 1.06; 95% CI: 1.00 – 1.03) & male gender: (OR: 4.34; 95% CI: 1.18 – 15.92) reported higher levels of knowledge regarding NETs. Those who felt they received adequate education materials/counselling following their initial diagnosis (OR = 21.22; (95% CI = 4.58, 98.29) and those who self-reported high levels of accessibility to NET resources (OR = 11.82; 95% CI = 2.50, 55.83) reported higher levels of knowledge regarding NETs. The main areas the respondents felt required improvement are: (1) Education/information about NETs at initial diagnosis (2) Access to more information resources about NETs; (3) Resources to help family and friends understand and cope with a NET diagnosis. The main sources used by respondents were as follows: websites (31.17), educational materials provided by healthcare providers (29.22%) and social media (20.78%).

Conclusion
Based on our surveys, ~80% of NET patients report low levels of knowledge about NETs, despite using several resources currently available. Efforts to educate newly diagnosed patients and provide information on available NET education resources to patients and their family members are needed.
Abstract ID 23699

DOI: 10.1530/endoabs.98.P3

P4

Determinants of financial distress in patients with neuroendocrine tumors

Sahithi Sonti, Shailesh Advani & Renuka Iyer
Department of Medicine, Roswell Park Comprehensive Cancer Center

Background
Neuroendocrine tumors are a rare group of cancers. The median overall survival of these patients is ~10 years, presenting a unique issue of accrued financial distress over a long period of time. We attempted to look at the potential determinants of financial distress in NET patients, focusing on their demographics, comorbidity burden, educational status and tumor symptoms.
Methods
A total of 155 patients have been enrolled in the Roswell Park NET Biobank database till date. Participants completed a "NET Biobank Questionnaire" that asked patients to self-report their demographics, financial condition, clinical characteristics and impact of NET on their life. Financial distress was defined based on patients' subjective impression about their current household income. Patients were classified as having no financial distress if they responded as "Living comfortably on present income", and were classified as having some form of distress if they responded "Getting by on present income", "Finding it difficult on present income" or "Finding it very difficult on present income". We compared the impact of financial distress on patient characteristics using chi-square tests. Further, multivariable logistic regression models were run to predict factors associated with financial distress among NET patients. These models were adjusted for patient's age, gender, marital status, education level, comorbidity burden and current tumor functional status. $P < 0.05$ was considered to be statistically significant.
Results
Of 150 patients who answered this question, 54 respondents (36%) reported some financial distress. In multivariable logistic regression models, key factors associated with financial distress were patient's age, comorbidity burden, marital status and educational level. Older age (OR = 0.94, 95% CI = 0.90 - 0.99), being married (OR = 0.09, 95% CI = 0.02- 0.30) and education level (college level vs others: OR = 0.32, 95% CI = 0.13- 0.75) were associated with lower odds of patients reporting financial distress. In contrast, higher comorbidity burden (3 + comorbidities vs 0-1: OR = 7.01, 95% CI = 1.32-37.03) was associated with higher odds of self-report of financial distress. In addition, we found that patients reporting financial distress were more likely to rent (vs own) and report lower levels of annual income. Finally, those under distress also expressed having trouble with activities like shopping or cooking.
Conclusion
Apart from the healthcare costs associated with NET treatment and care, sociodemographic factors and overall health, including comorbidity burden should be considered while assessing financial impact and quality of life in NET patients.
Abstract ID 23701

DOI: 10.1530/endoabs.98.P4

P5

Higher serotonin levels from ileum neuroendocrine tumors are associated with mesenteric mass progression

Akitada Yogo[1,2], Alan Paciorek[2,3], Farhan Moon[2,4], Emily K. Bergsland[2,4], Adnan Alseidi[1,4], Mohamed Adam[1,4], Ajay Maker[1,2], Carlos Corvera[1,2], Kenzo Hirose[1,2] & Eric K. Nakakura[1,2]
[1]Department of Surgery, University of California, San Francisco, San Francisco, CA; [2]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; [3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA; [4]Department of Medicine, University of California, San Francisco, San Francisco, CA

Background
Serotonin produced by ileum neuroendocrine tumors (i-NETs) promotes development of the mesenteric mass (MM) associated with lymph node metastases. We previously reported that more extensive MM progression along the superior mesenteric vessels predicts a lower rate of complete surgical resection. In this study, we hypothesized that tumoral serotonin production is associated not only with the development of MM but also its progression, and we examined serotonin levels and the extent of MM involvement.
Methods
One hundred eighty-two patients who underwent resection of primary i-NETs in a single institution between January 2007 and February 2023 were included retrospectively in this study. Serotonin production was measured by urine 24h 5-HIAA before the resection. The extent of MM progression was graded as 0 to 3 based on the distance from the MM and root of the ileocolic vessels. Mesenteric mass volume was calculated as diameter^3*Pi/6. Mann-Kendall trend test or linear regression model was utilized to examine the statistical correlations.
Results
The extent of MM progression correlated with levels of urine 24h 5-HIAA (p-value = 0.0013) in patients without hepatic or ovarian metastasis. However, there was no correlation in those with hepatic or ovarian metastasis (p-value = 0.79). Moreover, MM volume did not correlate with urine 24h 5-HIAA levels (R2 = 0.04, p-value = 0.20). Finally, urine 24h 5-HIAA levels were higher in cases with incomplete lymph node resection than in those with complete lymph node resection (mean (SD) 5.7 (3.0) vs 15.4 (10.9) mg/day, p-value = 0.020).
Table. Urine 24h 5-HIAA and MM progression/grade.

MM grade	0: No MM	1: MM > 2cm distant from the root of ICA/V	2: MM < 2cm distant from the root of ICA/V	3: MM involving SMA/V
Liver, Ovary Metastasis (-)	*n* = 21	*n* = 34	*n* = 17	*n* = 8
Urine 5-HIAA (mg/day)	3.6 (3.0, 5.4)	5.8 (4.7, 7.5)	6.7 (4.8, 9.0)	12.3 (7.5, 19.7)
Liver, Ovary Metastasis (+)	*n* = 15	*n* = 42	*n* = 18	*n* = 14
Urine 24h 5-HIAA (mg/day)	20 (13, 61)	37 (14, 90)	44 (17, 106)	26 (21, 102)

Median (IQR)
Conclusion
We observed higher urine 24h 5-HIAA levels associated with more extensive MM progression along the superior mesenteric vessels, but not tumor volume in the absence of distant disease. The mechanisms by which local serotonin may promote regional tumor progression are unknown but may provide new therapeutic targets for i-NETs.
Abstract ID 23711

DOI: 10.1530/endoabs.98.P5

P6

The use of antidepressants is associated with mesenteric mass formation of ileum neuroendocrine tumors

Akitada Yogo[1,2], Alan Paciorek[2,3], Farhan Moon[2,4], Emily K. Bergsland[2,4], Adnan Alseidi[1,4], Mohamed Adam[1,4], Ajay Maker[1,2], Carlos Corvera[1,2], Kenzo Hirose[1,2] & Eric K. Nakakura[1,2]
[1]Department of Surgery, University of California, San Francisco, San Francisco, CA; [2]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; [3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA; [4]Department of Medicine, University of California, San Francisco, San Francisco, CA

Background
Serotonin production by ileum neuroendocrine tumors (i-NETs) is considered a critical mediator of the fibrotic reaction in mesenteric mass (MM)/ lymph node metastasis. Antidepressants modify serotonin dynamics: however, their role in MM formation is uncertain. We hypothesized that histories of antidepressant use affect MM formation. This study examined the correlation between antidepressant use and MM formation.
Methods
One hundred eighty-two patients who underwent resection of primary i-NET in a single institution between January 2007 and February 2023 were included retrospectively in this study. Use of antidepressants, including SSRI, SNRI, Trazodone, Mirtazapine, Amitriptyline, Bupropion, and St John's Wort prior to referral, was collected from patient records. Mesenteric mass was defined as at least 1 cm diameter from pathological or radiological findings. A multivariable Cox proportional hazards regression model was used to calculate for antidepressant and exposure the hazard ratio of overall mortality from date of resection.
Results
Out of 182 patients, 42 (23%) had a history of antidepressant use. Specifically, 26 patients used SSRI or SSNI, 10 used non-SSRI/SSNI, and 6 used both SSRI or SSNI and non-SSRI/SSNI. Patients with an antidepressant history had a higher

frequency of MM formation than those without (93% vs 75%, p-value = 0.014). In detail, MM formation was observed in 96% of those with SSRI or SSNI, 80% of those with non-SSRI/SSNI, and 100% of those who used both SSRI or SSNI and non-SSRI/SSNI. There was no significant difference in the rate of complete surgical lymph node dissection (78% vs 79%, p-value > 0.9). On multivariate analysis, MM formation (3.3 [1.24-9.0], 0.017), tumor grade 2/3 vs 1 (2.6 [1.35-4.9], 0.004), and hepatic metastasis (4.0 [1.74-9.1], 0.001) were associated with overall survival; however, antidepressant use was not (hazard ratio 1.2 [95% CI 0.57-2.6], p-value = 0.62).

Table. Patient characteristics.

	Antidepressant use		
Characteristic	**NO**, $n = 140$[1]	**YES**, $n = 42$[1]	**P-value**[2]
Urine 24h 5-HIAA (mg/day)	20 (7, 62)	10 (6, 22)	0.084
Carcinoid syndrome (+)	80 (58%)	18 (43%)	0.077
Flushing (+)	44 (32%)	5 (12%)	**0.010**
Mesenteric Mass (+)	96 (75%)	37 (93%)	**0.014**
Tumor Grade (1)	74 (58%)	27 (69%)	0.22
Liver metastasis (+)	78 (57%)	15 (37%)	**0.022**
Follow-up (months)	54 (26, 91)	35 (9, 69)	**0.010**

[1]Median (IQR); n (%), [2]Wilcoxon rank sum test; Pearson's Chi-squared test

Conclusion

Antidepressant use was associated with an increase in MM formation in i-NETs. The reasons for this are unclear and deserve further study.

Abstract ID 23712

DOI: 10.1530/endoabs.98.P6

P7

Validity of geographic-level social determinant of health metrics in pancreatic neuroendocrine tumors

Andrea Gillis, Brendon Herring, Rachael Guenter, Weisheng Chen, Dai Chen, Herbert Chen, J. Bart Rose, Upender Manne & Smita Bhatia
University of Alabama at Birmingham, Heersink School of Medicine

Background

Various social determinant of health (SDOH) metrics and indices are utilized to evaluate access to cancer care and to explain disparities in outcome in pancreatic neuroendocrine tumors (PNETs). Little prior work has compared the validity of various geographic metrics. Therefore we aimed to examine different geographic metrics validity (from smallest to largest: census block group < census tract < zip code < county) utilizing single institutional data in a racially diverse patient population.

Methods

We reviewed all patients surgically treated for PNETs from 2006 to 2022 at a single NCI-designated comprehensive cancer center. We collected patient demographics including self-reported race (White or Black), billing address, tumor characteristics, and SDOH. We utilized individually reported or American Community Survey census block group or tract level as the gold standard for SDOH metrics. We then compared between- and within-race SDOH differences across different geographic levels, including zip code and county using Wilcoxon Signed Rank tests.

Results

A total of 179 patients were included; 49 (27%) patients self-identified as Black. The mean age at surgery was 59 y (SD 13). Black patients were younger at diagnosis (55y (SD: 14) vs. White patients: 60y (SD: 12) ($P = 0.0094$)) and were more likely to be female (69% vs. 45% ($P = 0.004$)). At the block group/census tract level, compared to White patients, Black patients lived in neighborhoods with lower educational attainment, lower income, higher rates of uninsurance, higher overall social vulnerability index (SVI), and higher Area Deprivation Index (all $p < 0.05$). These differences, however, were masked when examining county- and zip code-level SDOHs. Compared to census block/tract level data, county- and zip code-level neighborhood data were most inaccurate for White patients. For White patients, zip code level metrics underestimated income and overestimated uninsurance level ($p < 0.05$). County level metrics underestimated White patients' neighborhood median household income and high school graduation rate, but overestimated poverty, uninsurance rate, and SVI (all $P < 0.05$). For Black patients, zip code level metrics overestimated poverty level and uninsurance rates ($p < 0.05$); the only inaccurate county level metric was SVI ($p < 0.001$).

Conclusion

Black patients with PNETs experience more vulnerable SDOHs, a disparity which may be hidden when analyzing large geographic regional variations. It is imperative to consider the application of census SDOHs and the potential inaccuracies that may mask between-group differences. For the most robust conclusions about racial disparities in cancer research, we encourage investigators to obtain data for individuals or for the smallest geographic region available.

Abstract ID 23722

DOI: 10.1530/endoabs.98.P7

P8

Influence of social determinants of health on pancreatic neuroendocrine tumor stage at presentation

Andrea Gillis, Brendon Herring, Rachael Guenter, Weisheng Chen, Dai Chen, Herbert Chen, J. Bart Rose, Upender Manne & Smita Bhatia
University of Alabama at Birmingham, Heersink School of Medicine

Background

Tumor size and lymph node involvement (stage) have been utilized to prognosticate pancreatic neuroendocrine tumors (PNETs) but the influence of race and social vulnerability on these factors remains unexplored. Therefore we sought to explore this in a racially and socioeconomically diverse cohort.

Methods

We reviewed records of all patients who underwent surgical resection for PNETs from 2006-2022 at a single NCI-designated cancer center in the Deep American South. Patient demographics, including self-reported race, tumor characteristics, and contextual-level social determinants of health (SDOHs) were analyzed at the census track/census block level (where available) including: percent of neighborhood below federal poverty level, median household income, educational attainment, percent of neighborhood without health insurance, Area Deprivation Index (ADI) percentile, and Social Vulnerability Index (SVI) percentile. SDOHs were determined using publically available data from geocoding patient billing addresses at the time of surgery. Large tumor size (≥ 2 cm) and lymph node involvement (LNI) at presentation were the primary outcomes. Data was analyzed using descriptive statistics as well as chi-square, t- , and wilcoxon signed rank tests.

Results

A total of 179 patients were included. The median age at diagnosis was 60y, 52% were female and 27% were Black. Compared to their White counterparts, Black patients were younger (median age 57y vs 60y, $P < 0.01$), and more likely to be female (69% vs 45%, $P < 0.01$). Overall, 121 (68%) patients presented with large tumors. Black patients were more likely to have larger tumors (4.1 vs 3.1cm, $P < 0.01$). There were no differences in SDOH between those with and without large tumors at presentation. Overall, 35 (20%) patients presented with LNI; Black patients were not more likely to present with LNI ($P = 0.83$). Compared to those without, those with LNI lived in neighborhoods characterized by less poverty (12% vs 16%, $P = 0.05$), similar median income ($53K vs $48K, $P = 0.32$), higher educational attainment (92% vs 87% $P = 0.04$), and lower uninsurance rates (14% vs 17% $P = 0.03$), but there was no difference in median SVI or ADI ($p > 0.05$).

Conclusion

In our cohort, there were differences in SDOH between those with more aggressive tumor characteristics on presentation such as LNI being associated with less vulnerable neighborhoods. This may indicate a protective factor due to surgeon access or referral bias, indicating a need for targeted outreach among those diagnosing or caring for patients with PNETs.

Abstract ID 23727

DOI: 10.1530/endoabs.98.P8

P9

Contemporary incidence and survival of lung neuroendocrine neoplasms: a population-based study

Mathieu Rousseau[1], Elliott Wakeam[2], Simron Singh[3,4], Sten Myrehaug[4,5], Calvin Law[1,4], Victoria Barabash[6], Wing C Chan[7] & Julie Hallet[1,4]
[1]Department of Surgery, Université de Montréal, Montréal, QC, Canada; [2]Department of Surgery, University of Toronto, Toronto, ON, Canada; [3]Department of Medicine, University of Toronto, Toronto, ON, Canada; [4]Susan Leslie Clinic for Neuroendocrine Tumors – Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [5]Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada; [6]Sunnybrook Research Institute, Toronto, ON, Canada; [7]ICES, Toronto, ON, Canada

Background

While the epidemiology of overall and gastrointestinal neuroendocrine neoplasms (NENs) has been reported, data specific to lung NENs remain scarce. Such understanding is crucial in designing tailored strategies to improve care and

outcomes. We examined the incidence, overall survival (OS), and disease-specific death (DS-deaths) for lung NENs.
Methods
We conducted a population-based retrospective cohort study of adult patients with incident lung NENs over 2000-2019. We computed yearly incidence rates. Kaplan-Meier curves and Cox regression models examined OS. Cumulative incidence function and Fine-Gray models accounting for the competing risk of death from other causes were used to examine DS-deaths (for lung NENs).
Results
Of 4,479 patients with lung NENs, median age at diagnosis was 67 (IQR 57-74) years old and 56.3% were female. Tumors were 45.9% typical carcinoid, 8.3% atypical carcinoid, 22.3% large cell tumors, and 23.6% neuroendocrine carcinomas, and 24.6% presented as stage IV. The incidence of lung NENs went from 0.87 to 2.9/100,000 from 2000 to 2019. By stage, this rise in incidence was observe for stage I (0.68 to 1.15) but not for stages II to IV. It was more pronounced for typical tumors (0.52 to 1.2) than other tumor types. With median follow-up of 34 months, 1 and 5-year OS were 69.5% (95%CI 68,1-70.8%) and 50.1% (95%CI 48.6-5.6%) for all tumors. Advancing age, lower socioeconomic status, atypical, large-cell and neuroendocrine carcinoma tumors (vs. typical), and stage III and IV disease (vs. stage I) were independently associated with inferior OS. Cumulative incidence of DS-deaths was 25% (95%CI 23.7-26.3%) at 1-year and 36.8% (95%CI 35.3-38.3%) at 5-year. Advancing age, atypical, large-cell, and neuroendocrine carcinoma tumors, and increasing stage from II to IV were independently associated with higher hazards of disease-specific-death, but not socioeconomic status. The non-lung-NENs-deaths exceeded DS-deaths starting 1 year after NEN diagnosis for typical lung NEN and 3 years after diagnosis for stage I disease.
Conclusion
The incidence of lung NENs has increased over 19 years, mostly driven by rising incidence of stage I disease potentially owing to increased detection. Patients with typical lung NEN and stage I disease were more likely to die of non-lung-NEN causes than of disease-specific causes after 1 and 3 years, respectively. In addition to age and tumor characteristics, socioeconomic status was associated with OS, but not DS-death. These data are important to direct efforts in care organization, research design and prioritization, and patient counselling.
Abstract ID 23739

DOI: 10.1530/endoabs.98.P9

P10

Quality of life differs by age and sex for participants with advanced neuroendocrine neoplasms in the eNET study

Claire K. Mulvey[1,2], Alan Paciorek[1,3], Paige Steiding[1,2], Farhana Moon[1,2], 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 a high burden of chronic symptoms. We assessed symptom burden and overall quality of life (QOL) for eNET study participants and analyzed differences by age, sex, and NEN primary site.
Methods
eNET is a prospective, cohort study on the Eureka digital health platform enrolling individuals with advanced NENs. Participants completed validated surveys on an internet-supported device at baseline and then every 6 to 12 months for a total of 3 years. We compared baseline responses on two EORTC QOL questionnaires (QLQ-C30 and QLQ-GINET2) by Pearson chi-squared or Kruskal-Wallis tests.
Results
A total of 124 participants (71% women; 69% age >60 years; 26% pancreatic, 58% gastrointestinal, 16% other primary sites) completed the baseline EORTC questionnaires. Over 10% of participants reported they experienced "very much" of the following symptoms or problems in the prior week: abdominal discomfort (11%), worry about test results (12%), disease or treatment affecting sex life for the worse (12%), distress about illness or treatment to those close to you (15%), fear of recurrence (18%), and worry about health in the future (22%). Compared with older participants, those <60 years old were more likely to have been told by others they looked flushed ($P=0.042$), to be concerned about disruption of home life ($P=0.021$), to report their illness or treatment had been distressing to those close to them ($p<0.001$), to report problems receiving adequate information about disease and treatment ($P=0.002$), and to report financial difficulties ($P=0.039$). There was also a trend towards younger patients having a higher fear of recurrence compared with older patients ($P=0.054$). As to differences by sex, women were more likely than men to report problems receiving adequate information about disease and treatment ($P=0.040$) and reported more trouble sleeping ($P=0.043$) and worse overall physical function ($P=0.047$). The only significant difference by primary site across both surveys was that participants with "other" primary sites had more dyspnea than those with GI or pancreatic primaries ($P=0.031$). Otherwise, responses were similar by sex, age, and primary site.
Conclusion
eNET participants reported more social-emotional symptom burden (worries about future health, fear of recurrence, and relationship issues) as opposed to physical symptom burden. Younger participants were particularly affected by these issues and may represent a group to target for survivorship interventions to reduce distress and improve QOL. There are also opportunities to better inform patients, particularly women and younger patients, about their disease and treatment.
Abstract ID 23752

DOI: 10.1530/endoabs.98.P10

P11

Sex differences during hospital stay among patients with neuroendocrine neoplasms

Wan Ying Tan[1,2], Laura D. Cramer[3], Namrata Vijayvergia[4], Maryam Lustberg[5] & Pamela L. Kunz[5]
[1]Internal Medicine Residency, Department of Medicine, Norwalk Hospital / Yale University Program; [2]Surgical Oncology Research Laboratories, Department of Surgery, Yale School of Medicine; [3]Yale National Clinician Scholars Program, New Haven, CT; [4]Department of Hematology/Oncology, Fox Chase Cancer Center; [5]Department of Medicine, Section of Medical Oncology, Yale School of Medicine and Yale Cancer Center

Background
On the basis of prior large epidemiologic and retrospective studies on treatment-related side effects, it appears that there are sex-based differences in the epidemiology of NENs and treatment-related side effects. The purpose of this study was to examine sex differences in incidence, diagnoses present during hospital stay, and mortality among patients with NENs.
Methods
The NIS database was used to define an unweighted sample of patients with NENs who were discharged from US community hospitals during 2019. The International Classification of Disease, Tenth Revision (ICD-10), Clinical Modification codes were used to identify patients with NENs, and diagnoses present during hospital stay from the discharge records. Participant's demographics, diagnoses present during hospital stay and mortality by sex were evaluated by descriptive analysis.
Results
A total of 7334 patients with NENs were identified in the 2019 NIS database. 4284 patients had primary NEN, and 3050 patients had metastatic NEN. 48.7% were males and 51.3% were females. The mean age in years was 64.8 in males and 63.6 in females ($p<0.001$). Statistical differences were seen when comparing race by sex ($p<0.001$) and primary payer types by sex ($P=0.027$). There were more females than males in Black, White, and Native American races and Hispanic ethnicity. A female predominance was seen with Medicare, Medicaid, private insurance, and self-pay groups; there was a male predominance in the no charge group (although self-pay and no charge groups had lower numbers). There was no statistical difference by sex when combining all categories of diagnoses present during hospital stay. Gastrointestinal diagnoses were most common in both sexes. Specifically, nausea and vomiting were more common in females ($p<0.01$). Males experienced more ascites ($P=0.02$), dysphagia ($P=0.02$) and biliary ductal obstruction ($P=0.014$) in all NENs. However, when separated into primary vs metastatic NENs, ascites was associated with primary NEN ($p<0.01$), whereas dysphagia ($P=0.003$) and jaundice ($P=0.032$) were associated with metastatic NEN. Females experienced more headache ($p<0.01$) and oral-related diagnoses ($P=0.036$) and driven by primary NEN ($P=0.05$). Males with primary NEN experienced more cachexia ($P=0.03$). There was no statistical difference in length of hospital stays and mortality.
Conclusion
There were statistically significant sex differences in the demographics (race and primary payer) and diagnoses present during hospital stay (gastrointestinal, headache, stomatitis and mucositis) among the 2019 NIS discharge sample of patients with NEN.
Abstract ID 23761

DOI: 10.1530/endoabs.98.P11

Other

O1

Integrating advance care planning into nursing work-flow

Michael Lister RN, BSN, OCN, Cherie Adrian, Rebecca Brassfield & Sheila Lindsay NP.
UCSF Cancer Center

Background
UCSF Cancer Center is committed to offering all patients information on Advance Directives; however, many patients do not have their wishes well-documented in their EMR. Our clinic has implemented a workflow for introducing advance care planning discussion into treatment teaching sessions. We have begun to share this workflow throughout the cancer center. Many patients in our clinic have metastatic disease and are treated for months to years by our team. It is important that we provide patients the opportunity to discuss goals of care including advance directives. Medical providers in our clinic have shared challenges to addressing advance directives with patients during initial clinic visits as they address items including diagnosis, prognosis, and treatment at this first visit.
Methods
We began incorporating the introduction of advance care planning at the time of the treatment teaching session. This proved to be an effective time to discuss and receive patient input. The treatment teaching session occurs for all patients in our practice who are starting treatment with us. This is a structured conversation regarding treatment expectations. Patients and families are receptive to new information at this time as they are not dealing with absorbing a new diagnosis or reviewing results. It is a low stakes conversation where they are free to ask questions and discuss with the nurse. Implementation of this plan included universally incorporating this practice into all treatment teaching sessions and documenting this practice with a trackable smartphrase within the EMR.
Results
Our team began addressing advance directives in November of 2019 documenting these conversations with a trackable smartphrase, ".ACP" and as of June of 2020 the ".ACP" phrase had been used 67 times with Dr. Atreya's patients. Before November 2019, this phrase had not been used. We have implemented this practice throughout the GI medical oncology practices at UCSF. Since trialing this ".ACP" phrase in late 2021 across all GI medical oncology practices, we have seen a 6% increase in ".ACP" documentation throughout our practice.
Conclusion
This practice offers patients autonomy and provides more comprehensive care for the patient. The success of this practice relies on the integration into RN standard workflow to ensure all patients are offered this opportunity. Documenting advance directive conversations also satisfies Joint Commission standards: "Documentation in the medical record of a one-time discussion of advance directives/advance care planning with a healthcare provider..."
Abstract ID 23310

DOI: 10.1530/endoabs.98.O1

O2

Germline testing identifies pathogenic/likely pathogenic variants in patients with pancreatic neuroendocrine tumors

Chirayu Mohindroo[1,2], Seyda Baydogan[2], Parul Agarwal[7], Dan Laheru[1], Robin Wright[2], Laura R. Prakash[3], Maureen E. Mork[4], Alison P. Klein[1], Jess Maxwell[3], Matthew H.G. Katz[3], Arvind Dasari[5], Michael P. Kim[3], Jin He[6], Florencia McAllister[2,5] & Ana De Jesus-Acosta[1]
[1]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Department of Clinical Cancer Prevention; [3]Department of Surgical Oncology; [4]Clinical Cancer Genetics Program; [5]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [6]Department of Surgical Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; [7]Department of Oncology, Abramson Cancer Center at the University of Pennsylvania, PA.
Corresponding Author: Ana De Jesus-Acosta, Adejesu1@jhmi.edu

Background
10% of pancreatic neuroendocrine tumors (pNETs) are thought to be related to inherited syndromes, (MEN1, MEN4, VHL, NF1 and TSC). Growing evidence suggests, that clinically sporadic appearing pNETs can harbor germline mutations. Here, we report the prevalence of pathological/likely pathological germline variants (P/LP) in 2 cohorts: 1) High-risk and 2) Unselected.
Methods
We retrospectively collected clinical data of pNET patients seen at MD Anderson Cancer Center (MDACC) and Johns Hopkins Hospital (JHH). High-risk cohort included 132 patients seen at MDACC, who underwent germline testing based on high-risk criteria such as early onset, personal or family history of cancer and syndromic features between 2013 -2019. The unselected cohort included 106 patients seen at JHH, who underwent germline testing following their diagnosis of pNETs between 2020 to 2022
Results
In high-risk cohort, 33% ($n=44$) had P/LP mutations, and 17 % ($n=22$) had a variant of unknown significance (VUS). Majority of them had a mutation in MEN1 56% ($n=25$), followed by DNA Repair pathway 18% ($n=8$), Colon cancer genes 11% ($n=5$) , VHL 11% ($n=5$) and AXIN2 2%($n=1$). Patients with P/LPs mutations were younger (45 years vs 50 years $P=0.002$). In the unselected cohort ($n=106$), 21% ($n=22$) had P/LP, 28 % ($n=30$) had a VUS. P/LP were noted in DNA Repair pathway 40% ($n=9$), MEN1 36% ($n=8$), Colon cancer related genes 9% ($n=2$), VHL 5% ($n=1$) , RET 5% ($n=1$) and PRSS1 5% ($n=1$). Testing was performed using multigene panel testing in 93% of the patients. Multifocal tumors correlated with the presence of P/LP ($P=0.0035$). The presence of MEN1 germline mutation correlated with younger age (40 vs 56 years) ($P=0.0012$). presence of multifocal tumors ($p=<0.0001$), and WHO grade 1 histology ($p=0.0078$). Paired somatic testing in the unselected cohort identified that >70% of patients with P/LP had matching somatic mutations in the tumor specimen.
Conclusion
P/LP are prevalent in patients with sporadic pNET irrespective of high-risk features. We identified a high number of mutations in the DNA repair pathway and lynch syndrome associated genes, not previously described, which could affect subsequent therapies and surveillance for patients and their family members. The high concordance of somatic and germline mutations suggest that P/LP can often be the initiating drivers of pNET development. The findings support upfront universal germline testing in all patients with diagnosis of pNETs.
Abstract ID 23443

DOI: 10.1530/endoabs.98.O2

O3

Clinical characteristics of mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN): a single institution case series

Michael H. Storandt[1], Annie N. Cowan[2], Joleen M. Hubbard[3], Thorvardur R. Halfdanarson[3], Hee Eun Lee[4] & Zhaohui Jin[3]
[1]Department of Medicine, Mayo Clinic, Rochester, MN; [2]Mayo Clinic Alix School of Medicine, Rochester, MN; [3]Department of Medical Oncology, Mayo Clinic, Rochester, MN; [4]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

Background
Gastroenteropancreatic mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) is a rare entity consisting of two morphologically distinct populations of cells, one of which is neuroendocrine and one which is non-neuroendocrine. MiNENs typically contain high grade neuroendocrine carcinoma, conferring a poor prognosis. Due to the rarity of this diagnosis, data is limited and therefore, we sought to add to the current clinical understanding of this diagnosis.
Methods
We conducted a single-institution, multisite survey of the electronic medical record using key search words to identify patients with a diagnosis of MiNEN with a pathological specimen reviewed within our institution. Data are presented descriptively, and recurrence free survival (RFS) and overall survival (OS) are reported using the Kaplan-Meier method.
Results
Fifty-seven patients with a pathological diagnosis of MiNEN were included. Median age was 63.5 years, 60% were male, and 79% were white. The location of the primary malignancy included colorectal (CRC, 47%), esophagus/stomach (EGA, 18%), appendix, pancreas/ampulla (11% each), gallbladder, and small intestine (7% each). Fifty-one percent had stage 1-3 disease at diagnosis and 47% had stage 4 disease. Forty-six patients received systemic chemotherapy, including 12 in the neoadjuvant setting and 12 in the adjuvant setting as part of curative intent therapy, as well as 22 in the palliative setting. Twenty-eight patients underwent curative intent therapy with follow-up data available and manifested a median recurrence-free survival (mRFS) of 12 months. Patients with CRC had equivalent mRFS when compared to other primaries ($P=0.93$). Median overall survival (mOS) for the entire cohort was 22.0 months, with similar survival for CRC, GEA, and other primaries ($P=0.965$). Patients with synchronous metastatic disease had mOS of 13.0 months vs 53.0 months in stage 1-3 disease ($P=1.12e-05$). Patients who received first-line systemic therapy with platinum plus etoposide manifested a mOS of 23.0 months vs 22.0 months in those who received some other form of systemic therapy ($P=0.84$). However, 71% of patients receiving platinum plus etoposide did so in the palliative setting, whereas only 38% of those receiving some other chemotherapy did so in the palliative setting.
Conclusion
MiNEN remains a rare diagnosis, with poor prognosis. Primary location of the tumor was not predictive of survival, but metastatic disease conveyed a poorer

prognosis. MiNENs are often underdiagnosed, and it is essential that oncologists and pathologists be aware of this rare entity.
Abstract ID 23454
DOI: 10.1530/endoabs.98.O3

O4

Baseline grade discordance in patients with pancreatic neuroendocrine tumors (PanNETs)

Farhana Moon[1], Stephanie Wang[2], Alan Paciorek[3], Bryan Khuong Le[1], Eric Nakakura[4], Li Zhang[3], Nancy M. Joseph[5] & Emily Bergsland[6]
[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [2]School of Medicine, University of California San Francisco, San Francisco, CA; [3]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA; [4]Department of Surgery, Division of Surgical Oncology, University of California San Francisco, San Francisco, CA; [5]Department of Pathology, University of California San Francisco, San Francisco, CA; [6]Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, San Francisco, CA

Background
Pancreatic neuroendocrine tumors (panNETs) are heterogeneous, with grade (G) defined by Ki67 proliferation index (<3% G1, 3-20% G2, and >20% G3) or mitotic rate. Previous studies suggest that baseline Ki67 index may be confounded by biopsy site (primary or metastasis), biopsy technique and primary tumor size. Ki67 differences leading to grade discordance in PanNETs at baseline is relatively understudied. Our study aims to evaluate grade discordance in synchronous biopsy samples.
Methods
$n=59$ patients with two biopsies taken within 3 months of diagnosis between 2010 and 2021 were identified from an IRB approved database. Retrospective chart review was conducted to collect demographic and pathological data. Grade discordance proportion was estimated with Wald 95% CI. Comparison of biopsy characteristics and demographics were made using Pearson chi-square and Kruskal-Wallis test.
Results
Among 59 initial biopsy samples (B1), 95% were from FNA/Core biopsy and 5% from surgical resection; 90% ($n=53/59$) from primary tumor, 10% ($n=6/59$) from a metastatic site. Median initial Ki67 index 2% (range 0-47.6%) and 83% had locoregional disease. Median follow-up 3.8 years. The second biopsy (B2) was taken a median of 46 days (range 0-91) later, mostly in the context of surgical samples (84.6%); 16% collected as FNA/core biopsy. Only 8% ($n=5/59$) B2 was performed in the setting of suspicious clinical behavior. In 84.7% of cases, both B1 and B2 taken from primary site. Grade discordance was observed in 22% ($n=13/59$, 95%CI: 11-32%); with 18.6% ($n=11/59$) revealing higher grade in B2 (G1 to G2=9, G2 to G3=2) and 3.3% ($n=2/59$) lower grade (G2 to G1). Median Ki67 index in B2 5.2% (range: 1-57%). Grade discordance (higher grade in B2) was more common in Black patients (75%, $n=3/4$) compared to non-Hispanic White patients (15%, $n=6/33$) [OR: 16.5, 95% CI: 1.5-186, p-value=0.01]. In this cohort, there is no evidence that grade discordance at baseline is associated with differences in biopsy sites, ($P=0.73$), diagnostic stage ($P=0.86$) and biopsy acquisition type ($P=0.87$).
Conclusion
Our study suggests baseline grade discordance is present in 22% of panNETs, regardless of type of biopsy or initial tumor stage. The higher prevalence in Black patients warrants additional study. Ongoing work is focused on assessing the relationship between tumor size, grade discordance, and overall survival. Further research is needed to determine the significance of and mechanisms underlying baseline grade discordance, particularly in larger and more diverse cohorts and those with metastatic disease at diagnosis (underrepresented in this cohort).
Abstract ID 23667
DOI: 10.1530/endoabs.98.O4

O5

Chromogranin A as Surveillance biomarker in Patients with cARcinoids (CASPAR)

Qing Meng[1], Thorvardur R. Halfdanarson[2], Joshua Bornhorst[2], Henning Jann[3], Shagufta Shaheen[4], Run Zhang Shi[4] & Daniel M. Halperin[1]
[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Mayo Clinic, Rochester, MN; [3]Charité Universitätsmedizin Berlin, Berlin, Germany; [4]Stanford University Medical Center, Palo Alto, CA

Background
Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) have highly heterogeneous growth rates, yielding broad ranges of radiographic imaging intervals in standard guidelines, creating uncertainty for clinicians and patients. Chromogranin A (CgA) is released by GEP-NET cells and has been associated with increased tumor burden. However, clinical utility of CgA measurement has been limited by the lack of prospective validation studies and by different sensitivity for radiographic progression according to NET tumor type and volume. The aim of this study was to evaluate prospectively the performance of the B•R•A•H•M•S CgA II KRYPTOR immunoassay to monitor disease progression in patients with grade 1/2 GEP-NETs . This is the first prospective validation of a pre-specified clinical algorithm for the interpretation of CgA values in patients with advanced GEP-NETs.
Methods
This prospective, multi-center, observational study was designed to validate the performance of the B•R•A•H•M•S CgA II KRYPTOR assay in monitoring disease progression in a defined population of GEP-NET patients with minimal confounding from end organ dysfunction or concomitant medications (e.g. PPIs). Patients were followed for up to 36 months including the evaluation of tumor burden with RECIST 1.1 categorization by imaging (CT/MRI scans). A clinical cut-off for changes in CgA levels over time to indicate the risk that a tumor progression occurred was derived from an observational pilot study. An increase of at least 50% in CgA concentration to an absolute value of >100ng/ml was considered positive.
Results
175 adult patients were enrolled, and 153 patients had measurable disease at baseline and ≥1 follow-up visit. Using the cut-off for CgA increase resulted in a sensitivity of 34.4% (95%-CI: 25.6% - 44.3%, $p < 0.001$) and a specificity of 93.4% (95%-CI: 90.4% – 95.5%, $p < 0.001$) for radiographic progression. Positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) to diagnose whether a tumor progression occurred according RECIST 1.1 criteria were 57.9% (95% CI: 45.0-69.8), 84.3% (95% CI: 80.5-87.6), 5.20 (95% CI: 3.23-8.36), and 0.70 (95% CI: 0.61-0.81), respectively. The AUC was estimated at 0.731 (95% CI: 0.670-0.793).
Conclusion
B•R•A•H•M•S™ CgA II KRYPTOR™ can be used as an aid in monitoring disease progression dfor patients with grade 1/2 gastroentero-pancreatic neuroendocrine tumors, with NPV as its greatest strength.
Abstract ID 23676
DOI: 10.1530/endoabs.98.O5

O6

PRESTO 3: An international, simulated-use study assessing preferences of nurses between two lanreotide syringes (Somatuline® Autogel® vs Pharmathen)

Diego Ferone[1], Wendy Martin[2], Jessica Williams[3], Aude Houchard[4], Christelle Pommie[4], Xuan Mai Truong-Thanh[4], Antonio Ribeiro-Oliveira Jr. [5] & Ashley Grossman[6]
[1]IRCCS Ospedale Policlinico San Martino & Department of Internal Medicine and Medical Specialties, University of Genova, Genova, Italy; [2]Kings College Hospital Foundation Trust, London, UK; [3]Oregon Health and Science University Pituitary Center; [4]Ipsen, Boulogne-Billancourt, France; [5]Ipsen, Cambridge, MA; [6]Green Templeton College, University of Oxford, Oxford, UK & Neuroendocrine Tumour Unit, ENETS Centre of Excellence, Royal Free Hospital, London, UK

Background
Patients with neuroendocrine tumours (NETs) and acromegaly are commonly treated with somatostatin analogs (SSAs), such as octreotide and lanreotide depot formulations. The Pharmathen syringe is now available in several European countries and the USA for lanreotide depot injection. When using SSAs, confidence in and ease of use with syringes are important for decision-making in long-term therapy. The aim of the PRESTO 3 study was to compare nurses' preference for the Somatuline Autogel syringe vs the Pharmathen syringe after injection-pad testing. Here we report preferences for 11 syringe attributes.
Methods
This international, simulated-use study included oncology/endocrinology nurses (initial planned sample size 92) with ≥1 year experience in managing patients with NETs and/or acromegaly. Each nurse tested both syringes twice in a randomized order, before completing an electronic preference survey. The primary objective was to assess overall preference (%, 95% confidence interval [CI]) for the Somatuline Autogel syringe vs the Pharmathen syringe, assessed using a one-sample exact binomial test. Secondary objectives included ranking importance and rating performance (scored from 1 [not at all] to 5 [very much]; Wilcoxon 2-sided signed-rank test) of attributes for both syringes.

Results
Ninety-four nurses were enrolled: mean age, 41.0 (SD, 11.5) years; 72.3% in Europe (7 countries) and 27.7% in the USA. The proportion of nurses stating a preference ('strong' or 'slight') for the Somatuline Autogel syringe (86.2% [95% CI 77.5%–92.4%]) was statistically significantly higher than 50% ($p<0.0001$). The syringe attributes considered most important by nurses were "Easy to use from preparation to injection" (30.9%) and "Comfortable to handle during use from preparation to injection" (20.2%). The attribute most commonly rated as least important was "Fast administration from preparation to injection" (26.6%). Performance rating was statistically significantly higher with Somatuline Autogel than the Pharmathen syringe for 10/11 attributes ($p<0.05$).
Conclusion
This simulated-use study showed that nurses strongly preferred the user experience of the Somatuline Autogel syringe over the Pharmathen syringe. "Ease of use" and "comfortable to handle" were considered the most important syringe attributes, and performance rating was significantly higher with Somatuline Autogel than the Pharmathen syringe for all but one of the 11 attributes. The results from PRESTO 3 confirm the difference in these attributes (including confidence and ease of operation) for the different syringes, and illustrates the importance of offering syringe choice to nurses who are treating patients with SSA injections.
Abstract ID 23678
DOI: 10.1530/endoabs.98.O6

O7

Demographic characteristics and survival in young onset colorectal neuroendocrine tumors

Deepak Vadehra, Renuka Iyer, Kristopher Attwood, Adrienne Groman & Sarbajit Mukherjee
Roswell Park Comprehensive Cancer Center

Background
The incidence of young-onset colorectal adenocarcinoma is predicted to continue rising over the next decade. Overall, data about young onset neuroendocrine tumors (NET) is scarce. In this analysis, we sought to investigate trends and differences in survival for colorectal NET in the young-onset population and to compare this with the average onset population. In addition, we seek to compare differences between adenocarcinoma and NET in the young-onset population.
Methods
We conducted a retrospective study on colorectal NET patients and colorectal adenocarcinoma cancer patients between 1975 and 2016 using the Surveillance, Epidemiology, and End Results (SEER) database. Both univariate and multivariable analyses were performed to evaluate overall survival (OS) and disease-specific survival (DSS). Some data elements were separated by decade for analysis within this subgroup. The program used for analysis was SAS software 9.4 (SAS et al., USA.) Univariate and multivariable models were analyzed using Cox proportional models. Demographic differences between urban and rural populations were assessed using the Wilcoxon Rank Sum test (continuous variable) and Chi-square test (categorical variables).
Results
We studied 61,705 patients aged 20-49 years with any colon or rectal cancer. Of these, 8% had NET, and 92% had adenocarcinoma. We found that in the 20-39-year-old age group NETs were more common (33.4%) than adenocarcinoma (25%). The white population was overrepresented in the adenocarcinoma group compared to the NET group (57% vs 43%). On the other hand, the Black population was overrepresented in the NET group compared to the adenocarcinoma group (21% vs 13%). Rectum was the most common site of NET (79%), whereas the colon was the most common site for adenocarcinoma (57%). NET patients were likely to have a smaller tumor compared to adenocarcinoma. They were also more likely to have local procedures than the adenocarcinoma patients (64% vs 8%). Not surprisingly, NET patients within the young age group had much better 5-year OS (88% vs. 63%) and DSS (91% vs. 66%) than adenocarcinoma. However, this gap narrowed in the >60 yr population.
Conclusion
Our database analysis uncovered many demographic disparities in young-onset colorectal NET. At the same time, young-onset NET patients did much better in terms of survival compared to the adenocarcinoma patients in the same age-group; such differences dissipated in the elderly age group, which may be rooted in biological differences between tumors in the older population, and potentially differences in treatment effectiveness/ tolerance.
Abstract ID 23681
DOI: 10.1530/endoabs.98.O7

O8

Comparison of endoscopic ultrasound fine needle aspiration (FNA) vs fine needle biopsy (FNB) for preoperative grading of pancreatic neuroendocrine tumors: A systematic review and meta-analysis

Manik Aggarwal, MBBS[1], Rajat Garg, MBBS[2], Santhi Swaroop Vege, MD[1], Aliana Bofill-Garcia, MD[1], Thorvardur Halfdanarson, MD[3] & Vinay Chandrasekhara, MD[1]
[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN; [2]Digestive Diseases and Sciences, Cleveland Clinic, Cleveland, OH; [3]Division of Oncology, Mayo Clinic, Rochester, MN

Background
Preoperative grading of pancreatic neuroendocrine tumors (PNET) incorporating Ki-67 index can identify PNETs at low risk of progression and prevent unnecessary surgical resection. The aim of this study was to perform a comprehensive literature search and meta-analysis to compare the accuracy of Ki-67 based grading of PNETs between endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) vs fine needle biopsy (FNB).
Methods
Literature search was conducted on multiple databases (Cochrane, EMBASE, Medline, Google scholar) from inception to October 1, 2022, by an experienced librarian to identify studies assessing EUS in PNETs. The primary outcome was the accuracy for Ki-67 based PNET grading on EUS- FNA/FNB samples compared with surgical pathology as the gold standard reference. Analysis was conducted using R v4.1.0.
Results
The literature search identified 1014 studies that were independently screened by two individuals. In total, 29 studies with 1851 individuals were included (22 studies of EUS-FNA, 5 EUS- FNB and 2 with both EUS-FNA and FNB). Concomitant grading with surgical pathology was available in 1015 cases (827 for EUS-FNA and 188 for EUS-FNB). Median age and tumor size were similar between the two groups (**Table 1).** Overall pooled grading accuracy was (76.7%, 95%CI [72.2%-80.7%]) and was similar between FNA (76.1%, 95% CI [70.8 - 80.7]) and FNB (78.8%, 95% CI [69.2 - 86.0]; $P=0.58$). Upgrading of tumor grade on surgical specimen was seen in 17.5% cases and downgrading was observed in 5.0% cases. EUS-FNA had higher pooled rates for both tumor upgrading (19.2%, 95% [15.1 - 23.9] vs. 15.7%, 95% CI [10.0 - 23.8], $P=0.41$) and downgrading (7.5%, 95% CI [5.7 - 9.7] vs. 4.3%, 95% CI [2.2 - 8.3], $P=0.13$) suggesting less consistency with the surgical specimen; however, the results did not reach statistical significance **(Table 1).** On meta-regression, age, gender, tumor size or location were not associated with correct tumor grading for both EUS- FNA and FNB.
Conclusion
Overall pooled grading accuracy of PNETs with EUS sampling was 76.7% and similar between FNA and FNB. There was a trend towards lower changes in grading for specimens obtained via EUS-FNB. Prospective trials with head-to-head comparison are needed to select appropriate sampling strategy.
Abstract ID 23694
DOI: 10.1530/endoabs.98.O8

O9

Prevalence of clonal hematopoiesis (CH) in neuroendocrine tumor (NET) patients prior to lutetium 177 Dotatate (Lu177): A prospective study

Mohamad Bassam Sonbol[1], Yael Kusne[1], Terra Lasho[2], Zaid Elsabbagh[1], Abhishek Mangaonkar[2], Daniel Ahn[1], Rachel Eiring[2], Timothy Hobday[2], Jason Starr[2], Tanios Bekaii-Saab[1], Mrinal Patnaik[2] & Thorvardur Halfdanarson[2]
[1]Mayo Clinic Arizona, [2]Mayo Clinic Rochester

Background
Lu177 has shown efficacy in advanced NET with significant hematologic toxicity, including therapy-related myeloid neoplasm (t-MN). CH is defined by acquisition of somatic mutations in hematopoietic stem cells with potential for expansion over time. In this study, we aimed to assess the prevalence of CH in NET patients (pts) prior to Lu177 along with the incidence of cytopenia in NET pts treated with lu177 based on the CH status at baseline
Methods
Pre-Lu177 blood samples were prospectively collected from 37 NET pts with planned Lu177. Genomic DNA from mononuclear cells was analyzed for CH using a custom panel targeting 229 genes to a targeted depth of >1000X.
Results
A total of 37 NET pts were included (51% male, median age 68); 47% had exposure to either alkylating or platinum agents and most had well-differentiated

small bowel NET (51%). Almost half of the pts ($n=17$; 45.9%) had pathogenic variants meeting the operational definition of CH (DNMT3A, TET2, PPM1D, TP53, SF3B1, ASXL1). The most common pathogenic variants were in epigenetic regulators, DNMT3A (40%) & TET2 (13%), and TP 53 (13%). Median follow up was 15.9 months. At baseline, CH pts had a lower platelet count with a median of 180 x 10^9/L (range, 98 - 247) compared to 230 x 10^9/L (range, 125 – 473) without CH ($P=0.011$). During Lu177 treatment, there was no significant difference in cytopenias between groups, including in grade 3 or 4 cytopenias. Additionally, at 3 months, 6 months, and 12 months follow up, there were no significant differences in hemoglobin, MCV, platelet, leukocytes, neutrophils, or lymphocytes between groups. However, pts with CH were more likely to experience prolonged thrombocytopenia ($P=0.025$) defined as platelet count <150 for >3 months), but not prolonged anemia ($P=0.638$) or leukopenia ($P=0.756$). In total, 3 pts had post- Lu177 CH data available with bone marrow biopsy done. Two of these pts had CH at baseline and one without. Two of these pts were diagnosed with clonal cytopenia of undetermined significanceand developed new PPM1D mutations. None of the pts developed t-MN.

Conclusion

CH is observed in a substantial proportion (46%) of NET patients, and our findings suggest that it poses a potential risk for prolonged thrombocytopenia in those receiving Lu177 treatment. Additionally, the clonal expansion of the PPM1D mutation following Lu177 treatment may contribute to this risk. Further studies with larger sample sizes are required to comprehensively understand these mutations' impact on hematologic toxicities. Identifying high-risk patients prior to Lu177 treatment enables proactive management to prevent treatment delays.

Abstract ID 23702

DOI: 10.1530/endoabs.98.O9

O10

Single institution retrospective case cohort of adult cyanotic congenital heart disease and associated pheochromocytoma and paraganglioma

R. Benson Jones Jr.[1], Bonita Bennett[2] & Debbie Cohen[2]

[1]Division of Endocrinology, Diabetes, Metabolism, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [2]Division of Renal Electrolyte and Hypertension, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Background

Improved management for patients with cyanotic congenital heart disease (CCHD) has led to prolonged lifespan and an increase in patients with CCHD presenting with pheochromocytoma and paraganglioma (PPGL) has been noted. PPGL susceptibility genes including VHL, SDH(x), FH, EPAS1 have been connected to a common signaling pathway that activates hypoxia-inducible factors. 4 of 5 patients with CCHD and PPGL were previously noted to have a somatic gain-of-function mutation in EPAS1 encoding hypoxia-inducible factor 2α. One hypothesis is that the hypoxic environment positively selects for cells with gain-of-function mutations predisposing patients to develop PPGL even when environment is no longer hypoxic. PPGL was diagnosed 13-53 years after surgical correction of CCHD in these patients. We report a case series on 9 CCHD/PPGL patients treated at our institution.

Methods

A retrospective chart review of patients with CCHD treated for PPGL at our institution was performed describing demographics, CCHD and related treatments, symptoms of PPGL and Hct/SpO_2 at diagnosis, tumor size, catecholamine biochemistries, imaging, and genetic analysis when available.

Results

Four of 9 patients were female. Average age of diagnosis of PPGL was 30.7 years (SD 9.6 years, range 15-47 years). CCHD anomalies included Tetralogy of Fallot (2 patients), hypoplastic right ventricle (2 patients) and hypoplastic left ventricle (2 patients). Most surgeries to correct CCHD were performed within days of life; the latest reported surgical procedure was at age 12, 1 patient had a subsequent heart transplant. Patients experienced hot flashes (5), arrhythmias (4), hypertension (4), abdominal pain and nausea (2), and headaches (1); one patient was asymptomatic. Hct ranged from 38%-53%; SpO2 ranged from 85%-99%. Three patients had multiple PPGLs; two had metastatic or recurrent PPGL. Metanephrines at diagnosis ranged from normal to 23x the upper limit of normal. Catecholamines ranged from normal to 16x the upper limit of normal. The locations of PPGL included 6 mediastinal and abdominal paraganglioma (PGLs), 5 head and neck PGLs, and 3 pheochromocytomas. Tumor size ranged from 9-65mm at maximum diameter on pathology. 7/9 patients had germline mutation testing; two SDHB mutations, one SDHA mutation of undetermined significance, and one BARD1 mutation were identified. A table including each patient will be presented.

Conclusion

The extended timeframe between onset of cyanosis and development of PPGL supports long term regular monitoring of CCHD patients to detect PPGL. We suggest screening with plasma metanephrines and catecholamines at age 15 and every 3-5 years after.

Abstract ID 23726

DOI: 10.1530/endoabs.98.O10

O11

Head and neck paragangliomas: overview of institutional experience

Yonghong Huan, MD[1], Jason Brant, MD[2], Bonita Bennett, BSN[1], Maria Bonanni, NP[1], Tanaya Oliphant, MPH[2], Swar Vimawala, MD[2], Ayelet Isabel Rubenstein[3], Alex Z. Graboyes[3], Chris Ji[3] & Debbie Cohen, MD[1]

[1]Division of Renal Electrolyte and Hypertension, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [2]Division of Otolaryngology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [3]University of Pennsylvania, 3400 Spruce St, Philadelphia, PA

Background

Paragangliomas of head and neck (HNPPGLs) are rare and mostly slow growing tumors arising from neural crest-derived cell clusters and have high rate of genetic mutation, up to 40% germline mutations and 30% somatic mutations.

Methods

Retrospective review of institutional experience with clinical evaluation and management of HNPPGLs.

Results

Among 174 patients with HNPPGLs diagnosed from 1981 to 2023, 116 (67%) were women. The mean age at first tumor diagnosis was 50 years, ranging 11 to 82 years. Among 242 tumors identified for the entire cohort; carotid body tumors were the most common type (101), followed by jugular (59) and tympanic (27). Most patients had one tumor; however, many had multiple tumors (ranging 2 to 8), especially those with genetic mutations. Multiple tumors could present at the time of detection or developed over the years, sometimes over a decade apart. Among 98 patients (56% of cohort) with genetic screening, only 2 had additional somatic testing. Among 60 patients (61% of tested or 34.5% of cohort) with genetic mutations, SHDx mutations accounted for the vast majority, including SDHB (25), SDHD (21), SDHC (7), and SDHA (2). A few other known PPGL related mutations were identified, including VHL (1), MEN1 (1) and TMEM127 (1). HNPPGLs tend to be less biochemically active compared to non-HNPPGL. 118 patients (67.8% of cohort) had at least one biochemical evaluation of metanephrines or catecholamines. If biochemistries were elevated, patients were blocked with alpha antagonists prior to any procedures. CT and MRI were the most common imaging modalities. Functional scans with somatostatin analogs were used to evaluate multifocal and metastatic disease. Among the entire cohort, 120 patients had surgery, 22 had radiation therapy, and 5 had MIBG as treatment. Surgery remained the most definitive and commonly used treatment for local disease control, though radiation with stereotactic radiosurgery (SRS) or conventional external beam radiation (EBRT) was used in surgically challenging or inoperable cases. The current practice at our institution has evolved to refer all patients with suspected HNPPGLs for genetic screening and biochemical evaluation. We also have weekly multidisciplinary meetings to discuss the care.

Conclusion

Our experience highlights the need for referral for genetic testing and biochemical evaluation and for a team based approach to improve the clinical outcomes of patients with HNPPGLs.

Abstract ID 23771

DOI: 10.1530/endoabs.98.O11

O12

About a case of neuroendocrine carcinoma of the uterine cervix in peru

Ronald Calle Valdez

Hospital Nacional Alberto Sabogal Sologuren

Background

The diagnosis of neuroendocrine carcinoma of the cervix is rare, they are less than 2% of cervical cancers, and it is considered an unusual entity of diagnosis. In Peru there is only one published case record of this histological type of neoplasm.

Methods

Data was taken from a patient from the electronic medical record of the Alberto Sabogal Sologuren National Hospital in Lima - Peru, who received treatment with etoposide and cisplatin (EP), which is the most used scheme, with a partial response of only 36%. according to RECIST 1.1, so the second regimen in frequency, carboplatin, and paclitaxel, was subsequently used, which obtained a greater partial response of 76% in sequence.

Results

We present the case of a patient with locally advanced neuroendocrine carcinoma treated with two sequential neoadjuvant chemotherapy schemes followed by surgery and radiotherapy. So far with 2.4 years of disease-free survival.

Conclusion

Despite the efforts of aggressive therapies with surgery, chemotherapy and radiotherapy, a poor prognosis continues. For greater progression-free survival (PFS), they should receive at least 5 cycles of treatment with EP, however, there are frequent and high-grade adverse effects, which is why, and added to the poor response obtained in the present case, it was devised a sequential neoadjuvant scheme with good results.

Abstract ID 23780

DOI: 10.1530/endoabs.98.O12

Trials In Progress

T1

ACTION-1: A randomized Phase Ib/3 trial of RYZ101 compared with SoC in SSTR+ well-differentiated GEP-NET with progression following Lu-177 SSA

Thomas A. Hope[1], Daniel Halperin[2], Jonathan Strosberg[3], Heather Jacene[4], Margot E.T. Tesselaar[5], Pamela L. Kunz[6], Denis Ferreira[7], Joanne Li[7], Kimberly Ma[7], Jessica Rearden[7], Susan Moran[7] & Simron Singh[8]
[1]University of California San Francisco, CA; [2]MD Anderson Cancer Center, Houston, TX; [3]Moffitt Cancer Center, Tampa, FL; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Netherlands Cancer Institute, Amsterdam, Netherlands; [6]Yale University, New Haven, CT; [7]RayzeBio, San Diego, CA; [8]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 high-density expression of somatostatin receptors (SSTRs), which can be targeted by radiopharmaceutical therapy (RPT) via radiolabeled somatostatin analogues (SSAs). RYZ101 (^{225}Ac-DOTATATE) is a first-in-class, highly potent alpha-emitting RPT being developed for the treatment of SSTR+ solid tumors. Alpha-particles (such as those emitted by ^{225}Ac) 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) determined the safety, pharmacokinetics, and the recommended Phase 3 dose (RP3D) of RYZ101, 10.2 MBq (275 μCi). Part 2 (Phase 3) will compare RYZ101 at 10.2 MBq (275 μCi) with standard of care (SoC) in patients with advanced SSTR+ GEP-NETs with disease progression following prior ^{177}Lu-labeled SSAs.
Methods
Adults with grade 1–2, well-differentiated, inoperable, advanced, histologically-proven, SSTR+ GEP-NETs that have progressed (RECIST v1.1) following 2–4 cycles of therapy with ^{177}Lu-SSA are eligible. Patients unresponsive to prior ^{177}Lu-SSA (disease control <6 months after last dose of ^{177}Lu-SSA) are excluded. Patients must have ECOG performance status 0–2 and adequate hematologic and renal function. Phase 1b was an uncontrolled dose de-escalation study and has been completed with no dose-limiting toxicities observed. In Phase 3, patients will be randomized (1:1) to receive RYZ101 at a fixed dose of 10.2 MBq (275 μCi) 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 at time of centrally reviewed progression. Primary endpoint (Phase 3): 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.
Results
Phase 3 is currently enrolling and is planned at ~80 sites in North America, South America, Europe, and Asia.
Conclusion
Not applicable - the trial is currently in progress.
Abstract ID 23437
DOI: 10.1530/endoabs.98.T1

T2

Phase 2 study of nab-sirolimus in patients with well-differentiated and advanced/metastatic neuroendocrine tumors of the gastrointestinal tract, lung, or pancreas

Michael J. Demeure, MD[1], Allen L. Cohn, MD[2], Tara Seery, MD[1], Li Ding, MS, MA[3], Usman Aziz, MD[3], Willis Navarro, MD[3] & Scott Paulson, MD[4]
[1]Hoag Memorial Hospital Presbyterian, Newport Beach, CA; [2]Rocky Mountain Cancer Center, Denver, CO; [3]Aadi Biosciences, Inc., Pacific Palisades, CA; [4]Texas Oncology- Baylor Charles A. Sammons Cancer Center, Dallas, TX

Background
Neuroendocrine tumors (NETs; ~2% of all malignancies) commonly arise from the GI tract, pancreas, and lung and often present with metastatic disease. The PI3K/Akt/mTOR pathway is implicated in the pathogenesis and progression of NETs. The oral mTOR inhibitor (mTORi), everolimus, is approved for treatment of patients with NETs of the GI tract, lung, or pancreas. However, due to the rarity and heterogeneity, nonspecific clinical symptoms, and unique indolent biology, management of NETs remains challenging. Nanoparticle albumin-bound (nab)-sirolimus is a novel mTORi that utilizes nanoparticle technology to preferentially target tumors. nab-Sirolimus is approved in the US for adult patients with malignant PEComa. In preclinical animal models, nab-sirolimus demonstrated higher intratumoral drug accumulation and improved target suppression relative to similar weekly doses of sirolimus and everolimus, warranting further exploration of nab-sirolimus (Hou et al, Mol Cancer Ther, 2021). This study will evaluate efficacy and safety of nab-sirolimus in patients with advanced/metastatic NETs.
Methods
This is a phase 2, multicenter, open-label, single-arm study that will enroll up to 21 efficacy-evaluable patients. The study will enroll adults (≥18 years) with functional or non-functional, well-differentiated, locally advanced unresectable or metastatic NETs of the GI tract, lung, or pancreas who have received ≤2 prior lines of therapy excluding somatostatin analogs. Patients with functional NETS are eligible for enrollment if they have been on a stable dose of somatostatin analog for ≥12 weeks and experienced disease progression during treatment. Eligible patients must have ≥1 measurable target lesion (RECIST v1.1), an ECOG performance score of 0 or 1, and adequate organ function/hematologic parameters. Patients are not permitted to have previously received an mTORi, including nab-sirolimus, or to have tumors with known inactivating TSC1/TSC2 alterations. Patients will receive nab-sirolimus 100 mg/m^2 by intravenous infusion on Days 1 and 8 of every 21-day cycle. Treatment will continue until the patient experiences disease progression or unacceptable toxicity, or until discontinuation based on the discretion of the investigator or the patient. The primary endpoint is investigator-assessed objective response rate (ORR) based on RECIST v1.1. Secondary endpoints include duration of response, disease control rate, time to response, progression-free survival, and overall survival; safety and tolerability will be assessed throughout the study. Exploratory endpoints include correlation of baseline molecular biomarkers with clinical outcomes. Analysis of study objectives will be descriptive and hypothesis generating.
Results
Enrollment is expected to commence in the third quarter of 2023.
Conclusion
Trial in progress.
Abstract ID 23461
DOI: 10.1530/endoabs.98.T2

T3

Phase 1/2 trial of Pb-212-VMT-alpha-NET in GI neuroendocrine tumors and pheochromocytoma/paraganglioma previously treated with radioligand therapy

Frank I. Lin[1], Jaydira Del Rivero[1], Jorge Carrasquillo[1], Inna Shamis[1], Joy Zou[1], Baris Turkbey[1], Joanna Klubo[2], Esther Mena[1], Liza Lindenberg[1], Clara Chen[4], Peter Herscovitch[4], Corina Millo[4] & Karel Pacak[2]
[1]National Institutes of Health, National Cancer Institute; [2]National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; [3]National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development; [4]National Institutes of Health, Clinical Center

Background
Metastatic GI Neuroendocrine Tumors (GI-NET) and pheochromocytoma/paraganglioma (PPGL) are are tumors which overexpresses somatostatin receptors (SSTR) and can be treated with targeted radioligand therapy (RLT) such as Lu-177-DOTATATE. However, despite demonstrated clinical efficacy at stabilizing tumor growth, durable response is very rare and almost all patients inevitably progresses at some time after treatment. Good systemic therapy options after beta-emiting RLT are limited. Alpha emitters such as Pb-212 can be effective treatments in patients who have progressed on beta emitter therapy such as Lu-177-DOTATATE. This phase 1/2 trial will find the maximum tolerated dose of a novel alpha-emiting, SSTR-targeting agent Pb-212-VMT-alpha-NET and evalute its preliminary efficacy is GI-NET and PPGL patients who have previously been treated with RLT.
Methods
This is an open-label, single arm, single-center, phase 1/2 study evaluating the safety, tolerability, and pharmacokinetic properties of the alpha-emitting, systemic radioligand therapy agent Pb-212-VMT-α-NET in SSTR+ GI-NET and PPGL. The phase 1 dose escalation portion will be standard 3+3 design, and there will be 4 cycles of fixed dose Pb-212-VMT-α-NET starting at 2.5 mCi and increasing by 2.5 mCi per dose level until a maximum dose of 10.0 mCi or MTD is reached. Pb-203-VMT-α-NET will be used as an imaging agent is a selected dosimetry cohort. Urine and blood will be collected for pharmacokinetic analysis. Both FDG and DOTATATE PET scans will be acquired at baseline and in follow-up. The phase 2 primary objective will be to determine the RECIST 1.1 best overall response rate (ORR). Secondary objectives includes identifying Progression Free Surival (PFS), Overall Survival (OS), as well as imaging and biochemical correlatives. The statistical analysis will employ an optimal Simon 2-stage design with the goal of improving the ORR from 13% (historical response rate of Lu-177-DOTATATE)

to at least 38%. Total number of patients needed to complete the study is 53 patients.
Results
The study will open for enrollment in Q3 of 2023.
Conclusion
This phase 1/2 trial in progress with Pb-212-VMT-α-NET in SSTR+ GI-NET and PPGL is a promising new treatment protocol which can improvement management of patients refractory or who have progressed on beta-emitting RLT.
Abstract ID 23475
DOI: 10.1530/endoabs.98.T3

T4

Phase 2, multicenter, open-label basket trial of nab-sirolimus for malignant solid tumors harboring pathogenic inactivating alterations in TSC1/2 (PRECISION I)

Gopa Iyer, MD[1], Michael J. Demeure, MD[2], Li Ding, MS, MA[3], Anita N. Schmid, PhD[3], Willis Navarro, MD[3], David J. Kwiatkowski, MD, PhD[4] & Jordi Rodon Ahnert, MD, PhD[5]
[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Hoag Memorial Hospital Presbyterian, Newport Beach, CA; [3]Aadi Biosciences, Inc., Pacific Palisades, CA; [4]Brigham and Women's Hospital, Boston, MA; [5]MD Anderson Cancer Center, Houston, TX

Background
nab-Sirolimus, approved in the US for patients with advanced malignant PEComa, is a novel albumin-bound mTOR inhibitor (mTORi) that inhibits the mTOR pathway via suppression of the mTORC1 complex. When TSC1 or TSC2 is inactivated via mutation or loss, the mTOR pathway may be aberrantly activated. TSC1 and TSC2 alterations occur in a range of common cancers. Clinically, in the AMPECT exploratory analysis of nab-sirolimus in advanced malignant PEComa (NCT02494570), 8/9 (89%) and 1/5 (20%) patients with inactivating alterations in TSC2 and TSC1, respectively, had confirmed response. Most treatment-related adverse events in AMPECT were grade 1/2 (none grade ≥4), consistent with mTORi-class adverse events (Wagner, J Clin Oncol, 2021). Based on clinical observations from AMPECT and the underlying mechanism of action of nab-sirolimus, PRECISION I (NCT05103358) was designed to assess nab-sirolimus safety and efficacy in a tumor-agnostic study of advanced cancers with TSC1 and TSC2 inactivating alterations.
Methods
Eligible patients are ≥12yo and mTORi-naïve, possess advanced malignant solid tumors with TSC1 and TSC2 inactivating alterations identified using next-generation sequencing (NGS) in tumor tissue or liquid biopsy (confirmed by central review of NGS reports), and have received appropriate standard treatments, per investigator. nab-Sirolimus 100 mg/m^2 will be given intravenously over 30 min on D1 and D8 of each 21-day cycle. Primary endpoint: overall response rate per independent radiographic review (IRR) using RECIST v1.1. Other endpoints include duration of response, time to response, progression-free survival by IRR, overall survival, patient-reported QOL, and safety. Enrollment began March 2022. Collaboration with leading NGS providers will expedite the identification of patients with qualifying TSC1 and TSC2 mutations; ongoing study access is facilitated through a just-in-time approach to trial site activation. Based on the prevalence of TSC1 and TSC2 inactivating alterations, the most frequent tumor types expected are given in bold in the **Table**.
Table. Estimated frequency of definite impact TSC1/TSC2 alterations

Tumor Type	*TSC1* Alterations[a]	*TSC2* Alterations[a]	*TSC1/TSC2* Combined
Bladder	6.33	1.70	8.03
Hepatobiliary	1.27	3.31	4.58
Endometrial	2.10	1.22	3.32
Soft tissue sarcoma	1.28	1.71	2.99
Ovarian	1.85	0.92	2.77
Esophagogastric	0.65	1.46	2.11
Non-small cell lung cancer	0.77	1.16	1.93
Colorectal carcinoma	0.99	0.39	1.38
Breast	0.41	0.10	0.51

Data are %. [a]Proportion of patients with definite impact alterations (ie, alterations known to have a biological impact, including frameshift, nonsense, and splice-site mutations and deep deletions) derived from analysis of TCGA and cBioPortal by Gulati et al. Data on file.
Results
N/A
Conclusion
Trial in progress
Abstract ID 23649
DOI: 10.1530/endoabs.98.T4

T5

Phase 3 LEVEL trial of 177Lu-edotreotide vs everolimus in patients with advanced neuroendocrine tumors of lung or thymic origin (GETNE-T2217)

Jaume Capdevila[1], Nicola Fazio[7], Rosa Álvarez [2], Catherine Ansquer[3], Sergio Baldari[4], Eric Baudin[5], Marta Benavent[6], Lavinia Benini[7], Amandine Beron[8], Alfredo Berruti[9], Sara Cingarlini[12], Maribel del Olmo-García[13], Emmanuel Deshayes[14], Alejandro Garcia-Alvarez[1], Rocío Garcia-Carbonero[10], Magalie Haissaguerre[16], Jorge Hernando[1], Urbano Anido Herranz[17], Paula Jimenez-Fonseca[15], Come Lepage[18], Belén Llana[15], Javier Molina-Cerrillo[11], Francesco Panzuto[19], Virginia Pubul[20], Maddalena Sansovini[21], Salvatore Tafuto[22], David Taieb[23], Alex Teulé[24], Annibale Versari[25], Guillermo Villacampa[1] & Thomas Walter[26]
[1]Vall dHebron University Hospital, Vall dHebron Institute of Oncology (VHIO), Barcelona, Spain; [2]Gregorio Marañon Hospital, Madrid, Spain; [3]Nantes University Hospital, Nantes, France; [4]AOU Policlinico G. Martino, Messina, Italy; [5]Gustave Roussy, Paris, France; [6]Virgen del Rocío University Hospital, Seville, Spain; [7]European Institute of Oncology, Milan, Italy; [8]Lille University Hospital, Lille, France; [9]Azienda Ospedaliera Spedali Civili Brescia, Italy; [10]Hospital Universitario 12 de Octubre, Madrid, Spain; [11]Hospital Universitario Ramón y Cajal, Madrid, Spain; [12]Azienda Ospedaliera Universitaria Integrata Verona, Italy; [13]Hospital Universitario y Politécnico La Fe, Valencia, Spain; [14]Montpellier Cancer Institute (ICM Val d'Aurelle), Montpellier, France; [15]Asturias Central University Hospital, Oviedo, Spain; [16]University Hospital Bordeaux, Bordeaux, France; [17]University Clinical Hospital of Santiago de Compostela, Santiago de Compostela, Spain; [18]Hospital Center University Dijon-Bourgogne, Dijon, France; [19]Department of Medical-Surgical Sciences and Translational Medicine, Digestive Disease Unit Sant'Andrea University Hospital, ENETS Center of Excellence, Sapienza University of Rome, Italy; [20]Complexo Hospitalario Universitario de Santiago de Compostela; [21]IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - Irsì – Meldola, Italy; [22]National Cancer Institute IRCCS, Naples, Italy; [23]Department of Nuclear Medicine, La Timone University Hospital, CERIMED, Aix-Marseille University, Marseille, France; [24]Catalan Institute of Oncology Hospital, Barcelona, Spain; [25]Unit of Nuclear Medicine, S. Maria Nuova Hospital-IRCCS of Reggio Emilia, Reggio Emilia, Italy; [26]Edouard Herriot Hospital, Lyon, France

Background
Everolimus is the only approved drug for patients with advanced bronchopulmonary neuroendocrine tumors (NET), and there is an urgent unmet need for alternative treatments. Retrospective data for peptide receptor radionuclide therapy (PRRT) have demonstrated promising activity in somatostatin receptor (SST)-positive lung NET. This study aims to investigate the clinical efficacy, safety, and patient-reported outcomes when ^{177}Lu-edotreotide is used to treat advanced lung and thymic NET, as compared to everolimus.
Methods
The LEVEL trial is a randomized, open-label, phase 3 international trial of ^{177}Lu-edotreotide vs everolimus in patients with confirmed advanced, well/moderately differentiated NET of lung or thymic origin. Participants (target sample $n = 120$) must have WHO grade 1 or 2 disease (typical/atypical), SST-positive lesions and radiological evidence of disease progression in the last 12 months according to RECIST v1.1. They can be systemic treatment naïve or have experienced progression on somatostatin analogues and/or ≤2 additional systemic treatments (e.g., chemotherapy, targeted agents, immunotherapy). Prior PRRT or mammalian target of rapamycin (mTOR) inhibitor treatment is not permitted. Eligible participants will be randomly assigned 3:2 to 6 cycles of ^{177}Lu-edotreotide (total dose 7.5±0.7 GBq) or to oral everolimus 10 mg once daily until progressive disease (PD) or intolerable toxicity. CT or MRI scans will be performed every 12 weeks until PD. Blood samples will be analyzed at baseline, at the time of administration of the first dose of study drug, and at PD for pharmacodynamics and to identify potential predictive biomarkers of treatment response. Archival tumor tissue samples will be analyzed for ancillary studies. The primary endpoint is progression-free survival (PFS) according to RECIST v1.1. The sample size provides at least 80% power to demonstrate statistical significance of treatment differences on PFS based on the protocol assumption. The study uses an event-driven analysis, where the analysis will be performed once the prespecified number of events is reached. Secondary outcome measures include overall response rate, overall survival, safety (adverse events [AEs] and treatment-related AEs], and quality of life (assessed using the EORTC QLQ-C30).
Results
The LEVEL trial has received institutional review board/ethics committee approval, and site start-up is ongoing.
Conclusion
The results of this trial are anticipated to provide evidence regarding the efficacy, safety and effect on quality of life of ^{177}Lu-edotreotide in patients with advanced lung and thymic NET. The study is designed to demonstrate superiority of ^{177}Lu-

edotreotide compared to everolimus and may emerge as a new treatment option for this underserved patient population.
Abstract ID 23654
DOI: 10.1530/endoabs.98.T5

T6

Genetic profiling in the randomized controlled phase 3 COMPOSE trial of 177Lu-edotreotide for well-differentiated aggressive grade 2/3 gastroenteropancreatic neuroendocrine tumors

Thorvardur R. Halfdanarson[1], Jaume Capdevila[2], Daniel M. Halperin[3], Ken Herrmann[4], Grace Kong[5], Josh Mailman[6], Diane Reidy-Lagunes[7], Raj Srirajaskanthan[8], Cristina Sierras[9] & Amanda Rotger[9]
[1]Mayo Clinic, Rochester, MN; [2]Vall dHebron University Hospital, Vall dHebron Institute of Oncology, Barcelona, Spain; [3]MD Anderson Cancer Center, Houston, TX; [4]University Hospital Essen, Essen, Germany; [5]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [6]NorCal CarciNET Community, Ripon, CA; [7]Memorial Sloan Kettering Cancer Center, New York, NY; [8]Kings College Hospital, London, UK; [9]ITM Oncologics GmbH, Garching/Munich, Germany

Background
Targeted radionuclide therapies (TRTs) have changed the treatment paradigm of neuroendocrine tumors (NET) and are expected to be widely available for patients with various gastroenteropancreatic (GEP)-NET phenotypes. However, while they have great potential, TRT-based therapeutic strategies for high-grade GEP-NET demonstrate variable outcomes, and there is a current lack of tools to identify patients who are likely to respond to TRT. To address this need, the randomized, controlled, open-label, phase 3 COMPOSE trial of ^{177}Lu-edotreotide TRT vs best standard of care (CAPTEM, FOLFOX, or everolimus; chosen by the investigator) in patients with well-differentiated, aggressive, G2/G3 (Ki-67 index 15−55%), somatostatin receptor-positive GEP-NET will include a genetic profiling analysis. By applying an integrative, systemic multiomics approach, we aim to identify predictive and prognostic genetic markers to improve understanding of tumor progression and TRT responses and to guide individualized treatment of NET.
Methods
Participation in the genetic profiling analysis will be optional for COMPOSE trial participants and will not affect disease management or trial procedures. The genetic signatures of GEP-NET at the time of diagnosis will be analyzed by whole exome sequencing to understand predisposition and mutational drivers of oncogenesis. In addition, tumor biopsies and blood samples (the latter collected before treatment, during treatment, and at disease progression) will be analyzed to identify relevant genomic and gene expression signatures, with a focus on suppressive/activating genetic traits.
Results
We plan to create a bioinformatic pipeline for predicting TRT efficacy and disease progression. The pipeline will integrate genomic and gene expression signatures with structural and functional imaging data, histopathology, and patients' clinical characteristics.
Conclusion
Data from this study are expected to contribute to individualized management of GEP-NET by making it easier to predict which treatment(s) individual patients are likely to respond to.
Abstract ID 23655
DOI: 10.1530/endoabs.98.T6

T7

Phase 1 trial of Pb-212-VMT-alpha-NET in select metastatic or inoperable somatostatin receptor positive tumors

Frank I. Lin[1], Jaydira Del Rivero[1], Anish Thomas[1], Ramaprasad Srinivasan[1], Floudas Charalampos[1], Jorge Carrasquillo[1], Inna Shamis[1], Joy Zou[1], Baris Turkbey[1], Esther Mena[1], Liza Lindenberg[1], Clara Chen[4], Peter Herscovitch[4], Corina Millo[4] & Karel Pacak[2]
[1]National Institutes of Health, National Cancer Institute; [2]National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development;

Background
Somatostatin receptors (SSTR) is overexpressed in a number of different tumors, including GI Neuroendocrine Tumors (GI-NET), Pheochromocytoma/Paraganglioma (PPGL), small cell lung cancer (SCLC), renal cell carcinoma (RCC), and certain head and neck cancers (H&N) such as olfactory neuroblastoma. It has been demonstrated that these SSTR-expressing tumors can be treated with beta-emitting radioligand therapy (RLT) that binds to SSTR such as Lu-177-DOTATATE. However, there are known limitations of beta emitting radionuclides such as Lu-177-DOTATATE, such as having low objective response rates and lack of durable responses. As alpha particle emitters such as Pb-212 have significantly higher tumor-kill potential compared to beta particles due to their larger physical size and higher linear energy transfer (LET), it is hypothesized that SSTR-targeting alpha emitters will have greater efficacy than betas. Early clinical trial data of other similar SSTR-targeting alpha emitters such as of Pb-212-DOTAMTATE have already shown good clinical efficacy. This phase 1 trial will evaluate the efficacy of a novel agent Pb-212-VMT-alpha-NET in patients with SSTR+ tumors who are naïve to prior RLT.
Methods
This is an open-label, single arm, single-center, phase 1 study evaluating the safety, tolerability, and pharmacokinetic properties of the alpha-emitting, systemic radioligand therapy agent Pb-212-VMT-α-NET in five different SSTR+ tumors: GI-NET, PPGL, SCLC, RCC, and H&N. The phase 1 dose escalation will be using a standard 3+3 design, with the dose regimen being 4 cycles of fixed dose Pb-212-VMT-α-NET starting at 2.5 mCi and increasing by 2.5 mCi per dose level until a maximum dose of 10.0 mCi or MTD is reached. Pb-203-VMT-α-NET will be used as an imaging agent is a selected dosimetry cohort. Urine and blood will be collected for pharmacokinetic analysis. Both FDG and DOTATATE PET scans will be acquired at baseline and in follow-up. The primary objective is to determine the RECIST 1.1 response rate in treated patients. Secondary objectives includes identifying Progression Free Surival (PFS), Overall Survival (OS), as well as imaging and biochemical correlatives. At the MTD, there will be an expansion cohort so that at least 6 patients per histology will be treated on study.
Results
The study will open for enrollment in Q3 of 2023.
Conclusion
This phase 1 trial in progress with Pb-212-VMT-α-NET in SSTR+ tumors is a promising new treatment protocol which can improvement management of patients naïve to prior RLT in a variety of histologies.
Abstract ID 23656
DOI: 10.1530/endoabs.98.T7

T8

Status of the ongoing SORENTO clinical trial: Assessing efficacy and safety of high-exposure octreotide subcutaneous depot in patients with GEP-NET

Simron Singh[1], Jaume Capdevila[2], Jennifer Ang Chan[3], Wouter W de Herder[4], Simona Grozinsky-Glasberg[5], Thorvardur Halfdanarson[6], Daniel M Halperin[7], Josh Mailman[8], Lisa Hellström[9], Agneta Svedberg[9], Fredrik Tiberg[9] & Diego Ferone[10]
[1]Sunnybrook Health Sciences Center, Toronto, Canada; [2]Vall d'Hebron University Hospital, Barcelona, Spain; [3]Dana-Farber Cancer Institute, Boston, MA; [4]Erasmus MC, Rotterdam, The Netherlands; [5]Hadassah Medical Organization, Jerusalem, Israel; [6]Mayo Clinic, Rochester, MN; [7]The University of Texas MD Anderson Cancer Center, Houston, TX; [8]Northern California CarciNET Community, Oakland, CA; [9]Camurus AB, Lund, Sweden; [10]Endocrinology, Department of Internal Medicine & Medical Specialties, IRCCS Ospedale Policlinico San Martino, University of Genova, Italy

Acknowledgements
This study was funded by Camurus AB. Medical writing support was provided by Costello Medical and funded by Camurus AB.
Background
Somatostatin receptor ligands (SRLs) are first-line standard of care therapies for gastroenteropancreatic neuroendocrine tumors (GEP-NET), showing efficacy in tumor/symptom control with an established safety profile. However, disease progression usually occurs despite standard-dose SRL treatment, requiring more aggressive and potentially more toxic therapies. Retrospective/non-randomized data suggest higher-dose SRLs may benefit patients with GEP-NET who do not respond to standard-dose treatment, providing improved disease control. Octreotide subcutaneous depot (CAM2029) is a novel, long-acting, high-exposure formulation. Clinical trials showed ~500% higher octreotide bioavailability with CAM2029 vs octreotide long-acting release (LAR), and maintenance/reduction of NET symptoms. Prospective, randomized trial data are needed to confirm efficacy/safety of alternative high-exposure SRLs, such as CAM2029, vs standard-dose SRLs including octreotide LAR and lanreotide Autogel (ATG).
Methods
SORENTO (NCT05050942) is a randomized, multicenter, 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 somatostatin receptor-positive lesion (by nuclear imaging) according to RECIST 1.1; no/<6 months consecutive treatment with long-acting SRLs. Notably, patients with Grade 3 GEP-NET are eligible (unlike in the CLARINET/PROMID trials). Patients will be randomized 1:1 to CAM2029 20mg every two weeks or active comparator (octreotide LAR 30mg intramuscular or lanreotide ATG 120mg SC, every four weeks). CAM2029 self/carer-administration is permitted after appropriate training and supervised administrations. Randomization stratified by histological grade; tumor origin; intended comparator. The primary outcome is progression free survival (PFS; time from randomization to first documented disease progression [RECIST 1.1] or death), assessed by a Blinded Independent Review Committee. The study is powered to detect a 0.65 hazard ratio. Key secondary outcomes are overall survival; response rate; rescue medication use; patient satisfaction; adverse events. After primary PFS analysis, overall survival will be followed for up to 2 years. If the primary endpoint of CAM2029 superiority is met, the comparator group may switch to CAM2029. Patients in any group experiencing progressive disease in the randomized period may enter an open-label extension with intensified CAM2029 treatment to investigate effects of higher-frequency dosing. Readout will occur following 194 PFS events.

Results

Enrollment began Nov-2021. As of Jun-2023, 183 patients have been randomized across the 95 open sites in Australia (newly added country), Belgium, Canada, France, Germany, Hungary, Israel, Italy, the Netherlands, Romania, Spain, and the United States.

Conclusion

This novel head-to-head superiority trial is anticipated to demonstrate potential benefits of CAM2029 as a first-line therapy in patients with well-differentiated GEP-NET.

Abstract ID 23665

DOI: 10.1530/endoabs.98.T8

T9

Phase 1-2 trial of vesicular stomatitis virus expressing human interferon-β and NIS (VSV-IFNβ-NIS), with ipilimumab and nivolumab, in patients with neuroendocrine carcinoma

Patrick W. McGarrah[1], Shruthi Naik[2], Thorvardur R. Halfdanarson[1], Mohamed Shanshal[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; [2]Vyriad, Rochester, MN

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). 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. Dual checkpoint inhibition seems more promising, but response rates are quite modest. 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 ICIs.

Methods

This is a phase 1-2 safety run-in study designed to determine the safety of VSV-IFNβ-NIS in combination with ipilimumab and nivolumab, followed by dose expansion in patients with refractory non-small cell lung cancer (NSCLC) or NEC. Patients must have previously progressed on at least one line of systemic therapy. Prior treatment with checkpoint inhibitors is permitted. Patients are treated with ipilimumab and nivolumab on day 1, followed by one-time intravenous VSV-IFNβ-NIS on day 4, then nivolumab every 3 weeks and ipilimumab every 6 weeks 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 23773

DOI: 10.1530/endoabs.98.T9

T10

Phase Ib trial of cabozantinib (Cabometyx®) combined with Lu-177 DOTATATE radioligand therapy in patients with advanced, somatostatin receptor positive NETs.

Hagen F Kennecke MD, MHA, FRCPC[1], Lena Yamasaki, RN[1], Anup Kasi, MD, MPH[2], Katherine Herz[1] & Erik S. Mittra MD[3]

[1]Providence Cancer Institute, Portland, OR; [2]University of Kansas Medical Center, KS; [3]Oregon Health Sciences University, Portland, OR

Background

Combination peptide receptor radionuclide therapy (PRRT) with the multikinase inhibitor cabozantinib may result in enhanced tumor response and improved intratumoral delivery of Lu-177 DOTATATE by normalization of tumor vasculature through VEGFR inhibition.

Methods

In a phase Ib trial, patients with advanced somatostatin receptor (SSTR) positive, G1-3 neuroendocrine tumors (NETs) with a Krenning score of >2 are treated with 4 x 8 week cycles of Lu-177 DOTATATE 7.4 GBq (200 mCi) intravenously in combination with escalating doses of oral cabozantinib daily, starting 14 days prior to Lutathera®. Single-agent cabozantinib is continued to progression after completion of PRRT. The primary study endpoint is maximal tolerated dose (MTD) of cabozantinib and the secondary endpoint is radiographic objective response rate by RECIST criteria.

Results

The single-institution study was activated December 2022 and a total of 6 patients have been enrolled of which 3 entered the first dose cohort of cabozantinib 20mg daily. All 3 patients have well-differentiated, Grade 3 NETs of pancreatic (2) or unknown primary (1) origin. No dose limiting toxicities were identified during cycle 1 and no serious adverse events (SAEs) were reported. Hypocalcemia was the only grade 3 toxicity during cycle 1 reported in 1 of 3 patients. Initial imaging after cycle 2 of therapy documented a RECIST partial response in both patients with pNETs and stable disease in the patient with unknown primary NET. After review of the complete dose cohort 1, cycle 1 adverse event data, on May 15, 2023, the Data Safety Monitoring Committee approved dose escalation to level 2 with cabozantinib 20mg alternating with 40mg daily and 3 further patients were subsequently enrolled.

Conclusion

Cabozantinib 20mg daily starting 14 days prior to standard doses of Lu-177 PRRT had no dose limiting toxicities during cycle 1 allowing dose escalation to 20mg/40mg alternate daily dosing. Preliminary efficacy signals with initial response are promising. Updated safety and efficacy information will be reported for the first 6 patients enrolled.

Abstract ID 23776

DOI: 10.1530/endoabs.98.T10

T11

NET RETREAT: a Phase II Study of 177Lutetium-Dotatate Retreatment vs. Everolimus in Metastatic/Unresectable Midgut NET

Aman Chauhan[1], Chris O'Callaghan[2], Sten Myrehaug[3], Lisa Bodei[4], Pamela Kunz[5], Arvind Dasari[6], Jonathan Strosberg[7], Stefanie Alexander[2], Winson Cheung[8] & Simron Singh[3]

[1]Sylvester comprehensive cancer center, University of Miami, FL; [2]Canadian Cancer Trials Group (CCTG), Queen's University, Kingston, ON, Canada; [3]Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Canada; [4]Molecular Imaging and Therapy Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, USA; [5]Yale School of Medicine, New Haven, CT; [6]University of Texas MD Anderson Cancer Center, Houston, TX; [7]Moffitt Cancer Center, Tampa, FL; [8]Patient Advocate CCTG, Canada

Background

177Lu-DOTATATE is an FDA and Health Canada-approved treatment option for metastatic, progressive GEPNET patients. 177Lu-DOTATATE is now often considered the treatment of choice for small bowel/midgut patients who have progressed on somatostatin analogs (SSA). Despite 177Lu- DOTATATE's impressive disease stabilization, many patients will eventually progress.

Progression after prior use of PRRT does not necessarily render these tumors resistant to future PRRT treatments. PRRT retreatment strategies have been tested in various European centers where PRRT has been available for the past two decades. Several studies report single institute, non-randomized, retrospective data on PRRT retreatment with varying degrees of efficacy and relatively safe toxicity profiles. Despite a growing body of evidence favoring limited dose PRRT retreatment, prospective randomized data is lacking in support of a PRRT retreatment strategy. Prior studies also suffer from a heterogenous patient population and inconsistent PRRT regimens. Many times, Y-90-based PRRT treatment is incorporated either during the initial treatment or PRRT retreatment. Y-90 based PRRT is known to have a preponderance of nephrotoxicity. Currently, Y-90 based PRRT is not available commercially in the US. Hence, NET-RETREAT fulfills an unmet medical need by exclusively studying limited dose retreatment of 177Lu-DOTATATE PRRT in midgut NET patients who have previously benefitted from PRRT.

Rationale

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

Methods

This CCTG-SWOG, international multi-center, open-label, randomized phase II trial will evaluate the efficacy and safety of limited dose 177Lu-DOTATATE as compared to everolimus in metastatic/unresectable well-differentiated midgut neuroendocrine tumor patients who have previously experienced durable response (12 months of stable disease per RECIST 1.1) to 177Lu- DOTATATE. One hundred (100) midgut unresectable/metastatic NET patients will be randomized 2:1 in favor of the experimental arm. The primary objective is to evaluate progression-free survival (PFS) while secondary and correlative objectives include assessment for safety, objective responses, quality of life metrics, and evaluation of novel blood-based predictive and diagnostic markers (NETEST, PPQ, and hPG80). **ClinicalTrials.gov Identifier:** NCT 05773274

Results

NA

Conclusion

NA

Abstract ID 23777

DOI: 10.1530/endoabs.98.T11

T12

Neuroendocrine tumors AI-based clinical trial search tool eases clinical trial discovery for patients and health care professionals

Josh Mailman[1], Danielle Ralic[2], Jaydira del Rivero MD[3], Germo Gericke MD[4], Thorvardur R. Halfdanarson MD[5], Ken Herrmann MD[6], Ronald Hollander[7] & George Albert Fisher Jr. MD[8]

[1]Northern California CarciNET Community, Oakland, CA; [2]Ancora.ai AG, Zurich, Switzerland; [3]Developmental Therapeutics Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; [4]Ariceum International AG, Basel, Switzerland; [5]Mayo Clinic Comprehensive Cancer Center, Rochester, MN; [6]Department of Nuclear Medicine, University of Duisburg-Essen, and German Cancer Consortium-University Hospital Essen, Essen, Germany; [7]Research Committee International Neuroendocrine Cancer Alliance, Boston, MA; [8]Stanford Cancer Center, Stanford University, Palo Alto, CA.

Corresponding Author is Danielle Ralic, Ancora.ai AG, Zurich, Switzerland

Background

Finding relevant neuroendocrine tumor (NET) trials remains a challenge for patients and healthcare professionals (HCPs). Clinicaltrials.gov's taxonomy associates many conditions with NETs, complicating the discovery process. As of 6/30/23 clinicaltrials.gov listed 700 recruiting, phase 1-3 interventional trials using the terms Neuroendocrine Tumors, Pheochromocytoma, and Paraganglioma. Many of these trials are not relevant for patients with NETs. Even with several redesigns of clinicaltrials.gov, it can still be challenging to navigate the user interface to find trials for a patient's specific situation, especially with uncommon cancers. Here Ancora.ai and NorCal CarciNET Community present a joint project to leverage technology, specifically Artificial Intelligence (AI), to improve the discoverability of trials, and thereby help patients and HCPs more easily find relevant NET trials.

Methods

The project assembled an expert panel consisting of physicians, scientific experts, patients, and a healthcare technology partner (Ancora.ai) to assess which clinical trials should be brought in and what eligibility criteria should be considered. Ancora.ai's proprietary AI model automatically searches trials to recognize eligibility criteria and restructures them to enable patient-trial matching using a digital questionnaire. The trial extraction model was refined based on NET-specific criteria proposed by the expert panel. After testing the tool with scientific experts and patients, the beta trial finder tool was released at NANETS' annual symposium in 2022. At NANETs, the project team collected feedback from both HCPs and patient advocates. Once the feedback had been incorporated, the tool was officially launched with NorCal CarciNETs in January 2023. In April 2023, the tool was additionally deployed to patient advocacy partners including INCA, NETRF, LACNETs, and Para Pheo Alliance.

Results

With the trial extraction model, only relevant and validated trials for NETs are included in the digital search tool, reducing the number of trial options from 700 to 155. The questionnaire-based interface allows HCPs and patients to quickly navigate the trials database without prior knowledge of the clinicaltrials.gov taxonomy. Since its beta launch on November 1, 2022 to June 30, 2023, the tool has seen over 1,250 searches from across 44 countries. Current usage trends show 73% of users can complete the search and find personalized trial options in under 5 minutes.

Conclusion

By using AI technology and a curated questionnaire, we have been able to improve patients' and HCPs' ability to efficiently and effectively discover relevant clinical trials.

Acknowledgments

This project was funded by NorCal CarciNETs.

Abstract ID 23789

DOI: 10.1530/endoabs.98.T12

Author Index